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Transdermal Buprenorphine

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Contents

Abstract

▲ Buprenorphine is a low molecular weight, lipophilic, opioid analgesic. Recently, a transdermal matrix patch formulation of buprenorphine has become available in three dosage strengths designed to release buprenorphine at 35, 52.5 and 70 μg/h over a 72-hour period.

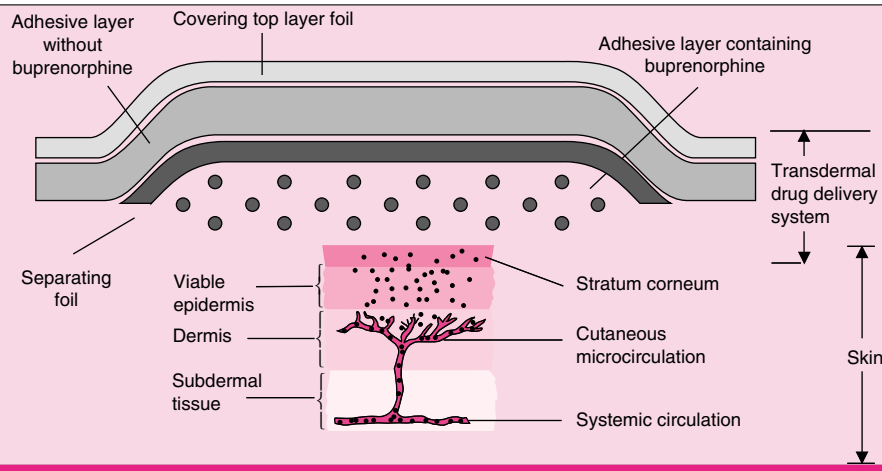
▲ At least satisfactory analgesia with minimal requirement for rescue medication (≤0.2 mg/day sublingual buprenorphine) was achieved by 34–50% of patients with chronic pain treated with transdermal buprenorphine 35, 52.5 or 70 μg/h and 31% of placebo recipients, in one double-blind, placebo-controlled, randomised trial.

▲ In one trial involving patients unsuccessfully treated with weak opioids or morphine, 36.6% and 47.5% of buprenorphine 35 μg/h and 52.5 μg/h recipients, respectively, experienced at least satisfactory analgesia and received ≤0.2 mg/day of sublingual buprenorphine compared with 16.2% of placebo recipients (both $p \leq 0.032$).

▲ The requirement for rescue medication was reduced from baseline in >50% of patients treated with transdermal buprenorphine, in two trials. Furthermore, despite the availability of rescue medication to all patients, those receiving transdermal buprenorphine tended to experience greater pain relief, reduced pain intensity and longer pain-free sleep.

▲ Transdermal buprenorphine was generally well tolerated. Systemic adverse events were typical of opioid treatment or were attributable to the underlying disease.

Features and properties of buprenorphine transdermal system (Transtec®)	
Indications	
Moderate to severe cancer pain and severe chronic pain unresponsive to nonopioid analgesics	
Mechanism of action	
Partial agonist at μ-opioid receptors and an antagonist at κ-opioid receptors	
Dosage and administration	
Dosage	35, 52.5 or 70 μg/h
Route of administration	Transdermal patch, preferably applied to the upper back, subclavicular region or chest
Frequency of administration	Replaced every 72h
Pharmacokinetic profile (35 μg/h single-patch application)	
Time to minimum therapeutic concentration (100 pg/mL)	21h
Maximum plasma concentration	305 pg/mL
Time to maximum plasma concentration	≈60h
Area under the plasma concentration-time curve	20 228 pg • h/mL
Elimination half-life	25.3h
Adverse events	
Most common (>5%)	Local: transient erythema, pruritus
	Systemic: nausea, vomiting, dizziness, tiredness, constipation



Buprenorphine transdermal patch system. A schematic representation of the matrix transdermal delivery system (not to scale) and the pathway of absorption across the skin. In the matrix system, buprenorphine is incorporated into the polymer matrix, which is located in the adhesive layer.[20] Matrix patch technology allows for continuous slow release of buprenorphine into the systemic system.[20]

Guidelines for the management of chronic pain have become more detailed in recent years,[1-4] yet many patients with chronic pain are inappropriately managed and experience inadequate pain relief.[5] WHO guidelines for the treatment of cancer pain advise a three-step pharmacological ladder based on pain intensity.[6] In the case of mild pain, a non-opioid analgesic is recommended, for pain of mild to moderate intensity, a weak opioid such as tramadol may be added, and pain of moderate to severe intensity should be treated with strong opioids such as morphine, methadone, fentanyl and buprenorphine.[5] More recently, opioids have also started to be used in the treatment of chronic pain of nonmalignant origin.[7-9]

