Buprenorphine and pain treatment in pediatric patients: an update

Erendira Vicencio-Rosas1
María Gabriela Pérez-Guillé2
Carmen Flores-Pérez2
Janett Flores-Pérez2
Francisca Trujillo-Jiménez2
Juan Luis Chávez-Pacheco2
1Anesthesiology Department, Hospital Regional de Alta Especialidad “Bicentenario de la Independencia”, ISSSTE, Tultitlán de Mariano Escobedo, México; 2Pharmacology Laboratory, Instituto Nacional de Pediatría, Ciudad de México, México

Introduction: The usual management of moderate to severe pain is based on the use of opioids. Buprenorphine (BPN) is an opioid with an analgesic potency 50 times greater than that of morphine. It is widely used in various pain models and has demonstrated efficacy and safety in adult patients; however, there are insufficient clinical trials in pediatric populations.

Purpose: The aim of this study was to perform an updated meta-analysis on the implementation of BPN in the treatment of pain in the pediatric population.

Methods: A bibliographic search was carried out in different biomedical databases to identify scientific papers and clinical trials with evidence of BPN use in children and adolescents.

Results: A total of 89 articles were found, of which 66 were selected. Analysis of these items revealed additional sources, and the final review included a total of 112 publications.

Conclusion: Few studies were found regarding the efficacy and safety of BPN use in children. In recent years, the use of this drug in the pediatric population has become widespread, so it is imperative to perform clinical trials and pharmacological and pharmacovigilance studies, which will allow researchers to develop dosage schemes based on the evidence and minimize the risk of adverse effects.

Keywords: buprenorphine, opioid, analgesia, child, adverse effects, pharmacokinetics

Introduction

Optimal pain treatment requires multimodal strategies based on the identification of the causal mechanisms and intensity to individualize treatment. Pain is defined as “an unpleasant sensory and emotional experience associated with real or potential tissue damage.”1,2

Pain is the most common health symptom during childhood and adolescence.3 Although the magnitude of the detrimental effects pain can have on a child is known, it is often inadequately evaluated and treated4,5 due to ignorance of the pathophysiological aspects of pain at this stage of life and limited clinical information on the use of certain drugs.6–8

Pain can be classified into acute and chronic pain. The former is defined as the expected normal physiological response to adverse chemical, mechanical, or thermal stimuli associated with surgery, trauma, or acute diseases.9 Over 80% of adult patients undergoing surgical procedures experience acute postoperative pain of moderate to severe intensity (75% of cases).10 In children, the prevalence of postoperative pain is reported in up to 50% of cases11 of which up to 20% develop postsurgical chronic pain.12 Chronic pain can be caused by a variety of conditions. Chronic pain is the main
symptom experienced by children with cancer and occurs in at least 89% of patients in advanced stages of this disease.\textsuperscript{13,14} Analgesic therapy established by the World Health Organization (WHO) aims to keep pediatric patients calm and free of pain and provides pharmacotherapeutic strategies based on their intensity and pathologic condition.\textsuperscript{15–17}

The recommendation for the use of analgesics is as follows:

1. non-opioid analgesics (paracetamol and anti-inflammatory drugs);
2. opioids (morphine, methadone, hydromorphone, buprenorphine [BPN], fentanyl and oxycodone);
3. local anesthetics (lidocaine, bupivacaine and ropivacaine); and
4. adjuvant analgesics (anticonvulsants, antidepressants, corticosteroids and ketamine).

Opioids are an important tool for treating moderate to severe persistent pain. Approximately 60%–90% of children in palliative care will receive this type of medication.\textsuperscript{18}

BPN is a semisynthetic opioid developed in the 1960s\textsuperscript{19} and, although not the first line treatment for pain, has proven to be a good analgesic with prolonged effect.\textsuperscript{20} In the 1980s, the US Food and Drug Administration authorized intravenous (IV) BPN administration, and subsequently other dosage forms were developed (Figure 1). In the 40 years of BPN use, there has been little information regarding its use and pharmacokinetics (PK) in children, especially in the treatment of chronic pain.

The aim of this study was to conduct an updated meta-analysis on the implementation of BPN in the treatment of pain in the pediatric population.

Methods

A search was performed on biomedical databases, The Cochrane Database of Systematic Reviews, EMBASE, MEDLINE (PubMed and Ovid), Scopus, KoreaMed, National Library of Australia, and LILACS, to identify articles concerning the use of BPN in children and adolescents. No time or language restrictions were applied.

The Medical Subject Headings terms used were as follows: BPN, pain, child, neonates, infant, adolescent, analgesia, pharmacokinetics, pharmacodynamics, adverse reaction, transdermal patch, sublingual, intravenous administration, and infusion intravenous.

The search in all databases yielded 89 results, duplicates and articles that after a critical reading were considered not relevant were eliminated, yielding 66 documents. From these sources, additional items were identified. The final review was performed with a total of 112 publications.

