Class: Opioid analgesic.

Indications: ***SL and injection*** moderate–severe pain, premedication and peri-operative analgesia, †intolerance to other strong opioids.
SL high-dose tablet withdrawal and maintenance therapy for opioid addicts.
TD severe opioid-responsive pain (Transtec®; BuTrans®) or moderate–severe cancer pain not responding to non-opioid analgesics (Transtec®), †intolerance to other strong opioids.

Contra-indications: TD buprenorphine should not be used for acute (transient, intermittent or short-term) pain, e.g. postoperative, and in those who need rapid dose titration for severe uncontrolled pain.

Pharmacology
Following the introduction of TD and high-dose SL formulations, buprenorphine is experiencing a renaissance in chronic pain management and opioid dependence.[1-5] Buprenorphine is a partial μ-opioid receptor and opioid-receptor-like (ORL-1) agonist and a κ- and δ-opioid receptor antagonist.[6-8] It has high affinity at the μ-, κ- and δ-opioid receptors, whereas affinity at the ORL-1 receptor is 500-fold less. It associates and dissociates slowly from receptors. Subjective and physiological effects are generally similar to **morphine** (agonist effects at the μ-opioid receptor).

Antagonist effects at the κ-opioid receptor may limit spinal analgesia, sedation and psychotomimetic effects.[9] In animal studies, buprenorphine demonstrates a ceiling effect or a bell-shaped dose-response curve for analgesic (>1mg/kg) and respiratory effects (0.1mg/kg). This is thought due to its partial agonist effect at the μ-opioid receptor. An agonist effect at the pronociceptive supraspinal ORL-1 receptor may also contribute.[10] In humans, a ceiling effect has been demonstrated for respiratory depression (~200microgram IV)[11,12] and other effects, e.g. euphoria (4–8mg/SL)[13,14], but not for analgesia.[12] Doses as high as 16mg/day provide effective analgesia.[15] Thus, the ceiling dose for analgesia in humans is much higher than the 'maximum' dose recommended by the manufacturer's, namely 3.36mg/day (70microgram/h patches x 2).

The oral bio-availability of buprenorphine is low (15%); after PO administration, it undergoes extensive first-pass metabolism in the gastro-intestinal mucosa and liver, where it is almost completely converted by CYP3A4 to norbuprenorphine. Norbuprenorphine has similar opioid receptor-binding affinities to buprenorphine but does not readily cross the blood brain barrier and has little, if any, central effect.[16] Both buprenorphine and norbuprenorphine undergo glucuronidation to inactive metabolites.[17]

SL buprenorphine is rapidly absorbed into the oral mucosa (2–3min), followed by a slower absorption into the systemic circulation (t_{max} 40min–3.5h after a single dose; 1–2h with repeat dosing).[16] After parenteral and SL administration, 70% of buprenorphine is excreted unchanged in the faeces and some enterohepatic recirculation is likely; whereas norbuprenorphine is mainly excreted in the urine.[18] Vomiting is more common with SL administration than IM or TD.

Buprenorphine is highly lipid-soluble making it suitable for TD delivery. It is available two formulations delivering either 5, 10 or 20microgram/h over 7 days (BuTrans®) or 32, 52.5 or 70microgram/h over 4 days (Transtec®) and, like other

strong opioids, is an alternative to both weak opioids and **morphine**.[19] Buprenorphine is evenly distributed in a drug-in-adhesive matrix. Its release is controlled by the physical characteristics of the matrix and is proportional to the surface area of the patch. Absorption of the buprenorphine through the skin and into the systemic circulation is influenced by the stratum corneum and blood flow. Thus, if the skin is warm and vasodilated, the rate of absorption increases. There are few practical differences in the use of the buprenorphine or **fentanyl** matrix patches. Compared with **fentanyl**, buprenorphine TD (as Transtec®) adheres better. However, after patch removal, it is associated with more persistent erythema (± localized pruritus), and sometimes a more definite dermatitis.[20] Retrospective analysis suggests that, compared with fentanyl TD, patients receiving buprenorphine TD (as Transtec®) have a slower rate of dose increase and longer periods of dose stability.[21] This requires confirmation in an RCT.