Treatment options for chronic pain have also improved as a result of the development of new modes of administration.[10] One such advance has been the introduction of the transdermal drug delivery system, which offers several advantages over the parenteral and oral routes of drug administration.[11,12] Firstly, a transdermal delivery system avoids the discomfort associated with multiple intramuscular injections and a patient's unwillingness to swallow oral preparations, and it is less labour intensive than intravenous infusions.[11] Secondly, transdermal drug delivery results in reasonably constant plasma drug concentrations due to rate-controlled delivery, and avoids issues associated with hepatic first-pass metabolism, poor absorption from the gastrointestinal tract and low or variable interpatient bioavailability.[11,12] Moreover, the frequency of administration is reduced with transdermal delivery systems, potentially improving patient compliance, and the site of drug delivery can be regularly changed, thus reducing the risk of developing local adverse events.[12,13]

A slow-release analgesic complies with recommendations for pain relief.[14,15] According to literature, one of the reasons for poor pain relief in cancer patients is the prescribing of analgesics on an 'as needed' basis rather than 'around the clock' administration.[14] Moreover, the WHO recommends 'around the clock' control for chronic nonmalignant pain.[15] A transdermal patch addresses this issue by providing constant plasma concentrations at an effective level for analgesia.

Buprenorphine is available in both parenteral and sublingual formulations[16] and is an effective analgesic in the treatment of acute and chronic pain (reviewed previously in *Drugs*[17]). Buprenorphine is indicated for the treatment of moderate to severe

pain and is classified as a step-three analgesic in the WHO analgesic ladder,[5,18] although it has been argued to be an intermediary between step two and three.[19]

Recently, a transdermal matrix patch formulation of buprenorphine has been developed (Transtec®[1]). The buprenorphine transdermal system (TDS; hereafter referred to as transdermal buprenorphine) is available in three strengths: the patches contain 20, 30 or 40mg of buprenorphine and are designed to release buprenorphine at a controlled rate of 35, 52.5 and 70 μg/h, respectively, each corresponding to a daily dose of 0.8, 1.2 and 1.6mg.[20] All of the patches are designed for a 72-hour application period.[20] This review provides an overview of clinically relevant data on the transdermal preparation of buprenorphine in the treatment of chronic pain.

1. Pharmacodynamic Profile

Buprenorphine is a synthetic opioid which is lipophilic, water soluble and has a low molecular weight; these properties allow for tissue penetration and make it suitable for transdermal delivery. The pharmacodynamic properties of buprenorphine administered as various formulations are well documented and have been reviewed previously in *Drugs*.[17] An overview of these properties in addition to limited data from studies using the transdermal patch are provided here.

Receptor-Binding Properties

- Buprenorphine is a partial agonist at μ opioid receptors and an antagonist at κ receptors in the CNS and peripheral tissues, and binds to both receptors with high affinity.[21-23] Effects on analgesia appear to occur as a result of μ-agonist activity.[24] Binding to and dissociation from the μ-receptor is slow; therefore, the effects of buprenorphine are slow in onset and long in duration.[21-23] The time to onset of action and the duration of action of buprenorphine is also affected by the route of administration (see section 2).
- The binding of buprenorphine to opioid receptors tended to follow a bell-shaped dose-response curve in animal studies, with dose-related increases of efficacy in the 'lower' dose range, but higher doses producing no greater or a decreased effect (reviewed by Budd[25]). Although a bell-shaped response has not always been evident in studies in volunteers and patients, it may occur at doses above those which are clinically relevant for analgesia.[25] For example, in opioid experienced, but not physically dependent, volunteers receiving sublingual buprenorphine 1–32mg in ascending doses, no ceiling effect for analgesia was observed within the dose range used for analgesia.[26]

CNS Effects

- Buprenorphine produces dose-related analgesia and is about 25–50 times more potent than an equivalent dose (by weight) of morphine.[22] Numerous studies conducted in patients with tumour-related or postoperative pain have shown that the required buprenorphine plasma concentration for the relief of moderate to severe pain lies between 100 and 500 pg/mL (reviewed in Sittl[23]).
- Following the cessation of buprenorphine therapy, withdrawal symptoms may occur.[21] Buprenorphine-related withdrawal symptoms can reach their peak at about 2 weeks, but appear to be milder than withdrawal symptoms associated with morphine therapy (reviewed in *Drugs*[17]). Moreover, the likelihood of drug dependence or tolerance developing after short-term or long-term therapy with buprenorphine may be lower than that of other opioids. An *in vitro* study conducted in 293-SF-MOR cells showed that 10 μmol/L fentanyl and 10 μmol/L morphine resulted in a 35% and 9% reduction, respectively, in cell surface μ receptors, whereas 10 μmol/L of buprenorphine resulted in a 10% increase ($p < 0.05$ vs control).[27] These results suggest that buprenorphine does not induce opioid receptor internalisation (loss of receptors from the cell surface), thus reducing the likelihood of tolerance developing.[27]

