

## REVIEW

### Transdermal buprenorphine for pain management in children

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#### Abstract

Pain is one of the main symptoms reported by sick children, particularly by those suffering from cancer. Opioids are very useful in controlling this symptom but they are burdened with significant side effects that limit their use in children. Buprenorphine is a strong opioid that, due to its particular pharmacological characteristics, ensures excellent pain relief with fewer side effects than other opioids. The transdermal formulation allows for good pain control associated with optimal compliance by patients and few limitations on daily life. Unfortunately, transdermal buprenorphine use remains off-label for the control of chronic

pain in children; therefore, it is desirable that new studies can validate its use in the paediatric population. This review aims to analyse the clinical advantages of transdermal buprenorphine in the paediatric population and the possible side effects registered in daily clinical practice.

**Keywords:** buprenorphine, children, opioids, pain, transdermal.

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#### Introduction

Pain is the most common symptom in children with cancer and chronic disease, causing a reduction in quality of life. Despite its high frequency, pain is often underappreciated and consequently undertreated because of an inadequate use of pain assessment systems due to poor compliance by children and because of a lack of experience in the use of certain pain relievers.<sup>1,2</sup> In the past, pain was classified by the WHO as mild, moderate or severe. For each level of pain, the use of specific categories of drugs was defined according to a principle of gradual intervention (WHO analgesic ladder), which included three steps. The first for mild pain required the use of non-opioid analgesic drugs, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs). The second for moderate pain, involved the use of weak opioids, possibly in association with adjuvant drugs. The third step concerned severe pain and indicated the use of strong opioids, possibly in association with adjuvants, NSAIDs and paracetamol.<sup>3</sup> In 2012, the WHO established guidelines for the management of chronic pain in children – the old three-step approach was abandoned in favour of a two-step approach. According to this approach, children with mild pain required paracetamol or NSAID treatment whilst, in moderate or severe cases, a strong opioid must be used. The use of weak opioids was therefore not recommended.<sup>4</sup>

In addition, the WHO guidelines recommended attention to the choice of the least invasive route of administration for the child as well as the use of a preventive treatment able to avoid the onset of pain, on a continuous or scheduled basis and not on request.

Therefore, opiates play a key role in the treatment of cancer pain even in children, and it is estimated that between 60% and 90% of children with cancer receive such treatment. Given the importance of these drugs in pain management, the most recent WHO guidelines have placed greater attention on the correct use of opioid drugs, on the control of side effects and on the correct discontinuation of therapy.<sup>5</sup>

Buprenorphine is a major semisynthetic opioid derived from thebaine, which has an analgesic potency that is equal to 30 times that of morphine. Buprenorphine was synthesized for the first time in the late 1960s and introduced into clinical practice in 1981, in parenteral and sublingual formulations, and used initially in the presence of opioid dependence and then as an analgesic drug.<sup>6,7</sup> It has a phenanthrene structure with a tert-butyl group in the C-7 position. This structure is responsible for buprenorphine lipophilicity that, with its low molecular weight, enabled the development of a transdermal formulation useful in the treatment of chronic moderate and severe pain that does not respond to non-opioid analgesics.<sup>8</sup>

## Methodology

We searched for papers dedicated to the use of transdermal buprenorphine in the paediatric population, performing a PubMed-based retrieval of articles using the search terms “transdermal buprenorphine” alone or matched with “children”, “childhood” and “pediatric”. After the original search, we used filters to select articles available in English and articles with available full texts. We then narrowed these down based on their relevance to the topic. The final search retrieved 57 articles, of which 19 exclusively related to paediatric patients.

## Review

### Pharmacological characteristics of buprenorphine

#### **Pharmacodynamic characteristics**

Buprenorphine is a partial and potent agonist of the  $\mu$ -opioid receptor, a complete agonist of the opioid receptor-like 1 (ORL1), and an antagonist of the  $\delta$  and  $\kappa$  receptor.<sup>9</sup> Buprenorphine has a high affinity for  $\mu$ -opioid receptors with a low intrinsic activity; it also dissociates from the receptor slowly. These characteristics can displace other opioids, such as morphine and methadone, from the link with the  $\mu$ -opioid receptors, realizing its ability to reduce dependence on these drugs and prolonging its therapeutic action.<sup>10–12</sup>