Pharmacological properties

BPN is a semisynthetic opioid derived from thebaine, with an antinociceptive effect 30–50 times more powerful than morphine.\textsuperscript{21} In trials, intramuscularly administered BPN has 25 times more potency than intramuscular (IM) morphine and sublingual (SL) administration is 15 times more potent than IM morphine.\textsuperscript{28}

BPN’s chemical structure is basically that of an opioid with multiple chiral centers. However, a tert-butyl group in carbon position 7 contributes to its lipophilicity. BPN has a low molecular weight (467.64 g/mol) and is a base with a pKa between 8.2 and 10.0 and a melting point of 218°C.\textsuperscript{27,29} BPN’s physicochemical properties favor tissue penetration in both transdermal and transmucosal formulations.\textsuperscript{29,30}

BPN is a centrally acting analgesic that binds to opioid receptors\textsuperscript{19,31} to generate inhibition of the transmission of nociceptive impulses from the periphery to the spinal cord and activation of downstream pathways inhibitory modulating pain transmission. In addition, BPN can modify activity in the limbic system (affective and sensory-discriminative components).\textsuperscript{32–34}
BPN’s pharmacological profile has not been fully resolved, since the union of BPN and the opioid receptor is high but not selective. Differences in the profile have been observed depending on the model (animal, human), conditions (in vitro/in vivo), and experimental model (pain, dependence, or respiratory depression). This finding has resulted in misconceptions that have limited the clinical utility in certain population groups.

**Pharmacokinetics**

Drug absorption is dependent on the route of administration and BPN can cross the blood–brain barrier and placenta. Parenteral administration generates brain concentrations 2–3 times greater than those achieved by oral administration. Some studies in rats indicate that BPN is rapidly distributed in the brain after IV administration. Due to its polarity, the metabolite norbuprenorphine rapidly penetrates the central nervous system (CNS) without modification.

BPN has high affinity for globulins type α and β (95%–98%) and poor binding to albumin. It possesses extensive first pass metabolism in the gut wall and the liver, primarily by cytochromes CYP3A4 and 3A5 (65%), CYP2C8 (30%), and with less active CYP2C9, CYP2C18, and CYP2C19. Cytochromes P450 (CYPs) transform BPN via N-dealkylation into norbuprenorphine (active metabolite). CYP3A4 may also catalyze hydroxylation of both compounds to generate hydroxybuprenorphine and hydroxynorbuprenorphine. Moreover, the uridine diphosphate glucuronosyltransferases (UGT1A1 and UGT2B7) perform glucuronidation to obtain the inactive metabolites BPN-3-glucuronide and norbuprenorphine-3-glucuronide. It is known that the maximum plasma norbuprenorphine concentrations are equal to or higher than BPN concentrations.

![Figure 2 Metabolism of BPN.](https://doi.org/10.1016/j.jpain.2018.09.010)
BPN is excreted in an unaltered or N-dealkylated form in the feces (50%–71%) and urine (10%–17%), which favors its administration in patients with renal failure. This drug can be used in elderly patients because the PK is not affected by age. It is also a safe opioid in patients with mild to moderate liver failure and does not require dosage adjustment. The plasma elimination of BPN follows a multi-exponential curve with a half-life of ~3–5 hours in postoperative patients. Its agonist and antagonist properties are related to the dosage and administration route.

**Pharmacokinetic parameters in adults**

These values are dictated by the administration route as follows.

**Intravenous**
Absorption is immediate with 100% bioavailability. The maximum plasma concentration (Cmax) is reached in 2–5 minutes. Elimination has a rapid phase half-life (t1/2a) of 2–5 minutes, followed by a redistribution time (t1/2b) of 20–30 minutes, and a slow phase time (t1/2δ) from 2 to 3 hours.

**Oral**
Absorption is very low due to extensive first pass metabolism, with 10%–16% bioavailability. BPN tablets produce plasma levels of 50% compared to those achieved with liquid preparations.

**Sublingual**
Absorption is rapid, with variable bioavailability of 30%–60% due to protein binding and interindividual variability. Cmax is reached at 2 hours. Plasma concentrations fall rapidly in the first 6 hours, then a gradual decrease is observed for 24 hours. Tmax is variable in healthy volunteers; doses of 0.4 and 0.8 mg (drops) give Tmax values of 30 and 60 minutes, respectively. The same doses in sublingual tablets have Tmax values of 90 and 360 minutes, respectively.

**Transdermal**
Distribution is rapid in nerve tissue, with 5% bioavailability. The administration in patches containing 20 and 40 mg (release rate of 35 and 70 mg/h) shows that the minimum effective concentration (100 pg/mL) is reached at 21 and 11 hours after patch application, respectively.

In another trial, the administration of a patch containing 20 mg (35 µg/h) achieved a Cmax of 300 pg/L and Tmax at 60 hours. The area under the curve was 20.22 pg/h. No differences were observed in PK parameters in patients with renal failure nor were there parameter changes in older adults.