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Other Effects

- The cardiovascular effects of transdermal buprenorphine have not been examined; however, intramuscular, oral or sublingual buprenorphine decreased heart rate and blood pressure in volunteers.[17,21] The reductions in heart rate following intramuscular buprenorphine (0.15–0.6mg) administration were similar to those observed with intramuscular morphine (5–12.5mg).[28] Changes in heart rate, but not blood pressure, were dose-dependent following oral (1–4mg) buprenorphine administration. Sublingual buprenorphine (0.4 or 0.8mg) produced reductions in heart rate in combination with a compensatory increase in stroke volume, resulting in a small change in mean arterial pressure (reviewed in *Drugs*[17]).
- Respiratory depression occurs infrequently with buprenorphine and is rarely of clinical significance;[21] nevertheless, buprenorphine treatment is contraindicated in patients with severe respiratory impairment (see section 5). In ten critically ill patients, intravenous buprenorphine (0.2 or 0.4mg) reduced mean respiration rate and increased arterial levels of carbon dioxide, but had no significant effect on heart rate, arterial oxygen levels or base excess values.[29] In volunteers, respiratory depression with intramuscular buprenorphine was linear over a dose range of 0.15–1.2mg, but was not considered clinically significant.[28]
- A ceiling effect to respiratory depression is observed with high doses of buprenorphine. A high-dose study conducted in 50 female postoperative patients found no evidence of respiratory depression following 0.4–7.0mg of intravenous buprenorphine over a 24 hour observation period.[30] One study demonstrated that in opioid-experienced, but not physically dependent, volunteers receiving sublingual buprenorphine (1–32mg), respiratory depression tended to plateau at doses ≥8mg.[31]
- As with other μ opioid receptor agonists, buprenorphine produces pupillary constriction in a dose-dependent manner. In a single-application study conducted in volunteers, dose-dependent reductions in pupil diameter were observed following application of a 35, 52.5 or 70 μg/h patch and reductions in pupil diameter were sustained from 36 hours after patch administration until the removal of the patch at 72 hours.[32] In a multiple-application study conducted in volunteers, replacement of the transdermal patch led to slight increases in pupil diameter for up to 12 hours, but remained constant until removal of the next patch.[23]

2. Pharmacokinetic Profile

The pharmacokinetic profile of parenterally or sublingually administered buprenorphine has been previously reviewed in *Drugs*.[17] Published data on the pharmacokinetic properties of buprenorphine administered by the transdermal delivery system are limited. Two randomised, nonblind studies have been conducted in volunteers including one single-application study (n = 24) [presented in a poster[33]] and one multiple-application study (n = 54) [data on file[23]] and have been presented together in a monograph.[20]

Absorption and Distribution

- Plasma concentrations of buprenorphine increased steadily after application of a single 35 or 70 μg/h patch, reaching the minimum effective therapeutic concentration (100 pg/mL; section 1) at 21 and 11 hours, respectively.[33] Thereafter, plasma concentrations continued to increase, reaching their peak (C_{max}) of 305 and 624 pg/mL after ≈60 hours and were maintained above 100 pg/mL until the end of the 72-hour application period.[23]
- As expected, the time to C_{max} was markedly longer with transdermal delivery than during intravenous infusion of 0.3mg of buprenorphine (0.41 hours) in this crossover study.[23] However, the systemic exposure to buprenorphine was greater with the 35 and 70 μg/h transdermal buprenorphine patches than with the intravenous dose, as demonstrated by their respective area under the plasma concentration-time curves (mean AUC) [20 228, 43 040 and 5562 pg • h/mL].[23]
- Buprenorphine plasma concentrations and AUC progressively increase with increasing number of patch applications and appear to reach steady state after the third application. In the multiple-applica-

tion study,[23] volunteers receiving buprenorphine 35 μg/h had mean buprenorphine C_{max} values ranging between 263.0 and 379.4 pg/mL during the 216-hour observation period. Corresponding values for the 52.5 and 70 μg/h patch strengths were 332.1–528.7 pg/mL and 390.1–578.2 pg/mL, respectively.[34] Evidence of a transfer to steady state was provided by the observation of a less pronounced increase in AUC between the second and third patch applications.[20,34]

- Transdermal buprenorphine has a bioavailability of ≈50%,[35] comparable to the 50–60% bioavailability following sublingual buprenorphine administration.[23] Buprenorphine is 96% plasma protein bound.[17]

Metabolism and Elimination

- In the liver, buprenorphine is bound to glucuronic acid and oxidised to *N*-dealkylbuprenorphine (norbuprenorphine) in a reaction mediated by cytochrome P450 (CYP) 3A4.[17,20,36] Buprenorphine is also metabolised to glucuronide conjugated metabolites that can be hydrolysed in the intestine to form buprenorphine, which is then reabsorbed via enterohepatic circulation.[17,36]
- Buprenorphine has a long elimination half-life ($t_{1/2}\beta$). In the single-application study, the $t_{1/2}\beta$ of buprenorphine 35 and 70 μg/h was 25.3 and 27.4 hours, respectively, compared with 8.47 hours for intravenous buprenorphine 0.324mg.[23] The $t_{1/2}\beta$ in the multiple-application study was 34.5, 32.6 and 36.8 hours for the 35, 52.5 and 70 μg/h transdermal patch, respectively.[23] Two-thirds of buprenorphine is excreted in the faeces and one-third is excreted in the urine.[17,36]

