Title:Transdermal buprenorphine in chronic pain: indications and clinical experience.
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Abstract:

Transdermal buprenorphine has been shown to be effective in managing moderate-to-severe cancer pain and severe pain that is unresponsive to nonopioid analgesics. In clinical trials, it provided better pain relief than placebo, despite a higher consumption of rescue analgesia by placebo patients. Analgesia was rated as satisfactory or better by 90% of patients in a long-term follow-up study and 94.6% considered the buprenorphine matrix patch to be user friendly. Transdermal buprenorphine is well tolerated; most adverse events are transient local reactions to the patch or systemic effects typical of treatment with opioids. Even in opioid-experienced volunteers, buprenorphine does not cause respiratory depression at doses up to 70-times higher than those used for analgesia. No problems have been encountered when switching from another opioid to transdermal buprenorphine, or in combining the buprenorphine patch with intravenous morphine or tramadol for breakthrough pain. There is a growing body of evidence that transdermal buprenorphine may be particularly useful for managing neuropathic pain. Most notably, it appears to be effective in treating hyperalgesic states and syndromes characterized by pronounced central sensitization.

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Keywords:

cancer pain; noncancer pain; opioid analgesia; pain management; transdermal buprenorphine

Chronic pain may be defined as an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage and has been present for more than 3-6 months. It has a huge impact on the lives of patients as it not only affects mood and cognition, but also inhibits mobility and physiological functioning. The effective treatment of chronic pain is, therefore, of the utmost interest to all branches of medicine. Various guidelines for the management of chronic cancer and also noncancer pain have been developed, with the aim of optimizing pain control and minimizing the potential for adverse events [1-3,101] . However, in daily practice, inappropriate management remains widespread and many patients still fail to obtain adequate pain relief.

The WHO has established a three-step pain relief ladder to manage cancer-related pain of increasing intensity [102] . In step I, nonopioid analgesics, such as aspirin and paracetamol (acetaminophen), are recommended. If necessary, weak opioids, such as tramadol and codeine, may then be given in step II. Finally, more efficacious opioids, such as morphine, fentanyl and hydromorphone, are administered in step III until the patient's pain is significantly reduced. To maintain freedom from pain, the WHO advocates stable plasma concentrations of analgesic to provide effective and long-lasting pain relief, avoidance of excessively high concentrations to minimize adverse events, a long duration of action and an immediate-release formulation for rapid pain relief (for example, in the treatment of breakthrough pain). The WHO guidelines also recommend regular administration of analgesic agents and the oral route of administration.

Opioid use has been restricted in the past owing to concerns regarding misuse, tolerance, possible addiction,

respiratory depression and other adverse events, such as nausea, vomiting, constipation and drowsiness. However, attitudes have had to be revised since transdermal delivery systems (TDS) became available for selected opioids. Transdermal patches fulfil virtually all the requirements for the successful treatment of chronic pain and offer several advantages over oral or parenteral routes of administration: noninvasiveness, slow and continuous release into the systemic circulation and constant serum levels over a prolonged period of time. Possible problems associated with oral dosage, such as low absorption or extensive hepatic first-pass metabolism and low bioavailability, can be avoided. Transdermal systems are particularly useful for patients who are unable to swallow because of head and neck cancer, gastrointestinal pathologies or stomatitis, and those who have pre-existing nausea or vomiting.

Overview of the market

Since fentanyl TDS became available in the 1990s, both professional and public awareness of transdermal analgesic application have increased and significant technological development has taken place. A buprenorphine patch was launched in Europe in 2001 and is increasingly being introduced in other countries. Fentanyl and buprenorphine are currently the only opioids commercially available in a TDS formulation and both drugs are the only recommended opioids by the WHO in patients unable to swallow [102] .

Buprenorphine

Buprenorphine is a strong, semisynthetic opioid derived from thebaine, a component of opium. Effective in the treatment of acute postoperative and chronic pain, it is indicated for the management of moderate-to-severe pain [4,5] , corresponding to steps II and III of the WHO pain ladder. Buprenorphine has been used extensively in clinical practice for approximately 30 years and is available in parenteral, sublingual and transdermal formulations. Research has recently overturned the widespread misconception that it has a ceiling effect for analgesia, and transdermal delivery avoids the poorly tolerated bolus effect that can result from parenteral and sublingual administration [6] .