**Intranasal**
The intranasal formulation is fast acting, with 50% bioavailability and a Tmax of 30 minutes. Lipophilic drugs such as BPN are generally well absorbed from the nasal mucosa and have PK profiles such as those obtained by IV administration. This formulation is interesting for the treatment of irruptive cancer pain. The intranasal formulation is currently under development and has been used only in animal models and healthy volunteers.

**Pharmacokinetic parameters in children**
The PK of this drug has been described using a model of two or three compartments. In children, there is limited information regarding the estimation of PK parameters. The first study used allometric pediatric models to estimate parameters in children older than 2 years using the PK parameters of adult patients.

In a 1989 study, BPN was administered intravenously at a premedication dose of 3 µg/kg among patients undergoing minor surgery (4.6–7.5 years). The PK showed a bi-exponential behavior (due to enterohepatic recirculation) with two half-lives, a quick half-life at 5 minutes and a slow half-life at 62 minutes. The mean clearance was 60 mL/min/kg and a volume of distribution at steady state was in the range of 1.2–8.3 L/kg. No correlation was found between the PK parameters and age, weight, or body surface area. The average clearance is three times higher in children than adults; this is because the liver/body weight ratio is greater in children. The values of the volume of distribution at steady state were similar in both populations. The author concluded that because the BPN clearance is higher in children than in adults, there are no contraindications for BPN use as an analgesic in children. A comparison of the PK values in adults and children is shown in Table 1.

In contrast, a study in preterm infants (27–32 weeks gestational age) receiving BPN at 0.72 µg/kg/h by continuous infusion concluded that this administration route does not provide stable sedation or analgesia and, therefore, its use is not recommended. Further, in this population the clearance is reduced due to the immaturity of glucuronidation systems.

**Pharmacodynamics**
BPN is a partial mu receptor agonist, partial or complete opioid receptor-like 1 (ORL1) agonist, and kappa and delta receptors antagonist, characterized by a lasting action.
associated with a slow dissociation from the receptor and low intrinsic activity in in vitro assays. These properties allow BPN to displace other mu-agonists and explain its therapeutic effect on opioid dependence. In contrast to the full mu receptor agonists, BPN has a pronounced anti-hyperalgesic effect and does not cause internalization of opioid receptors which decreases the possibility of inducing tolerance or dependence.

BPN is a potent opioid in low doses, but at higher doses it has a relative decreased potency, which is a feature of partial opioid agonists. In adults, BPN has a ceiling effect on respiratory depression but not in analgesia. The dose for the ceiling effect relates to the partial agonist activity of the receptors mu and ORL1. It is thought that the supraspinal component of the antinociception induced by BPN is not mediated by the opioid mu response, but by unique receptors.

BPN’s effects on ventilation are controversial. Hovell and Banks have reported that BPN has little effect on adult patients, but other authors report ventilator depression as with morphine. The magnitude of this respiratory effect is variable and independent of the interaction with the mu receptor. BPN ceiling effect in children is controversial and not well defined. It is known that the opioid interaction with the mu receptor can depress respiration; this side effect is variable and dependent of different factors such as genetics, age, sex, concomitant medication, and others. In fact, BPN and its active metabolite norbuprenorphine exhibit a respiratory depressant activity.

In previous studies performed by Dahan et al, they observed a nonlinear dose/response relationship, with a ceiling at above 0.1 mg/kg doses and a moderate increase of PaCO₂, providing lower rates of respiratory depression than other opioids, such as fentanyl. Further, they found that BPN’s analgesic effect increased significantly using two different doses, while the respiratory depression was similar in magnitude for both doses. They concluded that “over the dose range tested buprenorphine displays ceiling in respiratory effect but none in analgesic effect.”

The effective analgesic action of BPN is achieved with a relatively low occupancy of receptors (5%–10%). As a result, the analgesia degree is not closely correlated with plasma concentrations. Therapeutic concentrations between 100 and 500 pg/mL are enough to relieve moderate to severe pain.

### Pharmaceutical forms and administration

BPN is marketed in the form of SL tablets, tablets, an injectable solution, a transdermal patch, and an oral film. The administration routes described for the pediatric population are IV; IM; SL; subcutaneous; and neuraxial (peridural/caudal). Other routes of administration are intraarticular and intranasal; however, there is no clinical evidence of these uses in children.

In recent years, the use of a transdermal patch has been evaluated, although in children its safety and efficacy have not been well established. Several case reports have proved that the patch is useful in palliative care patients with pain associated with cancer at doses ranging from 7.5 to 52.5 μg/h.

Böhme notes that chronic pain patients treated with transdermal BPN could reduce the total consumption of SL tablets per day by almost 70%, and 50% of cases experienced relief of their severe pain. The highlighted advantages of the transdermal patch are the constant supply of active substance, painless administration, and greater comfort for the patient, all of which have a positive impact on the quality of life.