Drug Interactions

- Because buprenorphine is metabolised in a reaction mediated by CYP3A4, concomitant exposure to drugs that inhibit or induce this enzyme may intensify or weaken the action of buprenorphine.[20,21] Concomitant administration of monoamine oxidase inhibitors, other opioids, anaesthetics, hypnotics, sedatives, antidepressants or neuroleptics may potentiate the CNS depressant effects of buprenorphine. Similarly, alcohol can intensify the CNS effects of the drug.[20,21]

3. Therapeutic Trials

The efficacy of transdermal buprenorphine patches in treating chronic pain has been investigated in three multicentre, randomised, double-blind, placebo-controlled, parallel-group studies[37-39] and one nonblind follow-up study conducted in patients from the randomised trials who volunteered to continue receiving transdermal buprenorphine[40] (figure 1). To date, two of the randomised studies have been fully published[37,38] and all studies have been reported in brief[23,41-43] and in posters or conference proceedings.[39,40] Another report pooled data from the three randomised trials to present pain measures in patients with cancer compared with patients without malignancy.[44]

Patients had moderate to severe[39] or severe to very severe[37,38] chronic pain of malignant or nonmalignant origin. The fully published trials reported that ≈54% of patients were female and patients were aged between 26 and 86 years.[37,38]

When stated, the exclusion criteria were impaired respiratory function, raised intracranial pressure, hypersensitivity to opioids, previous extensive dermal damage to the patch area or a history of convulsions.[37,38] Patients receiving monoamine oxidase inhibitors,[37,38] radionucleotide therapy or opioids other than sublingual buprenorphine were also excluded.[37]

In two of the trials, patients underwent a run-in period (figure 1) during which they achieved satisfactory pain relief while receiving sublingual buprenorphine.[37,39] In the other trial, patients unsuccessfully treated with weak opioids or morphine were switched from their previous analgesics on the first day of transdermal buprenorphine treatment.[38] Patients were permitted to continue receiving their current dosage of sublingual buprenorphine[37] or their previous analgesic[38] on the first day of transdermal buprenorphine treatment in two of the randomised trials, while in the third study, this was not stated.[39] Concomitant chemotherapy was administered to 18 patients during one of the trials.[38] The

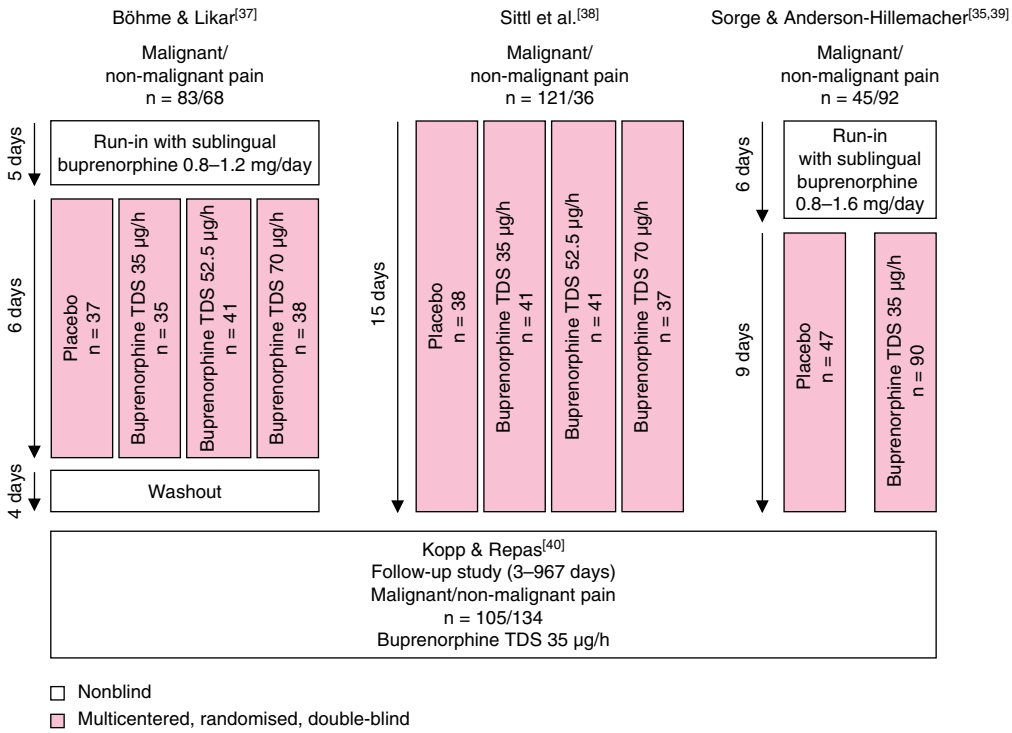


Fig. 1. Diagrammatic representation of the methodology of the three multicentre, randomised, double-blind, placebo-controlled trials[37-39] and one nonblind follow-up study[40] examining the efficacy of buprenorphine transdermal system (TDS). Patients in the trials had moderate to very severe chronic pain of malignant or nonmalignant origin. Patients participating in the follow-up study were volunteers from the randomised studies.