The use of opioids for treating neuropathic pain remains controversial, but there is a growing body of evidence that different opioids affect different pain pathways and that buprenorphine may be particularly useful for managing this type of pain [7] . Most notably, it appears to be effective in treating hyperalgesic states and syndromes characterized by pronounced central sensitization [8] . Unlike morphine and fentanyl, buprenorphine has no immunosuppressive effect, offering a potential advantage when individuals are already immunosuppressed; for example in elderly, cancer/chemotherapy or postoperative/post-trauma patients or patients with AIDS [9] . Long-term use has been shown not to impair driving ability, an important aspect of self-determination and quality of life [10] .

Buprenorphine TDS comprises a simple, flexible system in which the active agent is incorporated into a polymer matrix, which also acts as the adhesive layer. The drug is continuously released at a precise rate and passes through the skin into the systemic circulation [11] . Unlike a reservoir patch, a matrix patch is not easily damaged, minimizing the risk of dose dumping and its associated toxicity. The three strengths of patch that are widely available contain 20, 30 or 40 mg of the drug. These are designed to release buprenorphine at controlled rates of 35, 52.5 and 70 µg/h, corresponding to daily doses of 0.8, 1.2 and 1.6 mg, respectively [12] . These patches have all been approved for a 4-day application period, offering the advantage of twice-weekly application. A low-dose patch with release rates of 5, 10 and 20 µg/h has been introduced which can be applied for 7 days, but it is only available in a few countries and there are no published data on its clinical use, so this article will focus on the higher dose patches.

Careful titration is mandatory when commencing treatment because of the time lag before an effective plasma concentration is reached. It is also strongly recommended that the previous pain medication is continued

before using the patch alone. A fast-acting analgesic should be prescribed in case of sudden breakthrough pain, but the percentage of patients who require this medication is low with buprenorphine TDS [Kusnik S, Unpublished Data].

Chemistry

The chemical structure of buprenorphine is basically opioid in nature, but contains significant additions, including the C7 side chain containing a t-butyl group. This group occupies a spatial position analogous to the phenyl group in the phenylalanine moiety of enkephalins and renders the compound highly lipophilic, considerably influencing its pharmacology.

Pharmacodynamics

Buprenorphine is both highly lipophilic and water soluble, with a low molecular weight of 467 kDa. These properties, together with its small volume and molecular configuration, allow easy tissue and compartment penetration. The drug is, therefore, highly suitable for transdermal delivery.

Receptor binding

Buprenorphine has mixed agonist and antagonist properties. Its action as a partial agonist at the μ-opioid receptor is responsible for its analgesic properties [13] . It demonstrates high affinity for this receptor and a high analgesic potency ([proportional to]20-40-times that of morphine) [13,14] . The plasma concentration required to relieve moderate-to-severe pain lies between 100 and 500 pg/ml [15] . Binding to and dissociation from the μ-opioid receptor is very slow, so that the onset of effect is gradual but the duration of analgesia is long. These properties are also affected by the route of administration. Buprenorphine acts as an antagonist at the κ-opioid receptor [16] and as a weak agonist at the δ-opioid receptor [17] . Moreover, it is an agonist at the opioid receptor-like (ORL)-1 receptor [18] , indicating possible anxiolytic effects.

Buprenorphine has demonstrated a bell-shaped dose-response curve for pain relief and respiration in several animal models [13,14,19,20] , but a ceiling effect for analgesia has never been observed in humans [11,21,22] . As with other opioids, withdrawal symptoms may occur after the cessation of treatment with buprenorphine, peaking after approximately 2 weeks. However, these appear to be milder than after morphine treatment [22] , indicating a possible advantage over other μ-opioid agonists, such as fentanyl.

Pharmacokinetics

When administered orally, buprenorphine undergoes extensive first-pass metabolism. Its oral availability is approximately 15% and thus insufficient to achieve analgesic drug concentrations [23] . The pharmacokinetics of intravenous, intramuscular and sublingual dosing of buprenorphine have been reviewed previously [24,25] .