The transdermal system utilizes a matrix technology, and it is available in patches containing 5, 10, 20, 30, and 40 mg of BPN, with release rates of 5, 10, 35, 52.5, and 70 μg/h, respectively. The diversity of presentations allows an

### Table 1 Pharmacokinetic parameters in different pharmaceutical forms

| Pharmacokinetic parameters | Pharmaceutical forms | Adults | Children | Adults | Children | Adults | Children |
|----------------------------|-----------------------|--------|----------|--------|----------|--------|----------|
| Bioavailability (%)        | Intravenous           | 100    | 100      | 30–60   | 30–55    | 300    | 500      |
| Cmax (ng/mL)               | Sublingual            | 18.1±1.45 | 30–180   | 90–360  | 600–1260 |
| Tmax (min)                 | Transdermal           | 2–5    | 30–180   | 90–360  | 3600    | 660–1260 |
| T1/2 (h)                   |                       | 3.6±0.64 | 1.0±0.2  | 25.3±1  | 20±8    |
| Cl (mL/min kg)             |                       | 18.2±1.2 | 50      | 18.2±1.2 | 50      |
| Vss (L/kg)                 |                       | 2.7±0.5  | 3.2±2  | 2.7±0.5  | 3.2±2  |

Note: Pharmacokinetic values obtained in clinical studies for adults and children.

Abbreviations: Cmax, maximum plasmatic concentration; Tmax, time to obtain Cmax; T1/2, half-life for buprenorphine; Cl, clearance total; Vss, volume of distribution at steady state.
adequate dose to be administered without cutting the patch. This is a promising therapy in the treatment of chronic pain in children. Dosage regimens used to control pain in children are described in Table 2.

Drug interactions

The main drug interactions can be divided into mild and severe (Table 3). BPN interacts with drugs that cause CNS depression, increasing the risk of overdose.23 The mechanism of interaction is probably due to additive or synergistic pharmacological effects. Preclinical studies also suggest that benzodiazepines may alter the ceiling effect of respiratory depression induced by BPN.87

BPN and its major metabolites cause inhibition of CYP2D6 and CYP3A4; however, this effect is not clinically relevant at therapeutic concentrations with other drugs metabolized by CYP450. Drugs that interfere with CYP3A4, such as erythromycin, ketoconazole, and inhibitors of HIV protease (ritonavir, indinavir, saquinavir) may decrease norbuprenorphine production.76

Although 96% of BPN is bound to plasma proteins, there is no competition with transport proteins in the plasma, as BPN binds primarily to globulins α/β.35

Coadministration of BPN with other drugs that prolong QT interval may result in additive effects and increase the risk of ventricular arrhythmias and sudden death. Patients with congenital long QT syndrome, conduction abnormalities, or electrolyte abnormalities (eg, loss of magnesium or potassium due to diarrhea or vomiting) are more susceptible to such interactions.83,84

When starting BPN administration, it is advisable to prescribe the lowest effective doses and a drug administration at the minimum required, especially in patients receiving another CNS depressant. Close monitoring is also recommended.

Adverse drug reactions

Opioids definitively improve the quality of life among patients with pain; however, the use of these drugs has been limited by fears about safety and tolerability. Adverse reactions with opioids occur in up to 80% of cases, mainly affecting the gastrointestinal tract (30%) and, to a lesser extent, the other organs and systems.97

The mild or moderate adverse effects most frequently observed are constipation (25%), somnolence (23%), nausea (21%), dry mouth (17%), and symptoms of vomiting.

Table 2 Dosage and administration routes of buprenorphine in the pediatric population

| Dosage form                        | Route      | Indications                          | Recommended dose | Age (years) |
|-----------------------------------|------------|--------------------------------------|------------------|-------------|
| Injectable solution               | IV         | Premedication                        | 1.5–3 µg/kg      | 3–1777      |
| (0.3 mg buprenorphine hydrochloride) | PCA        | Chronic pain in palliative care      | 3 µg/kg          | >0.5*       |
|                                   |            | Postoperative analgesia              | (max 150 µg)    | >0.5*       |
|                                   |            | Chronic pain                         | 0.72–2.16 µg/kg/h | 27–32 WGA55 |
|                                   |            | Pain in palliative care              | 0.5 µg/kg/h      | >0.5*       |
|                                   |            | (max 30 mg/h)                        | (max 30 µg/h)    | >0.5*       |
|                                   | SC         | Postoperative analgesia              | 2.5–4 µg/kg      | 11.0178     |
|                                   | Epidural   | Postoperative analgesia              | 4–200 µg/kg      | >0.5*       |
|                                   | Sublingual | Premedication                        | 3 µg/kg          | 4.8–1551    |
| (0.2 mg buprenorphine hydrochloride) | TDS        | Chronic pain                         | 4–200 µg/kg      | >0.5*       |
|                                   | TDS        | Postoperative analgesia              | 17.5 µg/h        | 3–5*        |
|                                   | TDS        | Chronic pain in palliative care      | 35 µg/h          | 2–1799      |
|                                   | TDS        | Start: 8.75 µg/h                     | 35 µg/h          | 5–15 µg/h   |
|                                   | TDS        | End: 17.5 µg/h                       | 3–1092           |