remaining trials did not state whether any patients were receiving concomitant chemotherapy treatment.[37,39,40]

Patients were randomised to receive transdermal buprenorphine, at a dosage of 35, 52.5 or 70 µg/h, or placebo for a period of 6[37] or 15[38] days, or received transdermal buprenorphine at a dosage of 35 µg/h or placebo for 9 days (figure 1).[39] In the follow-up study, transdermal buprenorphine was administered at a dosage of 35 µg/h for 3-967 days (mean 4.7 months).[40] In all studies, transdermal patches were applied to the subclavicular chest or upper back region and replaced every 72 hours. Patients were also permitted to receive sublingual buprenorphine as rescue medication for breakthrough pain.[23,37-40]

When stated, efficacy analyses were conducted for the intent-to-treat population.[37,38] For the studies with the 6- and 15-day treatment periods, the primary endpoint was the number of responders (defined as any patient whose pain relief was rated as at least satisfactory at all timepoints and who received ≤0.2 mg/day of sublingual buprenorphine as rescue medication from the second treatment day).[37,38] In the third randomised trial, the primary endpoint was the number of sublingual tablets required during the second and third patch applications compared with the 6-day run-in.[39] The number of sublingual buprenorphine tablets[37] or buprenorphine equivalents[38] consumed during the transdermal patch application period was assessed as a secondary endpoint in the other two randomised trials.

Additional secondary endpoints from the randomised trials included patient assessment of pain relief, pain intensity and the duration of pain-free

sleep.[37-39] However, these secondary endpoints were not statistically examined.

In the follow-up study, endpoints included the mean daily consumption of sublingual buprenorphine tablets, pain-relief measured on a 4-point verbal rating scale, and user-friendliness of the transdermal patch.[40,41]

Placebo-Controlled Studies

- At least one-third of patients treated with transdermal buprenorphine responded to treatment in two randomised trials (figure 2).[37,38] Of note, >33% of patients who had been unsuccessfully treated with weak opioids or morphine responded to treatment with transdermal buprenorphine and the percentage of responders in the 35 and 52.5 μg/h treatment groups was significantly greater than the percentage of placebo responders in this study ($p \leq 0.032$).[38] However, an increase in response was not seen with the 70 μg/h patch (figure 2); this was attributed to a number of refractory patients in this treatment group.[38]
- Of the patients who had satisfactory pain relief with sublingual buprenorphine during a 5-day run-in phase, 34–50% responded in a dose-dependent manner to 6 days of treatment with transdermal buprenorphine.[37] Although a difference to placebo was observed, it did not reach statistical significance (figure 2). A retrospective subgroup analysis of the results from all three randomised trials, found that a response to treatment was seen both in patients with malignant-related pain and in patients without malignancy.[44]
- The requirement for rescue medication (sublingual buprenorphine) was reduced from baseline by approximately 50–70% in patients receiving treatment with transdermal buprenorphine.[38,45] In patients with satisfactory pain relief following a 5-day run-in period,[37] sublingual buprenorphine intake reduced in a dose-dependent manner for the active treatment groups (presented in a poster;[45] see figure 3). In patients with pain inadequately controlled by weak opioids or morphine, the requirement for additional oral opioid analgesic medication reduced by >50% with transdermal buprenorphine. For the active treatment groups, all reductions in rescue medication requirements were significantly greater ($p < 0.05$) than that observed in placebo recipients (8%; figure 3).[38]