Within the therapeutic ranges, buprenorphine also has a ceiling effect for respiratory depression whilst not presenting it for analgesia, which therefore makes it safer than other opioids; specifically, a significant difference in the safety margin has been demonstrated compared to fentanyl.<sup>13,14</sup>

Buprenorphine also increases the expression of the  $\mu$ -opioid receptors, behaving like a cellular ‘chaperone’, thus reducing the risk of developing tolerance and dependence. Even after chronic administration, buprenorphine induces a low level of physical dependence and causes a mild withdrawal syndrome after sudden withdrawal. These characteristics make it possible to use buprenorphine in the treatment of opioid addiction.<sup>15</sup>

Systemic opioids increase the expression of dynorphin, a  $\kappa$ -opioid receptor agonist, which is responsible for the appearance of hyperalgesia.<sup>16</sup> Because buprenorphine acts as an antagonist on  $\kappa$ -opioid receptors, it does not induce a state of hyperalgesia, unlike other opioids.

Opioid drugs act on the immune system causing a decrease in the production of antibodies, IL-2 and IFN $\gamma$ , with the inhibition of adaptive immunity and down-regulation of the function of natural killer (NK) cells and macrophages.<sup>17</sup> In addition, the link with the  $\mu$ -opioid receptors on the central nervous system activates the hypothalamic–pituitary–adrenal axis with consequent production of corticosteroids that cause further immunosuppression by acting directly on the cells of the immune system and stimulating the sympathetic nervous

system. Buprenorphine does not possess these abilities and does not change the activity of NK cells, T lymphocytes or macrophages; therefore, it has no immunosuppressive effect.<sup>18,19</sup>

These differences between buprenorphine and other opioids, such as morphine and fentanyl, are of considerable importance in the treatment of vulnerable patients, such as children and the elderly, and even more so in cancer patients, in whom a state of advanced immunodepression is often present.

Buprenorphine, unlike other opioids, does not affect the hypothalamus–pituitary–gonad axis and its prolonged use does not cause hypogonadism or a reduction in hormone production.<sup>20,21</sup>

Studies with endoscopic manometry have shown that buprenorphine does not induce Oddi’s sphincter spasm, a common effect of other opioids, but significantly decreases the amplitude of its contraction waves without altering other parameters, which makes this drug the first choice in the treatment of pancreatitis or biliary colic.<sup>22,23</sup>

Preclinical and clinical studies support the effectiveness of buprenorphine also in the management of neuropathic pain, with powerful effects on hyperalgesia and allodynia, probably linked to its independence from the link with pertussis toxin-sensitive G protein, which is often altered in neuropathic pain.<sup>24</sup>

#### **Pharmacokinetic characteristics**

Buprenorphine is currently available in several formulations, some licensed worldwide and others only in some countries. The main routes of administration are intravenous, oral, sublingual and transdermal. Subcutaneous, intranasal, intramuscular and rectal routes are less used.<sup>25</sup>

The absorption of the molecule is closely related to the route of administration. For the parenteral route, the bioavailability is 100% with a  $C_{max}$  of 2–5 minutes and a half-life consisting of an early phase of 2–5 minutes and a late phase of 2–5 hours. When administered orally, the bioavailability is very low (10–16%) due to extensive pre-systemic metabolism whilst, in the sublingual route, the bioavailability is between 28% and 51%, the  $C_{max}$  is about 2–3 hours and the half-life of 28 hours. Administered transdermally, it has a bioavailability of about 60% with a  $C_{max}$  that is reached at 60 hours.<sup>26,27</sup> Buprenorphine has a high affinity for plasma proteins (96–98%) by binding more to alpha and beta globulins and less strongly to albumin, with the consequence of less competition and interaction with other drugs.<sup>28,29</sup> Because of its elevated lipophilia, it is able to cross the blood–brain barrier.<sup>30</sup> It is metabolized on the liver by the cytochromes CYP3A4 and CYP2C8, which transform it into the active metabolite norbuprenorphine. In addition, the enzymes uridine diphosphate glucuronosyltransferases (UGT2B7 and UGT1A1) transform it into the inactive metabolite norbuprenorphine glucuronide.<sup>31</sup> Approximately 50–70% of the drug is eliminated in the stool and only 15% in the urine. Therefore, buprenorphine can be used in patients with renal insufficiency and in those with mild and moderate liver failure without any dose adjustment.<sup>32</sup>

Table 1 shows the different pharmacokinetic characteristics of transdermal buprenorphine in children and adults.

