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Commentary

The clinical analgesic efficacy of buprenorphine

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SUMMARY

What is known and objective: **Based on *in vitro* assays and select animal models, buprenorphine is commonly called a 'partial agonist'. An implication is that it should produce less analgesic effect in humans than so-called 'full agonists' such as morphine or fentanyl. However, buprenorphine has a multimechanistic pharmacology, and thus partial agonism at a specific receptor is not particularly relevant to its overall analgesic action. We review published clinical trials that directly compared the magnitude of buprenorphine's analgesic effect to analgesics commonly considered full agonists.**

Comment: **Due to different signal transduction pathways, a drug can be a full agonist on one endpoint and a partial agonist on another. Therefore, we limited the present review to buprenorphine's analgesic effect.**

What is new and conclusion: **Twenty-four controlled clinical trials were identified, plus a case report and dose–response curve. Based on complete or comparable pain relief, in buprenorphine had full clinical analgesic efficacy in 25 of the 26 studies.**

WHAT IS KNOWN AND OBJECTIVE

Buprenorphine is a centrally acting analgesic. It was first synthesized in 1966 and has been demonstrated to have antinociceptive and analgesic activity[1,2] against a wide variety of pains, including nociceptive, musculoskeletal, neuropathic and cancer-related[3] pains. Buprenorphine's oral absorption is limited, but its bioavailability is greater by other routes, and its physiochemical properties make it particularly well suited for use in transdermal 'patch' formulations.[4]

Buprenorphine's mechanism of action has previously been described[5–8] as has its clinical characteristics that warrant its consideration as a first-line analgesic.[9] However, the basis for its classification as a 'partial agonist' has undergone much less scrutiny. We focus on the single issue of whether buprenorphine produces the same or different clinical analgesic efficacy as analgesics considered to be full agonists.

When a drug is characterized as a 'full' or 'partial' agonist based primarily on *in vitro* assays, it can confuse the related, but distinct, pharmacologic principles of affinity and intrinsic activity (properties at the receptor level) and efficacy (manifested at a particular endpoint). 'Affinity' is the thermodynamically driven chemical attraction between a drug and a receptor[10]; 'intrinsic activity' is the biological stimulus imparted by a drug to a receptor[11]; and 'efficacy' relates to the level of drug-induced effect *in a given application*. Unfortunately, in certain contexts, the term 'efficacy' has sometimes been loosely used as if it is a fundamental property of a drug, rather than as being situation (endpoint) dependent. We use the term 'clinical efficacy' in order to be clear. As the definition of a partial agonist involves an inability to produce the same level of effect as some reference drug in a given situation, it is only meaningful in the context of a reference compound or drug. This review summarizes published comparisons of buprenorphine's clinical analgesic effect to reference drugs commonly considered to be full agonist analgesics.

Buprenorphine has high affinity for opioid receptors and low *in vitro* intrinsic activity as measured by [^{35}S]GTPγS binding in several receptor binding assays.[12] The latter has led to characterization of buprenorphine as a partial agonist, because it produces <100% effect produced by a 'full' agonist. However, a problem is that 100% depends on the conditions. For example, in the same *in vitro* assays in which buprenorphine produces <100% effect, morphine likewise produces <100% effect (a fact perhaps not widely known).[13] Yet morphine is generally considered to be a full agonist in most clinical settings. In addition, buprenorphine has a multifaceted pharmacology, so that its total analgesic effect derives from its activity at several receptors – partial agonism at one receptor might not be limiting to the clinical effect achieved. Further, due to differences in 2nd–messenger coupling, biased agonism, or other signal transduction phenomena, a drug can act as a full agonist on one endpoint and a partial agonist on another. That is why designation as a 'full' or 'partial' agonist is situational, that is, dependent on the endpoint of interest.

Because buprenorphine displays >98% antinociceptive efficacy in the majority of animal models and positron emission tomography (PET) scans of human brain have shown that full analgesia is achieved with buprenorphine doses that occupy <100% of opioid receptors,[14] there only remains the relevant clinical question: Does buprenorphine produce a full analgesic effect – or equivalent analgesia to a drug that is considered to be a full agonist, such as morphine, fentanyl or oxycodone? That is, despite acting as a partial agonist *in vitro*, does buprenorphine act as a full agonist in clinical pain settings?

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COMMENT

As the purpose of the current review was the assessment of buprenorphine-induced analgesia compared with opioids considered to be full agonists, inclusion criteria were as follows: human subjects; within-study comparison of the same pain type and with drugs commonly considered to be full agonists (e.g. morphine, fentanyl, oxycodone, etc.); quantification of measurement of pain severity or pain relief; and comparison using the same pain scales. All studies that met these criteria were included, regardless of the clinical outcome. Exclusion criteria were as follows: non-human studies; use as part of a combination; use in opioid addiction (e.g. suboxone); and comparison to drugs not commonly familiar in the USA (e.g. pethidine).