Buprenorphine has a large volume of distribution and is highly protein-bound (96%; α- and β-globulins).[16] It is generally safe to use in patients with renal impairment as buprenorphine does not cumulate; it is not removed by haemodialysis and thus analgesia is unaffected (see p.000).[22,23] Although cumulation of norbuprenorphine can occur, this may be of little clinical relevance given its lack of central effect.[16,22] Smaller starting doses and careful titration are advisable in patients with severe but not mild–moderate hepatic impairment. Buprenorphine crosses the placenta and enters breast milk. The incidence, severity and duration of the neonatal abstinence syndrome appears to be less than with **methadone**.[24,25]

Buprenorphine has either no effect or a smaller effect than **morphine** on pressure within the biliary and pancreatic ducts.[26,27] Buprenorphine does slow intestinal transit, but possibly less so than **morphine**.[28,29]

In contrast to other opioids, buprenorphine does not suppress the gonadal axis or testosterone levels (see p.000). This may relate to its κ-opioid receptor *antagonist* effect.[30] Because hypogonadism is associated with reduced sexual desire and function, mood disturbance, fatigue and other physiological effects, e.g. muscle wasting, osteoporosis, this may become an important consideration in patients requiring long-term opioid therapy.[31,32]

Compared to **morphine** and other opioids, buprenorphine has little or no immunosuppressive effect (see p.000).[3,33,34]

With typical clinical doses, it is possible to use **morphine** (or other μ-opioid receptor agonist) for episodic (breakthrough) pain[35] and to switch either way between buprenorphine and **morphine** (or other μ-opioid receptor agonist) without loss of analgesia.[36] Despite concerns that antagonism could occur, this is likely only with a very large dose; even with buprenorphine 32mg SL, only 84% of μ-opioid receptors are occupied.[37]

A recent study in volunteers suggests that buprenorphine may have an anti-hyperalgesic effect as well as an analgesic effect.[38,39] Animal studies and case reports also suggest that buprenorphine may be of particular benefit in neuropathic pain.[3] The implications for the clinical management of neuropathic pain, if any, need to be determined by controlled studies.[40,41]

Because buprenorphine has very strong receptor affinity (reflected in its high relative potency with **morphine**), **naloxone** in standard doses does not reverse the effects of buprenorphine and higher doses must be used (Box 5.A)[3,42-44] However, significant respiratory depression is rarely seen with clinically recommended doses. The concurrent use of benzodiazepines may increase the risk of serious or fatal respiratory depression.[45] The non-specific respiratory stimulant **doxapram** can also

be used, 1–1.5mg/kg IV over 30sec, repeated if necessary at hourly intervals or 1.5–4mg/min CIVI. [46,47]

Box 5.A Reversal of buprenorphine-induced respiratory depression

1. Discontinue buprenorphine (stop CSCI/CIVI, remove TD patch)
2. Give oxygen by mask
3. Give IV **naloxone** *2mg* stat over 90sec.
4. Commence **naloxone** *4mg/h* by CIVI
5. Continue CIVI until the patient's condition is satisfactory (probably <90min)
6. Monitor the patient frequently for the next 24h, and restart CIVI if respiratory depression recurs
7. If the patient's condition remains satisfactory, restart buprenorphine at a reduced dose, e.g. half the previous dose.

In an anecdotal report, two out of five patients with cholestatic pruritus responded to treatment with buprenorphine.[48] However, there is insufficient data at present to recommend its use in this circumstance (see p.000).

Buprenorphine has a longer duration of action than **morphine**. In postoperative single-dose studies, buprenorphine provided analgesia for 6–7h compared with 4–5h with **morphine**.[49] This is reflected in the recommended dose frequency (q6h–q8h *vs.* q4h for **morphine**). However, the longer duration of action of buprenorphine almost certainly means that potency ratios based on *single-dose* studies will *under-estimate* the potency of buprenorphine. Thus, the following ratios should be *not* be regarded as 'cast iron'. They merely provide a rough guide for use when switching route or opioids (see Opioid dose conversion ratios, p.000):

