Therapeutic Reviews

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Buprenorphine *AHFS 28:08:12*

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For international educational and comparative purposes, this article also refers to formulations not available in the USA.

Buprenorphine is experiencing a renaissance in the management of chronic cancer and non-cancer pain, and opioid dependence (high-dose SL formulation ± naloxone).[1–7] Preliminary data suggest that compared to morphine and other opioids, buprenorphine appears to cause less hyperalgesia and tolerance, and has less effect on the immune and endocrine systems. However, clinical trials are needed to find out if such differences represent real clinical advantages.

Class: Opioid analgesic.

Indications

In the USA, the injection (300microgram) and low-dose TD patches (5, 10, 20microgram/h) are approved for moderate–severe chronic pain. High-dose SL tablets (2mg, 8mg) and a SL film (2mg, 4mg, 8mg, 12mg) also containing naloxone are labeled for use as maintenance therapy in opioid addicts.

In many other countries, in addition to the injection, low-dose SL tablets (200microgram, 400microgram) and high-dose TD patches (35, 52.5, 70microgram/h) are approved for moderate–severe chronic pain.

Contraindications: Hypersensitivity to buprenorphine, significant respiratory depression, acute or severe asthma, known or suspected paralytic ileus. TD buprenorphine should not be used for acute (transient, intermittent, short-term) pain, e.g., postoperative, or when there is need for rapid dose titration for severe pain.

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Pharmacology

Buprenorphine is a partial μ-opioid receptor and opioid-receptor-like (ORL-1) *agonist* and a κ- and δ-opioid receptor *antagonist*.[8–10] It has high affinity at the μ-, κ- and δ-opioid receptors, but affinity at the ORL-1 receptor is 500 times less. It associates and dissociates slowly from receptors.[11] Subjective and physiological effects are generally similar to morphine (μ-opioid receptor agonist).

Studies in volunteers suggest that compared to morphine and other opioids, buprenorphine exerts a more prominent antihyperalgesic than analgesic effect;[12,13] however, this is not a consistent finding.[14] Animal studies and case reports also suggest that buprenorphine may be of particular benefit in neuropathic pain,[2,15] but controlled studies are needed to confirm this.[6,16–18] The co-administration of an ultra-low dose of an opioid antagonist potentiated the analgesic effect of buprenorphine (as with other opioids) in healthy volunteers but not in patients.[19,20]

Antagonist effects at the κ-opioid receptor may limit spinal analgesia, sedation and psychotomimetic effects.[21] In animal studies, buprenorphine shows a ceiling effect or a bell-shaped dose-response curve for analgesic (>1mg/kg) and respiratory effects (0.1mg/kg). This is thought to be due to its partial agonist effect at the μ-opioid receptor. An agonist effect at the pronociceptive supraspinal ORL-1 receptor also may contribute.[22] In humans, a ceiling effect has been shown for respiratory depression (~200microgram/70kg IV)[23,24] and other effects, e.g., euphoria (4–8mg SL),[25,26] but not for analgesia.[24] Total daily doses up to 24mg SL are reported to provide effective analgesia;[27–29] anecdotally, even higher doses have been used, with no upper dose limit clearly established (R. Portenoy, February 2013, personal communication). Thus, the ceiling dose for analgesia in humans is much higher than the "maximum" TD dose recommended in the UK, namely 3.36mg/day (70microgram/h patches x 2).

Studies of buprenorphine TD or SL up to 1.6mg/day confirm that it is possible to use morphine (or other μ-opioid receptor agonist) for breakthrough (episodic) pain[30] and to switch either way between buprenorphine and morphine (or other μ-opioid receptor agonists) without loss of analgesia.[31,32]

However, greater difficulties are experienced when switching patients on higher doses of opioids, using larger doses of buprenorphine.[29] When patients on various opioids (oral morphine equivalent 15–450mg/24h) were switched using doses of buprenorphine 2mg SL (resulting in maximum post-switch doses of 6–24mg/24h), over half experienced intolerable adverse effects and abandoned the switch. Generally, adverse effects related to opioid excess in patients receiving low doses of oral morphine equivalent (≤20mg/24h) and opioid withdrawal in those receiving high doses (>300mg/24h). This experience guided the development of a clinical protocol, although the modified dosing algorithm has not yet been tested formally.[29]