Absorption

Plasma concentrations of buprenorphine rise only slowly after transdermal application. Within 12-24 h they reach the analgesic threshold level (100 pg/ml) and then attain clinically effective concentrations over the next 30 h. After patch removal, plasma concentrations fall quite slowly over approximately 30 h. Dose proportionality has been demonstrated between the different patch strengths and a steady state is reached at the end of the third application period [26] . Kinetic data have been collected after consecutive use of three patches of each size (35, 52.5 and 70 μg/h) in three parallel patient cohorts. For all three doses, a constant and comparable release of the drug was demonstrated over a period of 9 days [11] . Transdermal buprenorphine has a bioavailability of approximately 50% [Grünenthal, Unpublished Data], comparable to the

50-65% after sublingual administration [27] .

Metabolism

Following the extensive first-pass metabolism in the gut wall and liver [28] , the main metabolite is buprenorphine-3-glucuronide, although some buprenorphine is partly oxidized to *N* -dealkylbuprenorphine (norbuprenorphine) in a reaction mediated by cytochrome p450 (CYP) 3A4 [29] . Norbuprenorphine shows only little analgesic efficacy and is hardly able to penetrate the blood-brain barrier. Both buprenorphine and norbuprenorphine undergo glucuronidation to inactive metabolites.

The primary elimination route is the biliary tract, which is responsible for removing approximately two-thirds of the drug. In humans, buprenorphine remains virtually unchanged in the feces. By contrast, only a third is eliminated by the kidneys, with the urine containing mostly conjugates of the parent compound and norbuprenorphine [30] . In short-term treatment with buprenorphine, end-stage renal failure does not seem to affect excretion of the drug [31,32] . This contrasts with fentanyl and especially with morphine, the clearance of which falls markedly in patients with terminal renal failure [33] .

In severe chronic liver disease, the expression of hepatic CYP3A proteins is significantly reduced and this is presumed to alter buprenorphine metabolism [23] . Patients with liver cirrhosis who are receiving buprenorphine should therefore be closely monitored regarding possible adverse effects, in case dose adjustments are required.

Clinical efficacy

Several randomized, double-blind, placebo-controlled parallel-group studies have investigated the efficacy of transdermal buprenorphine in treating chronic pain. In the first study, 151 patients with severe-to-very-severe chronic pain of malignant or nonmalignant origin, who obtained satisfactory pain relief with sublingual buprenorphine during an open-label 5-day run-in phase, were randomized to receive two consecutive buprenorphine patches 35, 52.5 or 70 µg/h, or placebo [34] . Responders were defined as patients reporting satisfactory pain relief and taking no more than 0.2 mg/day of sublingual buprenorphine rescue analgesic.

The proportion of responders in each active-treatment group increased dose dependently (34, 35 and 37% for the 35, 52.5 and 70 µg/h groups, respectively). However, these response rates did not reach statistical significance because of a high response rate in the placebo group (31%). Compared with the run-in phase, 20% fewer placebo patients experienced good-to-complete pain relief and the proportion reporting moderate-to-very-severe pain increased by 14%. By contrast, the proportion of active treatment patients who obtained good-to-complete pain relief increased by 5-13%, and the proportion reporting moderate-to-very-severe pain fell by 3-14%. The duration of sleep uninterrupted by pain was shorter in the placebo group than in the active-treatment groups.

A second double-blind, placebo-controlled study recruited 157 patients with chronic severe cancer or noncancer pain that was inadequately controlled by weak opioids, in most cases tramadol [35] . Patients were randomized to receive transdermal buprenorphine (35, 52.5 or 70 µg/h) or a placebo patch for up to 15 days. All patients were allowed rescue analgesia with sublingual buprenorphine tablets (0.2 mg) for breakthrough pain.