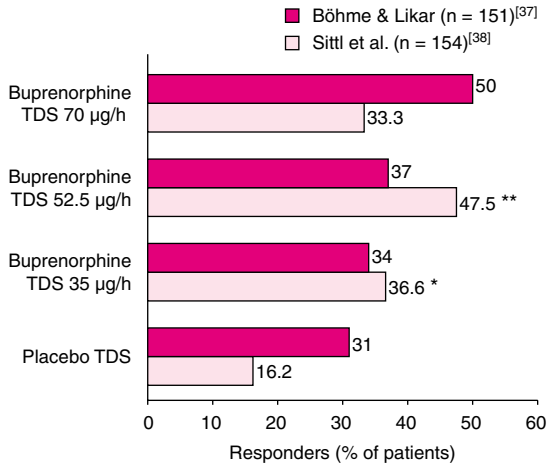


Fig. 2. Effect of buprenorphine transdermal system (TDS) or placebo TDS on the proportion of patients reaching response criteria (patients who rated pain relief as at least satisfactory at each patch application and who received ≤0.2 mg/day of sublingual buprenorphine as rescue medication from the second treatment day) in two multicentre, double-blind, parallel-group studies.[37,38] Patients with chronic severe pain of malignant or nonmalignant origin and who had maintained at least satisfactory pain relief during a 5-day run-in period with sublingual buprenorphine (0.8–1.2 mg/day)[37] or who had been unsuccessfully treated with weak opioids or morphine[38] were randomised to receive buprenorphine TDS at a dosage of either 35, 52.5 or 70 μg/h or placebo TDS. Treatment time was for 6[37] or 15[38] days and patches were replaced every 72 hours. * $p = 0.032$, ** $p = 0.003$ vs placebo in the study reported by Sittl et al.[38]

- Rescue medication requirements were also related to baseline sublingual buprenorphine requirements.[39] The study comparing transdermal buprenorphine 35 μg/h with placebo found that in patients receiving 0.4–0.8, 0.8–1.2, 1.2–1.6 or ≥1.6mg of sublingual buprenorphine during the run-in period, rescue medication requirements during the transdermal buprenorphine treatment period were 0.2, 0.4, 0.6 and 0.9mg, respectively.[39] When rescue medication requirements were considered in combination with the daily dose delivered by the transdermal buprenorphine patch (0.8mg), the total buprenorphine dose delivered was almost exactly equal to the dose received during run-in.[42]

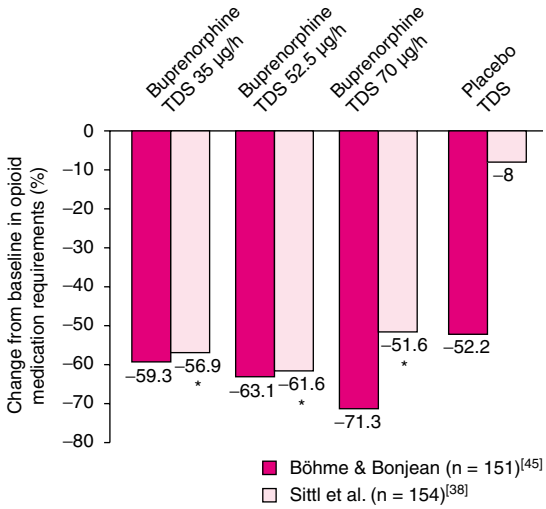


Fig. 3. Percentage reductions from baseline in opioid medication requirements for breakthrough pain in patients receiving buprenorphine transdermal system (TDS) at a dosage of 35, 52.5 or 70 µg/h or placebo TDS[38] (presented in a poster[45]). In these multicentre, randomised, double-blind, parallel-group studies, patients with severe to very severe chronic pain of malignant or nonmalignant origin underwent a 5-day non-blind run-in phase[45] or were switched directly from their previous analgesic medication[38] (baseline) to one of the three dosage strengths of buprenorphine TDS or placebo TDS. The treatment period was for 6[45] or 15[38] days and patches were replaced every 72 hours. All patients received sublingual buprenorphine as rescue medicine for breakthrough pain. The Böhme and Bonjean study[45] has also been reported by Böhme and Likar;[37] however, the percentage reduction in rescue medication was not reported in this fully published paper. * $p < 0.05$ vs placebo.

• Despite the availability of rescue medication to all patients, those receiving transdermal buprenorphine tended to experience greater pain relief than those receiving placebo.[37-39] Patients experiencing good to complete pain relief increased by up to 13.2% and 8.6% during the first and second patch phases of transdermal buprenorphine treatment, respectively, compared with a 20% and 11.4% reduction in placebo recipients in one trial.[37] Throughout 15 days of treatment, 40.0–46.3% of transdermal buprenorphine recipients had good to complete pain relief compared with 32.4% of placebo recipients.[38] This was also reflected in the mean pain relief scores recorded by patients during the study; mean verbal rating scores (assessed using a 4-point scale [1–4: poor, satisfactory, good, complete]) were 2.3, 2.4 and 2.5 in patients treated with transdermal buprenorphine 35, 52.5 and 70 µg/h, respectively, compared with 1.9 in placebo recipients.[38]

• A dose-dependent increase in the proportion of patients with no or mild pain was observed in the 15-day study on each study day and at study end.[38] On the final treatment day, 46.3%, 60.0% and 61.1% of patients receiving transdermal buprenorphine at a dosage of 35, 52.5 and 70 µg/h, respectively, experienced no or mild pain compared with 40.5% of patients receiving placebo.[38] Furthermore, on the final study day severe and very severe pain was reported by 17%, 7.5% and 13.9% of patients receiving transdermal buprenorphine versus 24.3% of patients receiving placebo.[38]