The use of other μ-opioid receptor agonists for breakthrough (episodic) pain in patients on higher doses of buprenorphine also may be less straightforward (see SL opioid-maintenance therapy in addicts). Nonetheless, various μ-opioid receptor agonists have been used in patients on SL buprenorphine 2–32mg/24h, although higher doses than usual may be required.[28,33]

Unlike morphine, buprenorphine has little or no effect on pressure in biliary and pancreatic ducts.[34,35] Buprenorphine slows intestinal transit, but possibly less than morphine.[36,37] Constipation may be less severe.[38]

Compared with morphine and other opioids, buprenorphine appears less likely to suppress the gonadal axis or testosterone levels.[39] This may relate to its κ-opioid receptor *antagonist* effect.[40] Because hypogonadism is associated with reduced sexual desire and function, mood disturbance, fatigue and other physiological effects (e.g., muscle wasting, osteoporosis), this may be an important consideration in patients requiring long-term opioid therapy.[41–43]

Compared with morphine and other opioids, buprenorphine has little or no immunosuppressive effect.[2,44–46] In an anecdotal report, 2 of 5 patients with cholestatic pruritus responded to buprenorphine.[47,48] However, there are insufficient data at present to recommend its use for this.

Effect on QT Interval

Compared with methadone, buprenorphine has less effect on the QT interval.[49,50] Doses of TD buprenorphine up to 140microgram/h are approved in countries other than the USA but, because of QT prolongation in healthy volunteers with 40microgram/h, the maximum approved dose in the USA is only

20microgram/h. However, the mean increase in QTc was 9msec, well below the level generally considered to be of concern (20−60msec) or serious concern (>60msec).[51] Such dose limitation seems excessively restrictive.

TD Buprenorphine

Buprenorphine is highly lipid-soluble making it suitable for TD delivery. It is available in formulations delivering 5, 10 or 20microgram/h over 7 days (BuTrans®).[52−54] Outside the USA, formulations delivering 35, 52.5 or 70microgram/h over 4 days are also available (Transtec®).[55] Like other strong opioids, buprenorphine is an alternative to both weak opioids and morphine.[56] 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, and similar safety considerations apply, e.g., not to expose the patch to external sources of heat. Compared with fentanyl, TD buprenorphine (as Transtec®) adheres better. However, after patch removal, it is associated with more persistent erythema (± localized pruritus), and sometimes a more definite dermatitis.[57] This is generally caused by the adhesive, but occasionally buprenorphine itself causes a contact dermatitis ± more widespread skin rash.[58]

Retrospective analysis suggests that, compared with TD fentanyl, patients receiving TD buprenorphine (as Transtec®) have a slower rate of dose increase and longer periods of dose stability.[59] This requires confirmation in a controlled study. Indeed, systematic reviews have highlighted a lack of high quality studies of TD buprenorphine.[60,61]

SL Opioid-Maintenance Therapy in Addicts

Buprenorphine binds to the μ-opioid receptor with a higher affinity than other μ-opioid agonists. Studies in addicts indicate that buprenorphine 16mg SL leads to 80% of the μ-opioid receptors in the brain being occupied which is sufficient to antagonize the subjective and respiratory depressant effects of hydromorphone, a μ-opioid receptor agonist.[11,62] This has implications for the management of acute pain in these patients, e.g., postoperative or traumatic pain (for an overview, see[63]) and potentially for patients on higher-dose buprenorphine for chronic pain (see above).

Respiratory Depression

Significant respiratory depression is rarely seen with clinically recommended doses. A lower risk of respiratory depression also may explain why buprenorphine (mainly SL ± naloxone) appears to have a better safety profile than methadone.[64] However, serious or fatal respiratory depression has occurred in addicts misusing buprenorphine, generally in high-dose IV and in combination with benzodiazepines or other CNS depressants, e.g., alcohol.[65,66] 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 A).[2,67] 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.[67−69]

Box 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.