At 35 and 52.5 µg/h, transdermal buprenorphine was associated with significantly higher response rates than placebo (36.6 and 47.5%, respectively, vs 16.2% with placebo; $p = 0.032$ and $p = 0.003$, respectively). The response rate was numerically higher at 70 µg/h (33.3%), but the difference did not reach statistical significance. Active-treatment groups reduced their consumption of rescue analgesia by an average of 56.7%,

compared with an 8% reduction in the placebo group. Good or complete pain relief was reported by 43.5% of buprenorphine patients, compared with 32.4% of patients receiving placebo ($p < 0.05$). Pain intensity decreased dose dependently with buprenorphine TDS and the duration of uninterrupted sleep improved. Transdermal buprenorphine was shown to be effective against chronic severe pain, and it was also shown that it is possible to switch from weak opioids to the buprenorphine patch without any problems.

The third randomized, double-blind, placebo-controlled clinical trial compared the analgesic efficacy of transdermal buprenorphine (35 µg/h) and placebo in 137 patients with moderate-to-severe pain related to cancer or other disorders [36] . It comprised a 6-day, open-label run-in phase, during which patients received sublingual buprenorphine as needed (0.8-1.6 mg/day), followed by a double-blind phase in which patients were randomized to receive three sequential patches containing either buprenorphine (35 µg/h) or placebo. Rescue medication (sublingual buprenorphine 0.2 mg/day) was available as required throughout the double-blind phase. Patients who required 40% fewer sublingual buprenorphine tablets during the double-blind phase and who reported at least satisfactory pain relief were considered to be responders.

The response rate was significantly higher in the buprenorphine TDS group than in the placebo group (p6 h, +6.4%), whereas in the placebo group it decreased (>6 h, -5.9%).

Aggregating the results of these three clinical trials, severe-to-very-severe pain persisted in more placebo ([proportional to]70%) than transdermal buprenorphine ([proportional to]50%) patients, despite a higher consumption of rescue analgesia in the placebo arm [37] . More patients treated with buprenorphine TDS reported either mild or no residual pain. Response rates for transdermal buprenorphine ranged from 41.9 to 47.2%, compared with 32.5% for placebo, and more buprenorphine patients slept for 3-6 h or more than 6 h than in the placebo arm.

Following the three studies described above, 239 patients volunteered for an open-label continuation study to examine the long-term efficacy and tolerability of transdermal buprenorphine (35 µg/h) [38] . The duration of treatment was up to 5.7 years (mean duration 7.5 months; [proportional to]4 months in cancer patients and [proportional to]12 months in noncancer patients). The criteria assessed were pain relief, the number of sublingual buprenorphine tablets taken in addition to the patch and ease of use.

Pain relief was assessed according to a four-point scale as unsatisfactory, satisfactory, good or complete. Analgesia was reported as at least satisfactory by 90% of patients (42.3% good/complete, 47.7% satisfactory). Almost 60% of patients could manage their pain with one patch alone or with one additional sublingual buprenorphine tablet per day throughout the period of treatment, indicating low tolerance development. The buprenorphine patch was considered to be user friendly by 94.6% of patients.

Data from a study of cancer patients unable to obtain relief from buprenorphine TDS at a dose of 70 µg/h indicates that even higher doses (105-140 µg/h) may bring analgesic benefit without increasing adverse effects [39] .

To evaluate the efficacy of transdermal buprenorphine in treating severe cancer pain, the 70 µg/h patch was compared with placebo using an enriched study design [40] . Opioid-tolerant patients with cancer pain requiring strong opioids in the dose range 90-150 mg/day oral morphine equivalents entered a 2-week run-in phase and were converted to buprenorphine TDS. Stabilized patients were then randomized into a 2-week maintenance phase to receive either buprenorphine TDS or placebo patch. Rescue medication (sublingual buprenorphine 0.2 mg/day tablets) was allowed as required. Response was defined as a mean pain intensity of less than 5 on a 0-10 scale and a mean daily intake of up to two tablets of rescue medication during the maintenance phase.

Of 188 patients, 70 in the buprenorphine group (74.5%) and 47 in the placebo group (50%) were classified as

responders, the difference in response rates being statistically significant (p = 0.0003). This result was supported by a lower daily pain intensity, lower consumption of rescue medication and fewer dropouts in the buprenorphine group.