• The proportion of patients reporting >6 hours of pain-free sleep per night increased in patients receiving buprenorphine (2.5–11.9% increase from baseline) and decreased in those receiving placebo (15.3% and 5.9% decrease) during 6[37] or 9[39] days of treatment. During the treatment phase of two trials, 40–55% of recipients of transdermal buprenorphine had sleep uninterrupted by pain compared with ≈35% of placebo recipients.[37,38]

Long-Term Follow-Up Study

• Of 445 patients from the three controlled trials, 239 (53.7%) opted to continue in the follow-up study (figure 1).[23] During the follow-up period in which all patients were treated with transdermal buprenorphine 35 µg/h, pain relief was rated as good/complete and satisfactory by 42.3% and 47.7% of patients respectively. Further, 94.6% of patients in the follow-up study rated the transdermal patch as user-friendly.[23,40]

4. Tolerability

• Transdermal buprenorphine was usually well tolerated and adverse events reported in clinical trials were generally mild to moderate in severity.[23] The most frequently reported adverse events in the three placebo-controlled trials are presented in figure 4. Analysis of randomised trials revealed that 65% of events were rated as mild to moderate intensity and 24.4% were rated as severe (pooled data[23]). In the long-term follow-up study, events were rated as

mild to moderate in 48.7% of cases and as severe in 44% of cases.[23] There were no clinically significant differences in vital signs or laboratory parameters between buprenorphine treatment groups or placebo in the one randomised trial that reported these parameters.[37]

- Adverse events could generally be attributed to either the patch (local skin events), buprenorphine (systemic events typical of opioids) or the underlying disease. Adverse events were reported more often in patients with malignancy than in those without (46.6% vs 34.2% of patients).[23] Similarly, in the long-term follow-up study, patients with tumours had a greater incidence of events (56.7% vs 50.4% of patients), but events were less likely to be attributed to buprenorphine in patients with malignancy (19.4% vs 39.1%).[23]

- Transdermal buprenorphine was associated with a low rate of withdrawals due to adverse events.[37,38] During the 15-day treatment period, 10.8% of patients withdrew because of adverse events.[38] Severe erythema and pruritus led to withdrawal in 2.4–4.9% of patients receiving buprenorphine 35–70 μg/h and 2.6% of patients receiving placebo.[38]

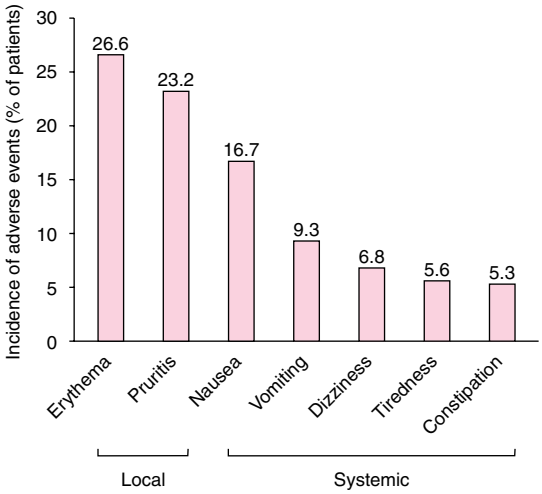


Fig. 4. Adverse events occurring in >5% of patients during transdermal buprenorphine treatment in multicentre, randomised, double-blind, placebo-controlled studies.[23] Patients (n = 323) with moderate to severe chronic pain of tumour or non-tumour origin received transdermal buprenorphine 35, 52.5 or 70 μg/h for 6–15 days. Transdermal patches were replaced every 72 hours.

Systemic Effects

- Across the three randomised studies, 38%, 50% and 44% of patients receiving transdermal buprenorphine 35, 52.5 and 70 μg/h had a systemic adverse event compared with 37.7% of placebo recipients. Overall, 63% of systemic events were judged to be related to the study medication and the majority of events were typical of opioids (pooled data[23]).
- The most common systemic events reported in placebo-controlled trials were gastrointestinal or CNS in origin (figure 4).[23] Dose-dependent increases were observed in the overall rate of gastrointestinal events (9.0–25.3% of buprenorphine recipients vs 12.3% of placebo recipients) and in the incidence of constipation (3.0–9.3% vs 4.1%), but not for the incidence of vomiting (5.4–13.3% vs 4.1%). Nausea, dizziness and tiredness were the most frequently occurring CNS events, but incidence did not significantly differ between buprenorphine dosage groups or from placebo. The incidence of nausea, dizziness and tiredness ranged between 16–18.3%, 4.9–10.7% and 3.0–8.5%, respectively, in the 35, 52.5 and 70 μg/h buprenorphine treatment groups, compared with an incidence of 10.7%, 4.9% and 2.5%, respectively, in placebo recipients.[23]
- In the pooled analysis,[23] 7.2–14.6% of patients receiving transdermal buprenorphine experienced events affecting the total body (including leg oedema and diaphoresis) compared with 8.2% of patients receiving placebo. Urinary tract events (including infection) and respiratory events (including dyspnoea) occurred in 1.2–6.7% and 1.2–5.3% of buprenorphine recipients, respectively, and 4.1% and 2.5% of placebo recipients, respectively.[23]
- In the long-term follow-up study,[40] systemic events were reported by 45.6% of patients; however, only 20% of events were associated with the study medication.[23] Similar to the placebo-controlled trials, the most frequently occurring adverse events were gastrointestinal- or CNS-related; however, the incidence was low with vomiting and constipation