Potency Ratio

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.[70] This is reflected in the recommended dose frequency (q8h–q6h vs. q4h for morphine). However, the longer duration of action of buprenorphine almost certainly means that potency ratios based on *single-dose* studies will *underestimate* 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 also Opioid dose conversion ratios, in *PCF*):[71]

- SL buprenorphine is about half as potent as IV/IM/SC buprenorphine; thus, in round figures, 200microgram SL is equivalent to 100microgram by injection[72,73]
- SL buprenorphine is about 80 times more potent than PO morphine[31]; thus, in round figures, 200microgram SL buprenorphine is equivalent to 15mg PO morphine (thus, use of the high-dose SL buprenorphine tablet is restricted to patients tolerant to very high doses of opioid, with the lowest strength available in the USA 2mg equivalent to 160mg PO morphine)
- IV/IM/SC buprenorphine is 30–40 times more potent than IV/IM/SC morphine[74]; thus, in round figures, 300microgram IV buprenorphine is equivalent to 10mg IV morphine
- TD buprenorphine is 70–115 times more potent than PO morphine.[75–77]

The lower limit of the last ratio is based on a small prospective study and the upper limit on a large retrospective chart review. As a convenient compromise, we recommend a potency ratio of 100:1. Thus, a 5microgram/h TD buprenorphine patch is equivalent to about 12mg/24h PO morphine.

A TD buprenorphine:PO morphine potency ratio of 100:1 also means that TD buprenorphine and TD fentanyl can be considered essentially equipotent.[78] However, a TD fentanyl:TD buprenorphine potency ratio of 1.4:1 is suggested by others,[32,77] making TD fentanyl 25 and 50microgram/h patches equivalent to buprenorphine 35 and 70microgram/h patches, respectively. Even so, when switching opioids because of possible opioid-induced hyperalgesia, it is prudent to reduce the calculated equivalent dose of the new opioid by 25–50%.

Switching Opioids

As with any opioid switch, patients changing from another opioid to buprenorphine may experience worsening pain and/or opioid-withdrawal symptoms. Careful monitoring and titration of buprenorphine is required to ensure any worsening pain is dealt with promptly.

Opioid-withdrawal symptoms manifest with GI and flu-like symptoms, e.g., abdominal pain, diarrhea, arthralgia, myalgia, and last several days. With TD and lower doses of SL buprenorphine, p.r.n. doses of the previous opioid will relieve troublesome symptoms.

However, in addiction medicine, when switching involves high-dose SL buprenorphine, the practice is to discontinue the first opioid, await the development of withdrawal symptoms and only then commence buprenorphine. In this way, opioid withdrawal will not be precipitated by buprenorphine (because of its greater affinity for the μ-opioid receptor) but, instead, once withdrawal symptoms are present, they should be relieved by it.

Pharmacokinetics

The bioavailability of PO buprenorphine is low (15%); it undergoes extensive first-pass metabolism in the GI 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.[79] Both buprenorphine and norbuprenorphine undergo glucuronidation to what in the past have been considered inactive metabolites, although recent animal work has questioned this.[80,81]

The bioavailability of SL buprenorphine is about 50%; it is rapidly absorbed into the oral mucosa (2–3min), followed by a slower absorption into the systemic circulation (t_{max} 30min–3.5h after a single dose; 1–2h with repeat dosing).[79] This, together with a duration of action of 6–8h, suggests that SL buprenorphine is *not* ideal for the treatment of breakthrough (episodic) pain. Nonetheless, onset of analgesia in 10–20min is reported for SL buprenorphine,[36] and it has been successfully used as a rescue analgesic in patients receiving higher dose TD buprenorphine (i.e., Transtec®).[82] After parenteral and

SL administration, 70% of buprenorphine is excreted unchanged in the feces and some enterohepatic recirculation is likely; whereas norbuprenorphine is mainly excreted in the urine.[83] Vomiting is more common with SL administration than IM or TD.

Buprenorphine has a large volume of distribution and is highly protein-bound (96%; α- and β-globulins).[79] Buprenorphine does not accumulate in renal impairment, nor is it removed by hemodialysis and thus analgesia is unaffected.[84,85] Although accumulation of norbuprenorphine can occur, this may be of little clinical relevance given its lack of central effect.[79,84]

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.[86,87]

The bioavailability of IV buprenorphine is by definition 100%, and that of SC essentially the same. Bioavailability 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. Extrapolating from data relating to TD fentanyl, the absorption of TD buprenorphine could also be impaired in patients with cachexia, possibly because of a loss of skin hydration.[88] Pharmacokinetic data are summarized in Table 1.