When buprenorphine is administered simultaneously with benzodiazepines, it can aggravate the respiratory depression caused by benzodiazepines.<sup>33</sup> Buprenorphine does not affect the cytochrome CYP450 activity and does not compete with other drugs regarding plasma transport because it binds predominantly to alpha and beta globulins. The coadministration with drugs that lengthen the QT interval should be avoided as it may worsen this effect.<sup>33</sup> Table 2 summarizes the interactions of buprenorphine with other drugs.

When used at high doses, buprenorphine, like all strong opioids, can have side effects such as constipation, urinary retention, nausea, vomiting, drowsiness and respiratory depression. However, such symptoms are less frequent, especially with regard to respiratory depression, compared to their presentation in morphine and fentanyl.<sup>13,14</sup> In the transdermal form, such effects are even less important whilst local effects may occur at the site of application of the patch, such as erythema and itching, reversible once the patch is removed.<sup>34</sup>

Several studies have evaluated equianalgesic conversion with morphine and fentanyl. Mercadante et al. identified a conversion ratio of 0.6–0.8 from transdermal fentanyl to transdermal buprenorphine (0.6 mg/day of fentanyl was converted to 0.8 mg of buprenorphine equal to 35 µg/h patch).<sup>35</sup> The equivalence ratio of transdermal buprenorphine to oral morphine was set at 1:75, but clinical experience suggests that transdermal

**Table 1. Pharmacokinetic characteristics of transdermal buprenorphine in children and adults.**

	Children	Adults
Bioavailability (%)	50	60
C <sub>max</sub> (ng/mL)	Unavailable	300
T <sub>max</sub> (hours)	11–22	60
T <sub>1/2</sub> (hours)	20±8	25.3

**Table 2. Drugs that interact with buprenorphine classified according to the mechanism of interaction.**

Central nervous system depression	Interference with CYP 450 metabolism	Lengthening of the QT segment
Benzodiazepines	Erythromycin	Escitalopram
Anaesthetics	Ketoconazole	Quetiapine
Antipsychotics	Inhibitors of HIV	Albuterol
Opioids		

**Table 3. Equivalent doses of transdermal fentanyl, transdermal buprenorphine and oral morphine.**

Transdermal buprenorphine (µg/h)	Transdermal fentanyl (µg/h)	Oral morphine (mg)
35	25	60
70	50	90
105	75	120
140	100	180

buprenorphine is more powerful than originally imagined and, therefore, a new ratio of 1:110–1:115 was proposed.<sup>36,37</sup> Table 3 shows the equivalent doses of transdermal fentanyl, transdermal buprenorphine and oral morphine.

## Transdermal buprenorphine

The analgesic effect of buprenorphine, its high lipophilicity and its low molecular weight, together with a low potential risk of abuse, make it adequate for transdermal use. This avoids the discomfort of intramuscular injections or oral ingestion and is less demanding than intravenous infusions.<sup>38</sup> In addition, the transdermal release allows a practically constant plasma level of the drug and avoids the effect of first passage on the liver and the poor absorption in the gastrointestinal tract. Together with fentanyl, at present, it is the only opioid available in the transdermal formulation.<sup>39</sup>

In the patch, the buprenorphine molecule is evenly distributed and incorporated into a solid matrix of polymers. The matrix allows a continuous release of the molecule into the systemic circle and avoids the risk of ‘dose-dumping’ and potential overdose as can occur with transdermal reservoir systems. This delivery system prevents excessive drug absorption when the patch is damaged and allows splitting of the dosage by cutting the patch.<sup>40</sup>

Plasma concentrations of buprenorphine increase progressively as the number of applications increases and reach steady state after the third application.<sup>41</sup>