reported by 3.8% and 3.3% of patients, respectively, and nausea, dizziness and tiredness reported by 8.8%, 4.2% and 2.5% of patients, respectively.[23]

Local Skin Events

- Local skin events (assessed at patch removal) were reported in approximately one-third of all patients wearing a transdermal patch (containing buprenorphine or placebo) in the randomised trials and were generally transient and mild to moderate in severity.[23] The most frequently occurring local events were erythema and pruritus (figure 4); which occurred in 22.7–28.0% and 22.0–24.1% of buprenorphine recipients, respectively, and 22.1% and 18.9% of placebo recipients (pooled analysis[23]). The broadly similar incidence of these events across buprenorphine dosage groups and placebo suggests the events were related to the patch itself rather than buprenorphine.
- The incidence of local events in the long-term follow-up study was low (10.5% of patients) and events included erythema (11.3% of events), pruritus (9.2%), exanthema (7.5%) and swelling (1.3%).[23]

5. Dosage and Administration

- Transdermal buprenorphine patches are indicated for the treatment of moderate to severe cancer pain and severe pain unresponsive to nonopioid analgesics. Buprenorphine patches are available in three dosage strengths.[20] The lowest strength releases 35μg of buprenorphine per hour and is 25 cm^2. The 37.5 cm^2 patch releases 52.5 μg/h. The largest patch releases 70μg of buprenorphine per hour and covers an area of 50 cm^2.[20] Transdermal buprenorphine patches should be applied to a flat and hairless area of nonirritated skin, preferably on the upper back, subclavicular region or chest. Transdermal patches should be changed every 3 days and a new patch should be applied to a different appropriate skin site. The same patch area can be reused after a period of at least 6 days. [20]
- According to recommendations from the manufacturer, patients who are opioid-naive should initially receive the lowest strength patch.[20] For patients who have previously received opioid treatment, the strength of the buprenorphine transdermal patch depends on the strength and the daily dose of the previous medication. Because buprenorphine plasma concentrations rise slowly with transdermal delivery, previous analgesic medication should be maintained for the first 24-hour period. The adequacy of the transdermal buprenorphine patch should be assessed at the end of the first patch period and dose should be individually titrated either by switching to another patch strength or applying a second patch of the same strength. No more than two patches of the same strength should be applied at one time.[20]
- Transdermal buprenorphine is not contraindicated in patients with renal dysfunction. However, because the metabolism of buprenorphine may be affected in individuals with liver dysfunction, this population should be monitored.[20] Additional monitoring is also required for patients with a fever, as increased body heat may enhance skin permeability. Buprenorphine is contraindicated in patients with severe respiratory depression (section 1), patients who are opioid-dependent, or who have concomitant myasthenia gravis or delirium tremens. Transdermal buprenorphine is also contraindicated in patients who are breast-feeding or pregnant.[20] Transdermal buprenorphine does not require dosage adjustment in elderly patients. It is not recommended for patients aged <18 years. Finally, care must be taken with concomitant administration of monoamine oxidase inhibitors, other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics and drugs which affect CYP3A4 (section 2).[20,21]
- Following the removal of transdermal buprenorphine patches, buprenorphine plasma concentrations gradually decrease resulting in the maintenance of an analgesic effect after patch removal (section 2). The manufacturers suggest that additional opioids should not be administered within 24 hours of buprenorphine patch removal.[20]

6. Transdermal Buprenorphine: Current Status

The transdermal matrix patch formulation of buprenorphine, an opioid analgesic, is indicated for

the treatment of moderate to severe cancer pain and severe pain unresponsive to nonopioid analgesics.[46] More than one-third of patients with chronic pain receiving transdermal buprenorphine had at least satisfactory analgesia with minimal requirement for rescue medication (≤0.2 mg/day of sublingual buprenorphine), in two clinical trials. Transdermal buprenorphine has also been found to reduce rescue medication requirements and pain intensity from baseline, provide pain relief and increase the duration of pain-free sleep from baseline in patients with chronic pain of a malignant or nonmalignant origin. Furthermore, transdermal buprenorphine has demonstrated clinical efficacy in patients with severe to very severe chronic pain unsuccessfully treated with weak opioids or morphine. Transdermal buprenorphine is usually well tolerated, with adverse events generally rated as mild to moderate in severity.

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