- SL buprenorphine is more than half as potent as IV/IM/SC buprenorphine; in round figures, 400microgram SL is equivalent to 200microgram SC[50,51]
- SL buprenorphine is about 80 times more potent than PO **morphine**;[36,52] in round figures, 400microgram SL buprenorphine is equivalent to 30mg PO **morphine**
- IV/IM/SC buprenorphine is 30–40 times more potent than IV/IM/SC **morphine**;[53] in round figures, 300microgram IV buprenorphine is equivalent to 10mg IV **morphine**.
- TD buprenorphine is >100 times more potent than PO **morphine**;[36,52]

This last ratio, based on retrospective chart review, suggests that TD buprenorphine and TD **fentanyl** are more or less equipotent (see Table 15.2, p.000). Pharmacokinetic data are summarized in Table 5.1. The bio-availability of IV buprenorphine is by definition 100%, and that of SC essentially the same. In contrast, SL buprenorphine is only some 50% bio-available. Bio-availability is irrelevant in relation to TD patches; the stated delivery rates reflect the mean amount of drug delivered to patients throughout the patch's recommended duration of use. Inevitably, there will be interindividual variation in the amount delivered.

Table 5.1 Pharmacokinetic data for buprenorphine

	IV	*TD (Transtec®)*	*TD (BuTrans®)*	*SL*
Onset of action	5–15min[49]	21h for 35microgram/h patch; 11h for 70microgram/h patch	18–24h	15–45min[54]
Time to peak plasma concentration	5min	60h	3 days	30min–3.5h single dose;1–2h multiple doses[9,16]
Plasma halflife	3–16h[16]	25–27h[a]	13–35h[a]	24–69h[16]
Duration of action	6–9h	4 days	7 days	6–9h

a. the halflife after a patch has been removed and not replaced.

Cautions
Liver impairment. A single case report describes respiratory depression when IM **ketorolac** was added to ED buprenorphine.[55] Buprenorphine is mainly a substrate of CYP3A4 and accordingly the manufacturers and others suggest caution with CYP3A4 inhibitors, or avoiding their concurrent use (e.g. **cimetidine, zileuton** (not UK), **fluoxetine, fluvoxamine, clarithromycin**, **erythromycin, troleandomycin** (not UK), **ketoconazole, indinavir ritonavir**, **saquinavir** and **gestodene**) which theoretically could lead to an increase in buprenorphine levels. Conversely, CYP3A4 inducers (e.g. **carbamazepine**, **phenobarbital**, **phenytoin** and **rifampicin**) could reduce buprenorphine levels.[56] Studies have confirmed that **ketoconazole** approximately doubles buprenorphine levels in patients receiving high-dose buprenorphine (8–16mg/day) SL but not 5–20microgram/h TD.[57,58] Thus, halving of the dose of buprenorphine is recommended in patients receiving high-dose buprenorphine SL if used with **ketoconazole** or other CYP3A4 inhibitors. The combination of high-dose buprenorphine SL with antiretrovirals, particularly **delavirdine** and **ritonavir** increases the QT interval, but the clinical significance of this is uncertain.[59]

Undesirable effects
For full list, see manufacturers' SPCs.
See Strong opioids, p.000.
***Very common (>10%)*:** dizziness, drowsiness, headache, nausea and vomiting, erythema and pruritus at the patch application site.
Common (<10%, >1%): anxiety, insomnia, asthenia, hypotension, fainting, oedema, anorexia.

Dose and use
SL
- starting dose 200–400microgram q6–8h
- use with a sip of water if mouth is dry
- typical dose 800microgram–1.2mg/day
- higher doses reported in chronic pain patients switched from other opioids (2–16mg/day).[15]

SC/IM/IV
- starting dose 300–600microgram q6–8h
- for patients receiving CSCI/CIVI buprenorphine, p.r.n. injections about 1/10 of the total daily dose can be used for episodic (breakthrough) pain.

TD
TD buprenorphine patches are available in two formulations: 7-day patches; 5, 10 and 20microgram/h (BuTrans®) and 4-day patches, 35, 52.5, 70microgram/h (Transtec®) (see guidelines, p.000). For patients who have not already been taking an opioid, the lowest patch strength should be prescribed, i.e. 5microgram/h (equivalent to 12mg of PO **morphine**/24h). General advice and recommended starting doses are detailed in the manufacturer's SPCs.