Abbreviations: IV, intravenous; PCA, patient-controlled administration; CI, continuous infusion; SC, subcutaneous; SL, sublingual; TDS, transdermal delivery system; WGA, week gestational age; max, single maximal dose at the start of continuous infusion.
Dizziness, and anorexia (together adding up to 13%). Other effects such as fatigue, diarrhea, insomnia, respiratory depression, and hallucinations add up to ≤5%.98

Transdermal administration causes less adverse reactions than other dosage forms, and there are reports of local erythema (25.4%), local pruritus (22%), nausea (1%–16.7%), vomiting (3.7%–9.3%), dizziness (6.8%), fatigue (5.6%), constipation (5.3%–7.8%), sweating (3.7%), somnolence (4%), and headache (1.3%). Swelling and infection at the site of application have been recorded in isolated cases.19,51,75,99,100 Most side effects at the patch application site are mild or moderate and generally transient.76

Epidural BPN administration considerably increased nausea and vomiting events (80%) and slightly increased urinary retention (10%) during the postoperative period.80 Symptoms of mild hypotension were also observed in 1%–5% of patients.22

Data regarding respiratory depression in children are rare. Side effects reported in studies comparing BPN and morphine show that nausea/vomiting occurs in 28% of patients taking BPN versus 16% taking morphine; and urinary retention occurs in 21% of patients taking BPN versus 19% taking morphine. This study did not report the effects on ventilation and BPN was considered safer than morphine in this population.101

Respiratory depression induced by BPN can be reversed by administering continuous naloxone infusion (4 mg/h for 30 minutes), with minimal possibility of renarcotization.102 Other reports suggest that 0.04–0.10 mg/kg doses of naloxone (maximum 5 mg) successfully reverse the respiratory depression induced by BPN.103–106

After the abrupt discontinuation of BPN therapy, patients may experience withdrawal symptoms, which are milder than the symptoms associated with other opioids. The possibility of tolerance after short-term treatment is minimal.108

No hepatic adverse effects have been reported in individuals receiving BPN at analgesic doses.23 In patients with prolonged therapy (1–2 months), effects such as decreases in erythrocytes number, hemoglobin, hematocrit, and total protein concentration have been observed, which reversed after stopping treatment.107

Discussion

The analgesic efficacy of potent opioids such as morphine is well established, and indirect evidence supports opioid use in children and their inclusion in the WHO Model List of Essential Medicines.16

Opioids are the basis for the treatment of moderate to severe pain in pediatrics. Although BPN is not the first line of treatment for various pain models, it has been proven to be an effective and safe treatment option for adults.

Due to the vulnerability of the pediatric population and the costs and challenges of conducting clinical studies in children, the current dosage regimen results cannot ensure optimum efficiency and minimal toxicity in these patients.108

| Table 3 BPN pharmacological interactions |
|------------------|------------------|------------------|
| **Drug**        | **Effect**                          | **Management**               |
| **Severe interactions** |                                     |                               |
| Benzodiazepines, muscle relaxants, anesthetics, antipsychotics, alcohol and opioids | Increases the risk of BPN overdose, hypotension, respiratory depression, coma, and death | Coadministration of these drugs should be avoided                        |
| Pregabalin      | Increases the risk of BPN overdose, hypotension, respiratory depression, coma, and death. Alters the usual ceiling effect on respiratory depression induced by BPN | Coadministration with BPN should be avoided                              |
| Escitalopram    | Increases the risk of a life-threatening irregular heart rhythm | Caution is advised                                      |
| **Moderate interactions** |                                     |                               |
| Albuterol       | Increases the risk of an irregular heart rhythm, which can be serious and fatal; however, this is a rare side effect | Avoid concomitant use                                      |
| Duloxetine      | Dizziness, drowsiness, confusion, and difficulty in concentrating | Coadministration should be avoided                             |
| Fluoxetine      | Dizziness, drowsiness, confusion, and difficulty in concentrating. Norfluoxetine (active metabolite) inhibits BPN dealkylation | During concomitant use, dosage adjustment may be necessary         |
| Quetiapine      | Increases the risk of an irregular heart rhythm, which can be serious and life threatening, but is rare | Caution and clinical monitoring if concomitant use is required      |
| Laxatives (Senna) | Irregular heartbeat, which can be severe and life threatening, but is rare | Caution in coadministration                                      |

Abbreviations: BPN, buprenorphine; CNS, central nervous system.
Data provided by the American Association of Poison Control Centers show that cases of accidental ingestion of BPN in children under 6 years have increased from only two in 2002 to 907 cases in 2008.\textsuperscript{109,110} This finding reveals a public health problem and reflects the risk of exposure at home when a family member is using this drug.