Table 1
Pharmacokinetic Details for Buprenorphine

	IV	TD (Transtec®; not USA)	TD (BuTrans®)	SL
Onset of action	5–15min[70]	21h for 35microgram/h patch; 11h for 70microgram/h patch	18–24h	10–20min[36]
Time to peak plasma concentration	5min	60h	3 days	30min–3.5h single dose;1–2h multiple doses[21,79]
Plasma half-life	3–16h[79]	25–36h[a]	13–35h[a]	24–69h[79]
Duration of action	6–8h	4 days	7 days	6–8h

[a]The half-life after a patch has been removed and not replaced.

Cautions

Hepatic impairment. Additive effects with other CNS depressants, particularly benzodiazepines. Increased risk of respiratory depression in elderly, cachectic, and debilitated patients, and in patients with chronic pulmonary disease. In patients with head injury, increased intracranial pressure or impaired consciousness, monitor for sedation and respiratory depression.

Avoid in patients with long QT interval or with family history of Long QT syndrome, or those taking Class IA or Class III anti-arrhythmic medications. 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.[89]

Drug Interactions

A single case report describes respiratory depression when IM ketorolac was added to epidural buprenorphine.[90]

Buprenorphine is mainly a substrate of CYP3A4, and the manufacturers and others advise caution if prescribed concurrently with CYP3A4 inhibitors (e.g., cimetidine, clarithromycin, erythromycin, troleandomycin, itraconazole, ketoconazole, protease inhibitors), or avoiding concurrent use, because of the potential to increase buprenorphine levels. Although for most CYP3A4 inhibitors this is a theoretical concern, ketoconazole, atazanavir, ritonavir and delavirdine have been shown to significantly increase buprenorphine levels in patients receiving high-doses SL (8–16mg/day).[91] Accordingly, it is recommended that the dose of buprenorphine is halved in patients receiving high-dose buprenorphine SL if used concurrently with ketoconazole or other CYP3A4 inhibitors.[91] No significant differences were seen when ketoconazole was used in patients on buprenorphine 5–20microgram/h TD.[92,93]

Conversely, CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) could reduce buprenorphine levels.[94]

Undesirable Effects

For *full list, see manufacturer's PI.*

Very common (>10%): nausea; erythema and pruritus at the patch application site.

Common (<10%, >1%): asthenia, drowsiness, dizziness, headache, edema, vomiting, constipation, sweating.

Dose and Use

BuTrans® is subject to the FDA extended-release or long-acting opioids Risk Evaluation and Mitigation Strategy (REMS).[95] The manufacturer is required to provide a Medication Guide for patients and to make training available to prescribers. Prescribers are strongly encouraged to undertake the training and to always counsel patients and caregivers about appropriate use, signs of opioid overdose, safe storage and disposal.

USA doctors prescribing SL buprenorphine formulations for maintenance therapy in opioid addicts require a Drug Enforcement Administration waiver. Their use for pain relief is off-label and, as such, could cause administrative difficulties.

As with all opioids, patients must be monitored for undesirable effects, particularly nausea/vomiting and constipation. Depending on individual circumstances, an anti-emetic and a laxative should be prescribed routinely for p.r.n. or regular use.[96]

In the USA, the use of the low-dose buprenorphine TD patches will be suitable only for patients with low opioid requirements (PO morphine <80mg/24h), unless higher off-label doses are used. Conversely, use of the high-dose 2mg SL film formulation, even when cut in half, requires the patient to be already tolerant to reasonable doses of a strong opioid (see below). The use of the injection formulation may provide greater flexibility for patients who fall between these extremes. Although a solution or low-dose tablet for SL use could theoretically be compounded to permit more practical doses of buprenorphine to be administered more conveniently, this would have cost and other implications.

In Europe, the low and high-dose TD patches are the commonest formulation of buprenorphine used in chronic cancer and non-cancer pain. Particularly for patients unable to take PO/SL products reliably, TD buprenorphine provide an alternative non-invasive route for opioid administration.[97]

Compared to SL and parenteral bolus doses, the TD patches permit smaller initial doses of buprenorphine to be delivered more consistently (without large peaks and troughs) and are thus better tolerated.[98]

TD

In the manufacturer's PI, advice on appropriate starting doses for the 7-day buprenorphine patches (5, 10 and 20microgram/h; BuTrans®) seem excessively restrictive/conservative, as suggested by the PO morphine equivalent doses given in italics below:

- for opioid-naïve patients, or those receiving PO morphine <30mg/24h (or equivalent), the lowest patch strength should be prescribed, i.e. 5microgram/h (*approximately morphine 12mg/24h*)
- for those receiving PO morphine 30−80mg/24h, attempt to taper the dose over 1 week to ≤30mg/24h and initiate treatment with 10microgram/h (*approximately morphine 24mg/24h*)
- titrate the dose every 3−7 days, based on p.r.n. use.