Supply
Unless indicated otherwise, all preparations are **CD**.

Temgesic® (Schering-Plough)
Tablets SL 200microgram, 400microgram, 28 days @ 200microgram t.d.s. = £9.
Injection 300microgram/ml, 1ml amp = £0.50.

Subutex® (Schering-Plough)
Tablets SL 400microgram, 2mg, 8mg, 28 days @ 4mg b.d. = £108.

Transdermal preparations
BuTrans® (Napp)
Patches (for 7 days) 5microgram/h, 1 = £2.50; 10microgram/h, 1 = £8; 20microgram/h, 1 = £15.

Transtec® (Napp)
Patches (for 4 days) 35microgram/h, 1 = £8; 52.2microgram/h, 1 = £12; 70microgram/h, 1 = £15.

---

1 Resnick RB (2003) Food and Drug Administration approval of buprenorphine-naloxone for office treatment of addiction. *Annals of Internal Medicine.* **138**: 360.
2 Sorge J and Sittl R (2004) Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapeutics.* **26**: 1808–1820.
3 Budd K and Raffa R (eds) (2005) *Buprenorphine - the unique opioid analgesic*. Georg Thieme Verlag, Stuttgart, Germany, p.134.
4 Muriel C *et al.* (2005) Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clinical Therapeutics.* **27**: 451–462.
5 Gowing L *et al.* (2006) Buprenorphine for the management of opioid withdrawal. *The Cochrane Database of Systematic Reviews.* CD002025.
6 Rothman R (1995) Buprenorphine: a review of the binding literature. In: A Cowan and J Lewis (eds) *Buprenorphine: combatting drug abuse with a unique opioid.* Wiley-Liss, New York, pp.19–29.
7 Zaki P *et al.* (2000) Ligand-induced changes in surface mu-opioid receptor number: relationship to G protein activation? *Journal of Pharmacology and Experimental Therapeutics.* **292**: 1127–1134.
8 Lewis JW and Husbands SM (2004) The orvinols and related opioids--high affinity ligands with diverse efficacy profiles. *Current Pharmaceutical Design.* **10**: 717–732.
9 Johnson RE *et al.* (2005) Buprenorphine: considerations for pain management. *Journal of Pain and Symptom Management.* **29**: 297–326.
10 Lutfy K *et al.* (2003) Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *Journal of Neuroscience.* **23**: 10331–10337.
11 Dahan A *et al.* (2005) Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *British Journal of Anaesthesia.* **94**: 825–834.
12 Dahan A *et al.* (2006) Buprenorphine induces ceiling in respiratory depression but not in analgesia. *British Journal of Anaesthesia.* **96**: 627–632.