A retrospective analysis (3 years) of overdoses in children under 6 years (54 cases) showed that the observed effects included drowsiness/lethargy (55%), vomiting (21%), miosis (21%), respiratory depression (7%), agitation/irritability (5%), and colonic symptoms (2%). No deaths were reported. All children required hospitalization, treatment with opioid antagonists, and/or mechanical ventilation. The study concluded that ingestion of <4 mg of BPN did not cause severe effects and overdoses are generally well tolerated in children.\textsuperscript{111}

Compared to adults, BPN in children has a longer clearance related to body weight and a longer duration of action. The risk of inducing respiratory depression when using BPN in combination with other centrally active drugs or opiates is still unknown.\textsuperscript{33}

As mentioned earlier, BPN is a drug of clinical interest in pediatrics and it is a choice to consider because of its various formulations and routes of application. BPN also has a prolonged duration of action and metabolism independent of renal function,\textsuperscript{33} which is advantageous in controlling postoperative pain\textsuperscript{61,80} and neuropathic pain. Furthermore, at analgesic doses, BPN has no effect on the immune system,\textsuperscript{19,112} which can be important for cancer pain treatment.

**Conclusion**

This meta-analysis makes it clear that there are few studies demonstrating the efficacy and safety of BPN use in children. In recent years, this drug has become widespread in the pediatric population; thus, performing controlled clinical trials in this population for adequate pain control is recommended.

Likewise, conducting pharmacological and biosafety studies to develop evidence-based dosing regimens and thereby minimize the risk of adverse effects is a priority.

**Acknowledgments**

We thank Instituto Nacional de Pediatría (INP) and the Pharmacology Laboratory for the federal funding assigned to the project INP-031/2016.

**Author contributions**

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. Loeser JD, Treede RD. The Kyoto protocol of IASP basic pain terminology. Pain. 2008;137(3):473–477.
2. International Association for the Study of Pain. Taxonomy. Available from: https://www.iasp-pain.org/Taxonomy?navItemNumber=576#Pain. Accessed July 20, 2017.
3. Hartling L, Ali S, Dryden DM, et al. How safe are common analgesics for the treatment of acute pain for children? A systematic review. Pain Res Manag. 2016;2016:5346819.
4. American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health; Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics. 2001;108(3):793–797.
5. Goldschneider K, Anand K. Long-term consequences of pain in neonates. In: Schechter N, Berde C, Yaster M, editors. Pain in Infants, Children and Adolescents. New York, NY: Lippincott Williams & Wilkins; 2003:58–70.
6. Mercadante S. Cancer pain management in children. Palliat Med. 2004;18(7):654–662.
7. Mercadante S, Giarratano A. Pharmacological management of cancer pain in children. Crit Rev Oncol Hematol. 2014;91(1):93–97.
8. Berde C, Solodiuk J. Multidisciplinary programs for management of acute and chronic pain in children. In: Schechter N, Berde C, Yaster M, editors. Pain in Infants, Children and Adolescents. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:471–486.
9. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353(9169):2051–2058.
10. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists’ committee on regional anesthesia, executive committee, and administrative council. J Pain. 2016;17(2):131–157.
11. Groenewald CB, Rabbitts JA, Schroeder DR, Harrison TE. Prevalence of moderate-severe pain in hospitalized children. Paediatr Anaesth. 2012;22(7):661–668.
12. Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: a systematic review and meta-analysis. J Pain. 2017;18(6):605–614.
13. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009;10(2):113–130.
14. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. J Pain. 2010;11(11):1230–1239.
15. Maunusela EL, Korpela R, Ollkola KT. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain of children. Br J Anaesth. 1988;60(1):48–55.
16. WHO. Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. Geneva: WHO; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK138534. Accessed May 7, 2017.
17. Zernikow B, Smale H, Michel E, Hasan C, Jorch N, Andler W. Paediatric cancer pain management using the WHO analgesic ladder—results of a prospective analysis from 2265 treatment days during a quality improvement study. Eur J Pain. 2006;10(7):587–595.
18. Zernikow B, Michel E, Craig F, Anderson BJ. Pediatric palliative care: use of opioids for the management of pain. Paediatr Drugs. 2009;11(2):129–151.
19. Davis MP. Buprenorphine in cancer pain. Support Care Cancer. 2005;13(11):878–887.
20. Tigerstedt I, Tammisto T. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. Acta Anaesthesiol Scand. 1980;24(6):462–468.
21. Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann NY Acad Sci.* 2012;1248:124–139.

22. Valderrama JC, Martínez-Raga J, Sancho A, La Buprenorfina [The buprenorphine]. *Trastornos Addictivos.* 2000;2(2):94–98. Spanish.

23. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *J Pain Symptom Manage.* 2005;29(3):297–326.

24. Likar R. Transdermal buprenorphine in the management of persistent pain—safety aspects. *Ther Clin Risk Manag.* 2006;2(1):115–125.