The PI contains no specific recommendations regarding p.r.n. analgesic use except to note that it should be with an appropriate dose of a non-opioid or immediate-release opioid. In studies involving patients with non-cancer pain, p.r.n. acetaminophen 500mg−1G or ibuprofen 200−400mg were permitted. Based on a conversion ratio of 100:1, reasonable doses of p.r.n. opioid would be about 2mg, 5mg and 10mg of PO morphine (or equivalent alternative opioid) for the 5, 10 and 20microgram/h patches respectively.

The 20microgram/h patch is the maximum approved dose in the USA. This is approximately equivalent to PO morphine 48mg/24h. Thus, for patients with higher opioid requirements, it will be necessary to either use an alternative strong opioid, or to use higher off-label doses of buprenorphine TD.

SL

Compared to the 2mg tablet, the 2mg film is preferred as it tastes better and can be cut in half, making 1mg the smallest practical SL dose (equivalent to about 80mg PO morphine):

- if switching from PO morphine 240mg/24h, start with 3mg/24h (i.e., 1mg t.i.d.), and so on
- use an appropriate dose of a strong opioid as a rescue analgesic
- titrate the dose every 4–5 days, based on p.r.n. use
- doses of 2–24mg/24h have been reported in chronic pain patients switched from other opioids.[27,29]

An induction and dosing protocol has been proposed for patients switching from between 60–200mg PO morphine (or equivalent)/24h using a starting dose of buprenorphine 2mg SL with an observed period of rapid titration on the first day of use.[29] The exclusion of patients falling outside of these dose limits, together with patients receiving >80mg methadone/24h, or >25microgram/h fentanyl TD, arose because of a high incidence of adverse effects.[29]

SC/IM/IV

- manufacturer's recommended starting dose = 300microgram q8h (equivalent to approximately morphine 10mg q8h SC/IM/IV); this is likely to be too much for some patients
- give IV over ≥2min
- if necessary, titrate to 600microgram q8h–q6h (the recommended maximum in acute pain; in chronic pain higher doses may be required).

CSCI/CIVI

- buprenorphine has been given CIVI diluted in 0.9% saline or 5% glucose at a concentration of 15microgram/mL; there are no compatibility data for mixing with other drugs used in palliative care
- for patients receiving CSCI/CIVI buprenorphine, p.r.n. injections about one tenth of the total daily dose can be used for breakthrough (episodic) pain.

Once a stable dose is established, some practitioners switch to SL buprenorphine for ongoing maintenance (see Potency ratios).

Supply

Unless indicated otherwise, all preparations are Schedule III controlled substances.

Buprenex® (Reckitt Benckiser)
Injection 300microgram/mL, 1mL amp = $4.

Buprenorphine HCl (Roxane)
Tablets SL (not scored) 2mg, 8mg, 28 days @ 2mg t.i.d. = $336.

With naloxone
Suboxone®
Film SL buprenorphine 2mg, naloxone 0.5mg, pack of 30 = $141.
Film SL buprenorphine 4mg, naloxone 1mg, pack of 30 = $253.
Film SL buprenorphine 8mg, naloxone 2mg, pack of 30 = $253.
Film SL buprenorphine 12mg, naloxone 4mg, pack of 30 = $507.

Transdermal products
BuTrans® (Purdue)
Patches (for 7 days) 5microgram/h, 1 = $38; 10microgram/h, 1 = $56; 20microgram/h, 1 = $98.

Abbreviations/Key

†	Off-label use
CIVI	Continuous intravenous infusion
CSCI	Continuous subcutaneous infusion
CYP	Cytochrome P450
GI	Gastrointestinal
IM	Intramuscular

IV	Intravenous
ORL-1	Opioid-receptor-like-1
PI	Package insert
PO	Per os, by mouth
p.r.n.	Pro re nata, as required
q4h	Every 4 hours etc.
QTc	QT interval corrected for heart rate
RCT	Randomized controlled trial
SC	Subcutaneous
SL	Sublingual
TD	Transdermal
t.i.d	Three times daily
T_{max}	Time to peak plasma concentration

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