13 Budd K (2002) *Buprenorphine: a review. Evidence Based Medicine in Practice.* Hayward Medical Communications, Newmarket.
14 Walsh S *et al.* (1994) Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology and Therapeutics.* **55**: 569–580.
15 Malinoff HL *et al.* (2005) Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. *American Journal of Therapeutics.* **12**: 379–384.
16 Elkader A and Sproule B (2005) Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. *Clinical Pharmacokinetics.* **44**: 661–680.
17 McQuay H and Moore R (1995) Buprenorphine kinetics in humans. In: A Cowan and J Lewis (eds) *Buprenorphine: combatting drug abuse with a unique opioid.* Wiley-Liss, New York, pp.137–147.
18 Cone EJ *et al.* (1984) The metabolism and excretion of buprenorphine in humans. *Drug Metabolism and Disposition: The Biological Fate of Chemicals.* **12**: 577–581.
19 Davis MP (2005) Buprenorphine in cancer pain. *Supportive Care in Cancer.* **13**: 878–887.
20 Schmid-Grendelmeier P *et al.* (2006) A comparison of the skin irritation potential of transdermal fentanyl versus transdermal buprenorphine in middle-aged to elderly healthy volunteers. *Current Medical Research and Opinion.* **22**: 501–509.
21 Sittl R *et al.* (2006) Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of noncancer and cancer pain: a retrospective data analysis in Germany. *Clinical Therapeutics.* **28**: 1144–1154.
22 Hand CW *et al.* (1990) Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *British Journal of Anaesthesia.* **64**: 276–282.
23 Filitz J *et al.* (2006) Effect of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *European Journal of Pain.* **10**: 743–748.
24 Fischer G (2000) Treatment of opioid dependence in pregnant women. *Addiction.* **95**: 1141–1144.
25 Lacroix I *et al.* (2004) Buprenorphine in pregnant opioid-dependent women: first results of a prospective study. *Addiction.* **99**: 209–214.
26 Pausawasdi S *et al.* (1984) The effect of buprenorphine and morphine on intraluminal pressure of the common bile duct. *Journal of the Medical Association of Thailand.* **67**: 329–333.
27 Staritz M *et al.* (1986) Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. *Gut.* **27**: 567–569.
28 Robbie Ds (1979) A trial of sublingual buprenorphine in cancer pain. *British Journal of Clinical Pharmacology.* **7 (suppl 3)**: s315–s317.
29 Bach V *et al.* (1991) Buprenorphine and sustained release morphine - effect and side-effects in chronic use. *The Pain Clinic.* **4**: 87–93.
30 Bliesener N *et al.* (2005) Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. *Journal of Clinical Endocrinology and Metabolism.* **90**: 203–206.
31 Daniell HW (2002) Hypogonadism in men consuming sustained-action oral opioids. *The Journal of Pain.* **3**: 377–384.
32 Rajagopal A *et al.* (2004) Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer.* **100**: 851–858.

33 Sacerdote P *et al.* (2000) The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. *Anesthesia and Analgesia.* **90**: 1411–1414.
34 Budd K and Shipton E (2004) Acute pain and the immune system and opioimmunosuppression. *Acute Pain.* **6**: 123–135.
35 Mercadante S *et al.* (2006) Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. *Journal of Pain and Symptom Management.* **32**: 175–179.
36 Atkinson R *et al.* (1990) The efficacy in sequential use of buprenorphine and morphine in advanced cancer pain. In: D Doyle (ed.) *Opioids in the treatment of cancer pain.* Royal Society of Medicine Services, London, pp.81–87.
37 Greenwald MK *et al.* (2003) Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology.* **28**: 2000–2009.
38 Koppert W *et al.* (2005) Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. *Pain.* **118**: 15–22.
39 Simonnet G (2005) Opioids: from analgesia to anti-hyperalgesia? *Pain.* **118**: 8–9.
40 Sanchez-Blazquez P and Garzon J (1988) Pertussis toxin differentially reduces the efficacy of opioids to produce supraspinal analgesia in the mouse. *European Journal of Pharmacology.* **152**: 357–361.
41 Likar R and Sittl R (2005) Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. *Anesthesia and Analgesia.* **100**: 781–785, table of contents.
42 van Dorp E *et al.* (2006) Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology.* **105**: 51–57.
43 Knape J (1986) Early respiratory depression resistant to naloxone following epidural buprenorphine. *Anesthesiology.* **64**: 382–384.
44 Gal T (1989) Naloxone reversal of buprenorphine-induced respiratory depression. *Clinical Pharmacology and Therapeutics.* **45**: 66–71.
45 Reynaud M *et al.* (1998) Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction.* **93**: 1385–1392.
46 Orwin JM (1977) The effect of doxapram on buprenorphine induced respiratory depression. *Acta Anaesthesiologica Belgica.* **28**: 93–106.
47 British National Formulary (2006) In: *British National Formulary* (No. 51). British Medical Association and Royal Pharmaceutical Society of Great Britain, London, p.167.
48 Juby L *et al.* (1994) Buprenorphine and hepatic pruritus. *British Journal of Clinical Practice.* **48**: 331.
49 Heel RC *et al.* (1979) Buprenorphine: a review of its pharmacological properties and therapeutic efficiency. *Drugs.* **17**: 81–110.
50 Ellis R *et al.* (1982) Pain relief after abdominal surgery-a comparison of i.m. morphine, sublingual buprenorphine and self-administered i.v. pethidine. *British Journal of Anaesthesia.* **54**: 421–428.
51 Bullingham RE *et al.* (1984) Mandatory sublingual buprenorphine for postoperative pain. *Anaesthesia.* **39**: 329–334.
52 Sittl R *et al.* (2005) Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. *Clinical Therapeutics.* **27**: 225–237.
53 Cuschieri RJ *et al.* (1984) Comparison of morphine and sublingual buprenorphine following abdominal surgery. *British Journal of Anaesthesia.* **56**: 855–859.