25. Chapleo CB, Crossley DJ. Terapias de buprenorfina para el tratamiento de la dependencia a opiáceos (Subutex® y Suboxone®) [Buprenorphine therapies for the treatment of opioid dependence (Subutex® and Suboxone®)]. *Trastornos Addictivos.* 2003;5(4):320–328. Spanish.

26. Pergolizzi J Jr, Taylor R Jr, Plancarte R, Bashkansky D, Muniz E. Buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations in chronic pain patients treated with transdermal buprenorphine. *Eur J Pain.* 2006;10(8):743–748.

27. Ikeda P, Kaya H, Sittl R. Long-term management of chronic pain with transdermal buprenorphine: a multicenter, open-label, follow-up study in patients from three short-term clinical trials. *Clin Ther.* 2006;28(6):943–952.

28. Br J Clin Pharmacol. 1989;28(2):202–204.

29. Br J Clin Pharmacol. 1989;28(2):202–204.

30. Oikolka KT, Maunukela EL, Korpela R. Pharmacokinetics of intravenous buprenorphine in children. *Br J Clin Pharmacol.* 1986;28(11):2000–2009.

31. Br J Clin Pharmacol. 1989;28(2):202–204.

32. Br J Clin Pharmacol. 1989;28(2):202–204.

33. Br J Clin Pharmacol. 1989;28(2):202–204.

34. Br J Clin Pharmacol. 1989;28(2):202–204.

35. Br J Clin Pharmacol. 1989;28(2):202–204.

36. Br J Clin Pharmacol. 1989;28(2):202–204.

37. Br J Clin Pharmacol. 1989;28(2):202–204.

38. Br J Clin Pharmacol. 1989;28(2):202–204.

39. Br J Clin Pharmacol. 1989;28(2):202–204.

40. Br J Clin Pharmacol. 1989;28(2):202–204.

41. Br J Clin Pharmacol. 1989;28(2):202–204.

42. Br J Clin Pharmacol. 1989;28(2):202–204.

43. Br J Clin Pharmacol. 1989;28(2):202–204.

44. Br J Clin Pharmacol. 1989;28(2):202–204.

45. Br J Clin Pharmacol. 1989;28(2):202–204.

46. Br J Clin Pharmacol. 1989;28(2):202–204.
65. Lufty K, Eitan S, Bryant CD, et al. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *J Neurosci.* 2003;23(32):10331–10337.

66. Hovell BC. Comparison of buprenorphine, pethidine and pentazocine for the relief of pain after operation. *Br J Anaesth.* 1977;49(9):913–916.

67. Banks CD. Overdose of buprenorphine: case report. *N Z Med J.* 1979;89(633):255–257.

68. Kamel MM, Geddes IC. A comparison of buprenorphine and pethidine for immediate postoperative pain relief by the i.v. route. *Br J Anaesth.* 1978;50(6):599–603.

69. Dahan A, Teppema LJ. Influence of anaesthesia and analgesia on the control of breathing. *Br J Anaesth.* 2003;91(1):40–49.

70. Dahan A, Yassen A, Bija H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth.* 2005;94(6):825–834.

71. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth.* 2006;96(5):627–632.

72. Hambrook JM, Rance MJ. The interaction of buprenorphine with the opiate receptor: lipophilicity as a determining factor in drug-receptor kinetics. In: Kosteritz HW, editor. *Opiates and Endogenous Opioid Peptides*. Amsterdam: Elsevier/North Holland Biomedical Press; 1976:295–301.

73. Drugs.com. Butrans patch. Available from: http://www.drugs.com/pro/butrans-patch.html. Accessed July 20, 2017.

74. Attinà G, Ruggiero A, Maurizi P, Arlotta A, Chiaretti A, Riccardi R. Transdermal buprenorphine in children with cancer-related pain. *Pediatr Blood Cancer.* 2009;52(1):125–127.

75. Böhme K. Buprenorphine in a transdermal therapeutic system—a new option. *Clin Rheumatol.* 2002;21(Suppl 1):S13–S16.

76. Kress HG. Clinical update on the pharmacology, efficacy and safety of intramuscular buprenorphine. *Eur J Pain.* 2012;16(3):278–289.

77. Ferguson GT, Funck-Brentano C, Fischer T, Darken P, Reisner C. Cardiovascular safety of salometrol in COPD. *Chest.* 2003;123(6):1817–1824.

78. Girotra S, Kumar S, Rajendran KM. Postoperative analgesia in children following caudal bupivacaine and buprenorphine—a comparative study. *J Postgrad Med.* 1994;40(2):61–64.

79. Banks CD. Buprenorphine/naloxone: a case review. *J Emerg Nurs.* 2001;27(5):303–309.

80. Kamel MM, Geddes IC. A comparison of buprenorphine and pethidine for immediate postoperative pain relief by the i.v. route. *Br J Anaesth.* 1978;50(6):599–603.

81. Dahan A, Yassen A, Bija H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth.* 2005;94(6):825–834.

82. Hovell BC. Comparison of buprenorphine, pethidine and pentazocine for the relief of pain after operation. *Br J Anaesth.* 1977;49(9):913–916.