Patients who are naive to opioids should initially be treated with the lowest-dose patch. For patients with previous opioid treatment, the dose depends on the pattern and extent of previous treatment. As plasma concentrations of buprenorphine rise slowly with transdermal administration, the previous therapy should be maintained for the first 24 hours. The suitability of the patch should be assessed at the end of the first application and the dose adjusted individually. The increase is possible using a patch with a higher dosage of the drug or applying no more than two patches of the same size at the same time.<sup>42,43</sup> It is important to keep the body temperature under control during transdermal treatment, as the increased heat of the skin causes

an increase in its permeability. When necessary, transdermal buprenorphine can be combined safely and effectively with other  $\mu$ -opioid receptor agonists, such as rescue medication (for example, Tramadol), and it is possible to switch from buprenorphine to other opioids and *vice versa* without problem. The application site must be clean, dry, without abrasion or damage. Before application, no soap or topical alcohol products should be used. The patient should be instructed on the correct technique of adhesion of the patch to the skin. The site may be the upper back, chest or sub-clavicular region.<sup>44</sup> Sometimes, local adverse reactions of the skin are possible, such as erythema, itching, exanthema and swelling, usually reversible following the removal of the patch.

Figure 1 summarizes the mechanism of release and absorption of transdermal buprenorphine.

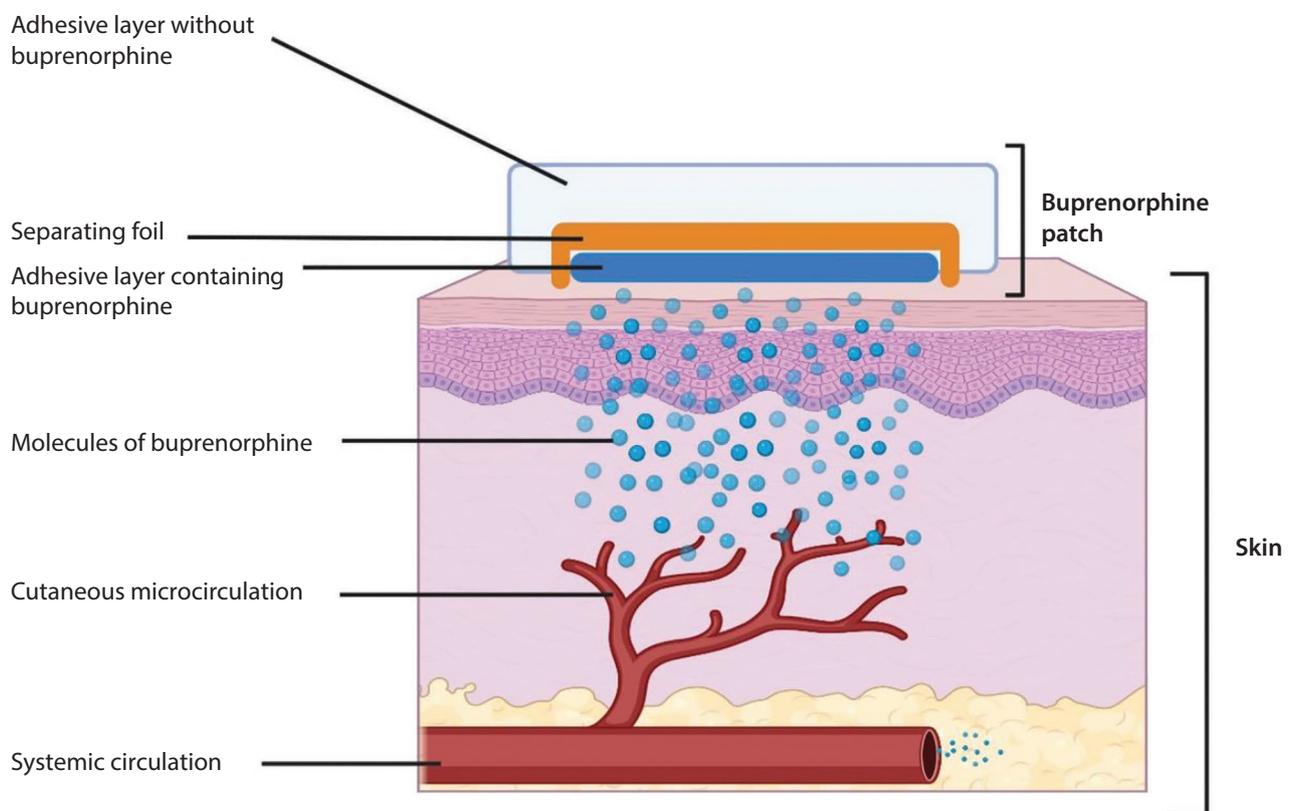
## Transdermal buprenorphine in children