54 Bullingham RE *et al.* (1981) Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. *British Journal of Clinical Pharmacology.* **12**: 117–122.
55 Jain PN and Shah SC (1993) Respiratory depression following combination of epidural buprenorphine and intramuscular ketorolac. *Anaesthesia.* **48**: 898–899.
56 Genelex Corporation (2006) GeneMedRx Database. (Subscription required).
57 Schering-Plough Limited (2006) Data on file. Personal communication.
58 Noveck R *et al.* Lack of effect of CYP3A4 inhibitor ketoconazole on transdermally administered buprenorphine (abstract). In: Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics. Orlando; 2005.
59 Baker JR *et al.* (2006) Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. *Annals of Pharmacotherapy.* **40**: 392–396.

1 Indications for using TD buprenorphine instead of morphine include:
- intolerable undesirable effects with morphine, e.g. nausea and vomiting, constipation, hallucinations, dysphagia
- renal failure (no centrally active metabolites)
- 'tablet phobia' or poor compliance with oral medication
- high risk of tablet misuse/diversion (although the patch can still be abused).

2 TD buprenorphine is contra-indicated in patients with acute (short-term) pain and in those who need rapid dose titration for severe uncontrolled pain.

3 TD buprenorphine patches are available in two formulations:
- 7-day patches; 5, 10 and 20microgram/h (BuTrans®)
- 4-day patches, 35, 52.5, 70microgram/h (Transtec®).

The maximum *licensed* dose is two 70microgram/h patches.

4 Use Table 1 below to decide a safe starting dose for TD buprenorphine and Table 2 to decide an appropriate rescue dose. These recommendations are based on a PO morphine:TD buprenorphine dose ratio of 100:1; *this differs from the manufacturer's SPC which uses ~ 70:1*. Patients not previously receiving opioids should start on 5 or 10microgram/h patches; patients with unrelieved pain despite maximum dose of a step 2 analgesic should commence on 20 or 35microgram/h patches, according to circumstances.

5 For patients taking a dose of morphine that is not the exact equivalent of a buprenorphine patch, it will be necessary to opt for a patch which is either slightly more or slightly less than the morphine dose. Thus, if the patient still has pain, round up to a higher patch strength; if pain-free and frail, round down.

Table 1 Comparative doses of morphine/diamorphine and TD buprenorphine (based on dose ratio 100:1)

Morphine PO		*Morphine SC/IV*		*Diamorphine SC/IV*		*Buprenorphine patch*	
mg/24h	*p.r.n. mg*[a]	*mg/24h*[b]	*p.r.n. mg*[a]	*mg/24h*[b]	*p.r.n. mg*[a]	*microgram/h*	*mg/24h*
						BuTrans	
12	2[c]	6	1	4	1	5	0.12
24	5[c]	12	2.5	8	1.5	10	0.24
48	10	24	5	16	3	20	0.48
						Transtec	
84	15	42	7.5	28	5	35	0.84
126	20	63	10	42	7	52.5	1.26
168	30	84	15	56	10	70[d]	1.68

a. using traditional 1/6 of total daily dose as p.r.n. dose and rounded to a convenient dose
b. assuming potency ratio of morphine SC/IV to PO of 2:1 and diamorphine SC/IV to PO of 3:1
c. at these doses, p.r.n. codeine/dihydrocodeine (30–60mg)or tramadol (50mg) may suffice
d. for combinations of patches, add the p.r.n. doses together, e.g. 70 + 52.5microgram/h patches = 15 + 10mg morphine SC/IV = 25mg morphine SC/IV, but can round up to 30mg or down to 20mg for convenience.

Table 2 Comparative p.r.n. doses of buprenorphine.