83. Keller GA, Ponte ML, Di Girolamo G. Other drugs acting on nervous system associated with QT-interval prolongation. *Clin J Pain.* 2012;28(8):722–725.

84. Kalso E, Edwards JE, Moore RA, McCay JJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372–380.

85. Scott DH, Arthur GR, Scott DB. Haemodynamic changes following ingestion in an infant. *Ann Emerg Med.* 2006;48(1):109.

86. Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodeone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. *Cochrane Database Syst Rev.* 2014;5:CDO10156.

87. Muriel C, Failde I, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. *Curr Med Res Opin.* 2005;21(8):1147–1156.

88. Lemberger L, Failde I, Micó JA, Neira M, Sanchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther.* 2005;27(4):451–462.

89. Plushner SL. Adverse effects of laxatives: fact and fiction. *Pharmacology.* 1993;47(Suppl 1):138–145.

90. Muller-Lissner SA. New generation antipsychotic drugs and QTc interval prolongation. *Prim Care Companion J Clin Psychiatry.* 2003;5(5):205–215.

91. Ferguson GT, Funck-Brentano C, Fischer T, Darken P, Reisner C. Cardiovascular safety of salometrol in COPD. *Chest.* 2003;123(6):1817–1824.

92. Plushner SL. Valerian: Valeriana officinalis. *Clin Ther.* 2006;28(8):722–725.

93. Lemberger L, Rowe H, Bosomworth JC, Tenbarge JB, Bergstrom RF. Use of buprenorphine in children with chronic pseudoobstruction of the colon following pelvic surgery. *Clin J Pain.* 2012;28(8):722–725.

94. Vieweg WV. New generation antipsychotic drugs and QTc interval prolongation. *Prim Care Companion J Clin Psychiatry.* 2003;5(5):205–215.

95. Pedapati EV, Bateman ST. Toddlers requiring pediatric intensive care unit admission following at-home exposure to buprenorphine/naloxone. *Pediatr Crit Care Med.* 2011;12(2):e102–e107.

96. Plushner SL. Valerian: Valeriana officinalis. *Clin Ther.* 2006;28(8):722–725.

97. Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. *Cochrane Database Syst Rev.* 2014;5:CDO10156.

98. Muriel C, Failde I, Micó JA, Neira M, Sanchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther.* 2005;27(4):451–462.

99. Maunuksela EL, Korpela R, Oiklolkka KT. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth Analg.* 1988;67(3):233–239.

100. Muriel C, Failde I, Micó JA, Neira M, Sanchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther.* 2005;27(4):451–462.

101. Maunuksela EL, Korpela R, Oiklolkka KT. Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth Analg.* 1988;67(3):233–239.

102. Dahan A, Aarts L, Smith TW. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112(1):226–238.

103. Pedapati EV, Bateman ST. Toddlers requiring pediatric intensive care unit admission following at-home exposure to buprenorphine/naloxone. *Pediatr Crit Care Med.* 2011;12(2):e102–e107.

104. Cho CS, Calello DP, Osterhoudt KC. Exploratory buprenorphine ingestion in an infant. *Ann Emerg Med.* 2006;48(1):109.

105. Landry L, Ji Z, O'Neal A, et al. Ondansetron reduces the incidence of opioid-related side effects in children following caudal bupivacaine and buprenorphine. *Pediatric Anaesthesia.* 2005;15(9):1468–1475.

106. Martin HA. The possible consequences of combining lorazepam and buprenorphine/naloxone: a case review. *J Emerg Nurs.* 2011;37(2):200–202.

107. Landsverk AL, Horsley DS, Rodríguez R, et al. Opioid polytherapy: a post-marketing surveillance study in 13,179 patients. *Clin Ther.* 2006;28(8):722–725.

108. Kalso E, Edwards JE, Moore RA, McCay JJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372–380.

109. Wiffen PJ, Derry S, Moore RA. Impact of morphine, fentanyl, oxycodone or codeine on patient consciousness, appetite and thirst when used to treat cancer pain. *Cochrane Database Syst Rev.* 2014;5:CDO10156.

110. Muriel C, Failde I, Micó JA, Neira M, Sanchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter, open-label, uncontrolled, prospective, observational clinical study. *Clin Ther.* 2005;27(4):451–462.
109. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict.* 2010;19(1):89–95.

110. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Dart RC. 2010 Annual report of the American Association of Poison Control Centers’ national poison data system (NPDS): 28th annual report. *Clin Toxicol (Phila).* 2011;49(10):910–941.

111. Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. *Pediatrics.* 2008;121(4):e782–e786.

112. Gomez-Flores R, Weber RJ. Differential effects of buprenorphine and morphine on immune and neuroendocrine functions following acute administration in the rat mesencephalon periaqueductal gray. *Immunopharmacology.* 2000;48(2):145–156.