Postmarketing surveillance

A total of 13,179 patients suffering from moderate-to-severe cancer or noncancer pain were recruited from hospitals, out-patient clinics and general practitioners' surgeries in Germany for an open, observational study on transdermal buprenorphine [41] . Of this population, 57.4% had musculoskeletal disorders, 28% had cancer, 12.3% had neuropathic pain and 7% had other diseases. Buprenorphine patches (35, 52.5 or 70 µg/h) were prescribed at the physician's discretion, most subjects (78%) starting treatment with the 35 µg/h patch. Patients assessed their pain relief as very good, good, satisfactory, poor or no effect.

In the total population, good or very good pain relief was reported by only 6% of subjects at the initial assessment, but this increased to 71% at the first follow-up and 80% at the final assessment. Fewer than 5% discontinued treatment owing to unsatisfactory pain relief. The initial dose needed to be increased in only 18% of subjects, suggesting that the development of tolerance was not a significant problem. The survey concluded that transdermal buprenorphine provided effective, sustained and dose-dependent analgesia in patients with cancer and noncancer pain, irrespective of their age or pain syndromes.

Five separate retrospective studies from Spain focused on patients whose pain had not responded to previous analgesic treatment and who were subsequently treated with transdermal buprenorphine. Study one included 367 patients with chronic, moderate-to-severe, nociceptive pain of noncancer origin [42] . After 8 weeks of treatment with buprenorphine TDS, the meanvisual analog scale (VAS) score fell from 7.7 to almost 3.4, a reduction of 56%. The proportion of patients reporting a score of seven or more fell from just under 90% at the start of buprenorphine treatment to 52% after 1 week and 7.6% after 8 weeks. The differences in average scores between visits were all statistically significant (p< 0.001).

Study two evaluated 237 patients with chronic, moderate-to-severe, noncancer, neuropathic pain who had a VAS pain intensity score of five or greater [43] . At the start of treatment with buprenorphine TDS, the mean VAS score was 7.7, with 90% of subjects recording a score of seven or higher. At the end of the 8-week study, the mean VAS score had fallen to 3.5, a reduction of almost 55%, and almost 88% of patients reported a level of 4 or below. Differences between the mean values for each of the visits were statistically significant (p < 0.001).

Study three documented 164 patients with confirmed local or metastatic cancer [44] . After 8 weeks of treatment with transdermal buprenorphine, the mean VAS score was 3.2, corresponding to a decrease of approximately 57%. Almost 76% of subjects rated their pain at a level of 4 or below and only 6% at a level of 7 or above. Differences between mean values for the visits were statistically significant (p < 0.001), except for between weeks 4 and 8 (p = 0.028).

The aim of study four was to establish whether tramadol, prescribed as rescue medication, could be combined with buprenorphine TDS [45] . At the beginning of the study, 297 patients with chronic pain caused by various conditions had a mean VAS score of 7.7, with 64% of patients rating their pain at 8 or higher, and almost 86% rating it at 7 or higher; 8 weeks later, only 4.3% of patients reported pain at level 7 or higher, while 75% rated it at 4 or below, compared with just 0.3% at baseline. The mean score of 3.6 at week 8 represents a reduction of 54%. Again, the differences between mean values for visits were statistically significant (p < 0.001), except for weeks 4-8 (p = 0.036). Tramadol was given to approximately half the subjects over the 8-week period and no interaction between the two drugs or additional adverse events from tramadol, were observed.

The 93 patients in study five suffered from chronic pain of any type and etiology that had not responded to

nonopioid analgesics, and had previously received morphine for breakthrough pain [46] . At the time of inclusion in the study, the mean VAS score was 7.8, with approximately 64% scoring their pain at 8 or above and almost 87% at 7 or above. Patients were treated with morphine during the first week, which brought a statistically significant reduction to 4.4. A buprenorphine patch corresponding to the individual morphine dose was then applied; the mean VAS score remained unchanged during week 2, indicating that the equianalgesic dose was correct. Pain intensity decreased further in weeks 4 and 6, and the reduction to 3.7 in week 8 represents a decrease of 53% from baseline. Statistically significant differences were seen between the mean values at weeks 1 and 6, and between baseline and each of the other timepoints ($p < 0.001$).