Buprenorphine SL		*Buprenorphine SC/IM/IV*		*Buprenorphine TD patch*	
microgram/24h[a]	*p.r.n.*[b]	*microgram/24h*	*p.r.n.*[b]	*microgram/h*	*microgram/24h*
				BuTrans	
240	[c]	120	20	5	120
480	[c]	240	40	10	240
960	200	480	80	20	480
				Transtec	
1680	200–400	840	140	35	840
2520	400	1260	210	52.5	1260
3360	600	1680	280	70	1680

a. assuming potency ratio of buprenorphine SC/IV to SL of 2:1
b. using traditional 1/6 of total daily dose as p.r.n. dose, rounded to a convenient dose; give q6–8h
c. in the UK, the smallest tablet is 200microgram (unscored); smaller doses could be given by using the solution for injection SL (300microgram/ml); otherwise use morphine or other strong opioid.

6 The date of application and/or the date for renewal should be written on the patch. Apply to dry, non-inflamed, non-irradiated, hairless skin on the upper trunk or arm; body hair may be clipped with scissors but not shaved. If the skin is washed beforehand, use only water; do not use soap and do not apply oils, cream or ointment to the area. Press patch firmly in place for 30+ seconds. Micropore® or Tegaderm® can be used to ensure adherence. Careful removal of the patch helps to minimize local skin irritation.

7 Systemic analgesic concentrations are generally reached within 12–24h but levels continue to rise for 32–54h. If converting from:

- 4-hourly PO morphine, give regular doses for the first 12h after applying the patch
- 12-hourly m/r morphine, apply the patch and the final m/r dose at the same time
- 24-hourly m/r morphine, apply the patch 12h after the final m/r dose
- CSCI/CIVI, continue the syringe driver for about 12h after applying the patch.

8 Steady-state plasma concentrations of buprenorphine are reached after 9 days (1–2 days with patch strength of ≤20microgram/h); the patient should use p.r.n. doses liberally initially, particularly during the first 24h. Safe rescue doses of SL buprenorphine/PO morphine are given in the Tables above.

9 After 72h, if a patient continues to need 2 or more rescue doses of analgesic/day, the next strength patch should be used.

10 Potentially, patients could experience opioid-withdrawal symptoms that manifest like gastric flu and last for a few days when changed from another opioid (particularly large doses) to TD buprenorphine. Giving p.r.n. doses of the previous opioid during this period may help.

11 Buprenorphine is less constipating than morphine; halve the dose of laxatives when starting buprenorphine and re-titrate.

12 Buprenorphine may cause nausea and vomiting; if necessary, prescribe an anti-emetic, e.g. haloperidol 1.5mg stat & o.n. for the first 7 days, and then p.r.n.

13 In febrile patients, the rate of absorption of buprenorphine increases, and could cause toxicity, principally drowsiness. Absorption may also be enhanced by an

external heat source over the patch, e.g. electric blanket or hot-water bottle; patients should be warned about this. Patients may swim or shower with a patch but should not soak in a hot bath.

14 Remove and replace patches once (7-day patch) or twice (4-day patch) a week. The 4-day patch can be replaced on fixed days in the week, i.e. after 3 and 4 days alternatively. Change the position of the new patches so as to rest the underlying skin for at least 9 days.

15 A reservoir of buprenorphine cumulates in the body, particularly in adipose tissue, and significant plasma levels persist for at least 24h after discontinuing TD buprenorphine.

16 Because of undesirable effects (e.g. nausea, vomiting, dizziness), TD buprenorphine is unsatisfactory in about 10% of all patients, but only 3% in cancer patients.

17 In moribund patients, continue TD buprenorphine and give additional SC morphine p.r.n. (see Table above). If >2 p.r.n. doses are required/24h, give morphine by CSCI, starting with a dose equal to the sum of the p.r.n. doses over the preceding 24h. If necessary, adjust the p.r.n. dose taking into account the total opioid dose (i.e. TD buprenorphine + CSCI morphine).

18 Used patches still contain buprenorphine; after removal, fold the patch with the adhesive side inwards, and then discard in a sharps container (hospital) or dustbin (home), and wash hands. Ultimately, any unused patches should be returned to a pharmacy.