Although buprenorphine is not indicated as the first line in the treatment of pain, it has been proven to be an effective and safe therapeutic option in adults.<sup>45</sup> Several studies have shown that the use of buprenorphine is effective in pain control in patients with chronic pain: such studies have

shown pain reduction, lower demand for breakthrough therapy, improvement of sleep and a high compliance to treatment with a general improvement in the quality of life associated with a lower incidence of side effects.<sup>46,47</sup>

Most studies on the use of buprenorphine in children concern cases of accidental ingestion and its use in the treatment of neonatal abstinence syndrome but, despite these limitations, the data seem to indicate that both the efficacy and safety of buprenorphine overlap in the paediatric population with those in adults.<sup>48</sup> In the past, buprenorphine was utilized in children mainly for acute postoperative pain, shown to be safe and effective regardless of the route of administration. It is currently used as a premedication under anaesthesia for postoperative, acute, and chronic pain and in palliative care as well as to treat opioid dependence in infants and adolescents.<sup>49</sup> The most utilized routes of administration are the intravenous, sublingual, spinal and transdermal ones, whilst the oral, subcutaneous, intranasal and rectal ones are less utilized. The parenteral route is mainly used for the management of acute pain (e.g. trauma in the emergency room) and for postoperative analgesia and has proven effective in pain relief, with an excellent safety profile in several adult and paediatric studies.<sup>50,51</sup> The epidural route was used for postoperative pain

**Figure 1. Mechanism of release and absorption of transdermal buprenorphine patch.**



The buprenorphine patch constantly releases drug particles that diffuse through the skin layer and are absorbed by the capillaries in the dermis. In this way, buprenorphine reaches systemic circulation without undergoing the first-pass metabolism in the liver.

control in association with bupivacaine or alone, with excellent analgesia and a longer duration of action.<sup>52,53</sup>

The sublingual formulation is not available in all countries and there are still insufficient data to assess its use in children. In a study by Massimo et al., the administration of sublingual buprenorphine in 13 paediatric patients with cancer provided good pain control in the absence of significant side effects. The dosage used was between 2.5 and 10 µg/kg every 12 hours with a defined satisfactory response at the dosage of 5 µg/kg.<sup>54</sup> Quirk et al. reported on a case of a 16-year-old patient who achieved good pain control with sublingual buprenorphine administration.<sup>55</sup>

The transdermal formulation is an ideal therapeutic tool for children for the complete absence of invasiveness and prolonged analgesia.<sup>56</sup> In several European countries, transdermal buprenorphine is available in three patches with different dosages releasing the drug 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 1.6 mg. In addition, due to their matrix structure, the patches can be cut into halves or quarters, thus obtaining a handy dose adjustment for younger patients. All patches have a duration of application of 72 hours, although a recent study has shown that plasma concentrations are kept stable even after 96 hours from application. In other countries (i.e. the United States and the United Kingdom), 5 µg/h and 10 µg/h formulations are available with a duration of application of 7 days.

Side effects are usually less frequent than those reported when other routes of administration are used, except for local

reactions, such as erythema and itching, which occur in 25% of cases but are reversible.

In the work of Ruggiero et al., in 11 out of 16 patients treated with transdermal buprenorphine at an initial dosage based on body weight ranging from 8.75 µg/h to 35 µg/h, there was an improvement in painful symptoms without evidence of relevant side effects.<sup>57</sup> Similar results were reported by Smyth et al. in 11 patients who achieved good pain relief, with negligible local side effects.<sup>58</sup>

## Conclusion

Buprenorphine has been proven to be effective in treating chronic neoplastic and non-neoplastic pain as well as neuropathic pain. Its pharmacological characteristics make it particularly safe due to the presence of a ceiling effect for respiratory depression, the lack of hyperalgesia, the low renal excretion, the minimal interaction with other drugs and the low incidence of side effects (nausea, constipation, itching).

In addition, the transdermal route is a non-invasive and easy-to-use method of administration in children that does not interfere with daily activities and overcomes the difficulties of swallowing in young patients. Therefore, transdermal buprenorphine is a valid option in the treatment of pain in paediatric patients; however, other studies are needed to confirm its safety and efficacy.

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