The percentage of patients who rated the efficacy of transdermal buprenorphine as very good or good was 60% or above in these five retrospective studies. The figure for study four was slightly lower at 57%.

Safety & tolerability

Transdermal buprenorphine was generally well tolerated and the adverse events reported in clinical trials were usually mild-to-moderate in intensity. Adverse events could normally be attributed to the patch causing local skin reactions, the systemic effects of buprenorphine or the underlying disease.

Local effects

The most common local adverse events were mild or moderate erythema and pruritus, usually of short duration; in one study, 50% of erythema and 12% of pruritus cases resolved within 24 h [34] . In the first randomized, placebo-controlled trial, between 10 and 20% of patients in all groups (buprenorphine 35, 52.5 or 70 µg/h, or placebo patches) experienced local adverse events [34] . In the second and third trials, approximately a third of patients experienced a skin reaction, the most common being erythema or pruritus at the patch site [35,36] . The incidence was lower in the retrospective high-dose study (18.29%) [39] and the long-term follow-up study (erythema 11.3%, pruritus 9.2%) [38] , and lower still in the postmarketing surveillance study (local symptoms 3%) [42] .

Systemic effects

The most frequent systemic side effects were typical of opioids: nausea, vomiting, dizziness and constipation. The overall incidence of adverse events in the first randomized, placebo-controlled trial (23%) may be explained by the fact that 90% of subjects were already receiving buprenorphine prior to the study and only events that emerged during the study were recorded [34] . In the second trial, 69.3% of patients reported systemic adverse events, with no significant differences between the treatment and placebo groups [35] . CNS adverse events affected 52.6% of placebo patients, and 56.1, 46.3 and 54.1% of the buprenorphine 35, 52.5 and 70 µg/h groups, respectively. Gastrointestinal side effects were experienced by 26.3% of the placebo group and 17.1, 36.6 and 43.2% of the buprenorphine 35, 52.5 and 70 µg/h groups, respectively. The incidence of systemic events in the third trial was similar in the placebo and buprenorphine groups at approximately 28% [36] .

Systemic effects were reported by 45.6% of patients in the long-term follow-up study [38] and were typical of opioid therapy; for example, nausea (8.8%), dizziness (4.2%), vomiting (3.8%) and constipation (3.3%). The incidence of adverse events in the postmarketing surveillance study [41] was lower than in the clinical trials. The number classified as adverse drug reactions was 2220 in 1330 patients (10.1%), the most frequent being nausea (4%), dizziness (1.9%), vomiting (1.6%) and constipation (1%).

In clinical practice, respiratory depression occurs infrequently [20] . Even in opioid-experienced volunteers,

no respiratory effect occured at doses up to 70-times higher than those used for analgesia [22] . To date, not a single case of respiratory depression caused by transdermal buprenorphine has been reported [47] . Were this to occur, the respiratory depressive effect of buprenorphine can be completely reversed by a 30-min infusion of naloxone [48] .

The use of buprenorphine in association with other opioids has been of concern previously because of a possible antagonistic effect, which might reduce analgesia or induce withdrawal symptoms. However, recent animal data suggest that there is no interference between buprenorphine and other µ-opioid agonists [49] . Furthermore, problems have not been encountered in clinical studies when switching from another opioid to transdermal buprenorphine [46,50] , or when combining the buprenorphine patch with tramadol or intravenous morphine for breakthrough pain [45,51] .

It should be borne in mind that plasma levels of buprenorphine are likely to be elevated if CYP3A4 inhibitors - such as fluoxetine, erythromycin or highly active antiretroviral therapy drugs - are administered simultaneously. Conversely, levels may be reduced by carbamazepine, phenobarbital, phenytoin or rifampicin, which all act as CYP3A4 inducers and accelerate buprenorphine metabolism.

Regulatory affairs

Currently, transdermal buprenorphine is available in 23 countries around the globe. It was first launched in Switzerland and Germany in 2001 and the first non-European country in which Transtec® became available was Chile in 2004. The low-dose patches with release rates of 5, 10 and 20 µg/h (Norspan®) were launched in 2004 in Denmark and are now available in four different European countries and Australia. In 2005, low-dose patches also became available in the UK and Ireland (BuTrans®).

Conclusion

Transdermal buprenorphine is effective in the management of all levels of chronic cancer and noncancer pain. Switching from WHO step II opioids or low doses of step III opioids is uncomplicated. More than 90% of patients in the long-term, open-label, follow-up study considered their pain relief to be at least satisfactory [38] , and 70% of patients in the German postmarketing surveillance study rated it as good or very good [41] . The development of tolerance was low. Buprenorphine patches were considered to be user friendly by 94.6% of patients. Systemic adverse events were rare, typical of opioid analgesics and generally mild or moderate in intensity. Local adverse events, such as pruritus and rash, were transient, often subsiding within 24 h and rarely led to discontinuation of treatment. Studies have confirmed this efficacy and safety in nociceptive and neuropathic pain.

Thus, transdermal buprenorphine is a promising option for the effective management of chronic cancer and noncancer pain.

Expert commentary

Buprenorphine TDS is indicated for treating moderate-to-severe pain and severe chronic pain conditions that do not respond to nonopioid analgesics. It effectively relieves pain, increases the duration of sleep, reduces the consumption of rescue medication and improves quality of life. An overwhelming majority of patients find the patches user friendly and 70% obtain good or very good pain relief. The development of tolerance to buprenorphine appears to be low. Patches are usually well tolerated with no unpredictable adverse effects. Studies and case reports have shown buprenorphine TDS can effectively treat neuropathic pain.

Five-year view

Large-scale studies involving thousands of patients have demonstrated the efficacy and safety of transdermal buprenorphine in treating moderate-to-severe chronic pain, and its effectiveness has now been established in neuropathic pain. Such pain is normally difficult to treat with opioids but buprenorphine appears to be by far the best, and its use in this indication is likely to increase. Wider introduction of the new low-dose patches will provide release rates ranging from 5 to 70 µg/h that can effectively treat a variety of routine and practice-relevant pain conditions. A possible future option is the use of buprenorphine TDS for pediatric pain, particularly as there are numerous clinical trials of transdermal fentanyl in this patient group. The excellent safety profile (limited respiratory depression, no immunosuppression, few interactions with other medicines and excretion unaffected by renal failure) indicates that transdermal buprenorphine is suitable for geriatric patients, and controlled clinical studies should be carried out. In addition, the isolated positive case reports relating to transdermal buprenorphine use in pregnant women [52] should be verified by large-scale investigations.

If further studies confirm that buprenorphine TDS has all these advantages in the aforementioned patient groups, it would be effective for treating many forms of chronic pain of different intensity and also selected forms of acute pain. Its favorable safety and adverse effect profile mean it can also be prescribed in problematic subgroups of patients, as mentioned above.

Key issues

* Transdermal buprenorphine is widely available in three patch sizes, corresponding to release rates of 35, 52.5 and 70 µg/h. Patches are applied every 4 days.

* Since 2004, low-dose-patches with 5, 10 or 20 µg/h have been available in Europe and Australia for 7-day use.

* The efficacy of transdermal buprenorphine has been demonstrated in a number of clinical trials and postmarketing surveillance studies.

* In clinical trials, transdermal buprenorphine provided significantly better pain relief than placebo, despite a higher consumption of rescue analgesia by placebo patients.

* In an open-label, long-term, follow-up study of the 35-µg/h patch, 90% of patients rated their pain relief as at least satisfactory and 94.6% considered the treatment to be user friendly.

* Buprenorphine seems to be a very useful opioid for the management of neuropathic pain conditions.

* Transdermal buprenorphine is well tolerated. Most adverse events are transient local reactions to the patch or systemic effects typical of treatment with opioids.

* A ceiling effect for buprenorphine analgesia has never been observed in humans.

* To date, not a single case of respiratory depression caused by transdermal buprenorphine has been reported.

* Switching from another opioid to transdermal buprenorphine or combining the buprenorphine patch with other opioids for breakthrough pain do not appear to cause any problems.

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