A total of 24 clinical trials were identified using the database search terms and searching of the reference lists and other sources. In addition, two additional studies were identified that related directly to the question of buprenorphine's clinical analgesic efficacy.

The earliest identified study that met all the criteria was published in 1977.[15] The analgesic efficacy of i.m. buprenorphine (0·6 mg) was compared with i.m. morphine (15 mg) for post-operative pain in a double-blind trial involving 58 women (average age 25–30 years) following elective Caesarean section. Buprenorphine produced essentially equal pain relief as morphine during the first two post-operative hours and greater pain relief at 3 and 4 h post-operatively (Figure S1 in online Appendix). Similar results were obtained for i.m. buprenorphine (0·3 mg) compared with i.m. morphine (10 mg) for post-operative pain in a randomized, double-blind, multiple-dose, non-crossover trial involving 60 patients following upper abdominal surgery (Fig. 1)[16]; for i.m buprenorphine (0·15–0·40 mg) compared with i.m morphine (5 or 10 mg) for post-operative pain in a randomized, double-blind, parallel study involving 133 patients (17–70 years) who had undergone a major abdominal, orthopaedic or thoracic surgery procedure (Figure S2)[17]; for i.m. buprenorphine (0·3 mg) compared with i.m. morphine (10 mg) in a double-blind study of 50 patients after surgery (mostly abdominal) (Figure S3)[18]; for i.m. buprenorphine (0·3 mg) compared with i.m. morphine (10 mg) in a prospective study of 80 patients undergoing elective abdominal surgeries randomly assigned to either morphine or buprenorphine (both groups were started with i.m. dosing, then i.m. morphine or s.l. buprenorphine) (Figure S4)[19]; and for i.m. buprenorphine (0·2 and 0·4 mg) compared with i.m. morphine (5 and 10 mg) in a double-blind study of post-operative abdominal surgery patients (Figure S5).[20] In the latter study, both doses of buprenorphine produced greater analgesic effect than did 5 mg of morphine and at least as great an effect as 10 mg of morphine. In a study of 52 patients following open prostatectomy, randomly assigned sublingual buprenorphine was equi-analgesic to patient-controlled analgesia (PCA) morphine (Figure S6).[21] Sublingual buprenorphine also produced the same or greater analgesic effect than i.m. morphine in a double-blind study of 101 patients undergoing general surgery (Fig. 2).[22]

Several studies administered buprenorphine via routes that bypass the metabolic first-pass effect. I.v. buprenorphine produced equi-analgesia to i.v. morphine in a double-blind randomized study of 80 patients following elective abdominal surgery (Figure S7)[23]; in a double-blind study of 13 patients following coronary bypass surgery (at rest or on coughing) (Figure S8)[24]; in a double-blind, multidose study of 57 children (6 months–6 years) after lateral thoracotomy (Fig. 3)[25]; and by PCA in a randomized, double-blind study of 120 patients following abdominal surgery (Figure S9).[26] I.v. buprenorphine (0·3 mg) produced a greater analgesic effect than i.v. morphine (10 mg) in a double-blind comparison study of 51 patients who had undergone major abdominal surgery (Figure S10).[27] Either epidural or extradural buprenorphine produced equi-analgesia to i.m. morphine: in a prospective randomized study of 20 patients undergoing spinal fusion (Figure S11)[28]; against epidural or extradural morphine in a

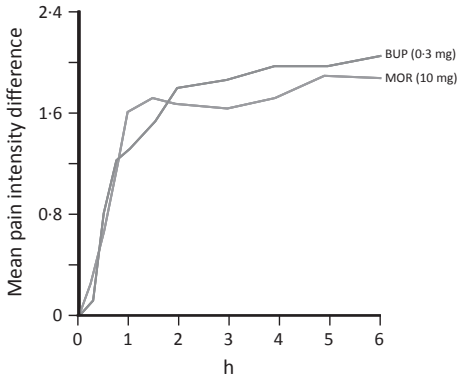

Fig. 1. The analgesic efficacy of i.m. buprenorphine (0·3 mg) was compared with that of i.m. morphine (10 mg) for post-operative pain relief in a randomized, double-blind, multiple-dose, non-crossover trial involving 60 patients (26M/34F; 17–78 years) scheduled for upper abdominal surgery. Post-op pain intensity was assessed using a visual analog scale (0 = none, 1 = slight, 2 = moderate, 3 = severe) and measured prior to the first dose of drug and every 15 min thereafter up to 2 h and every hour thereafter up to 6 h post-injection. Morphine and buprenorphine produced similar decreases in pain intensity. Redrawn from Tigerstedt and Tammisto.[16]

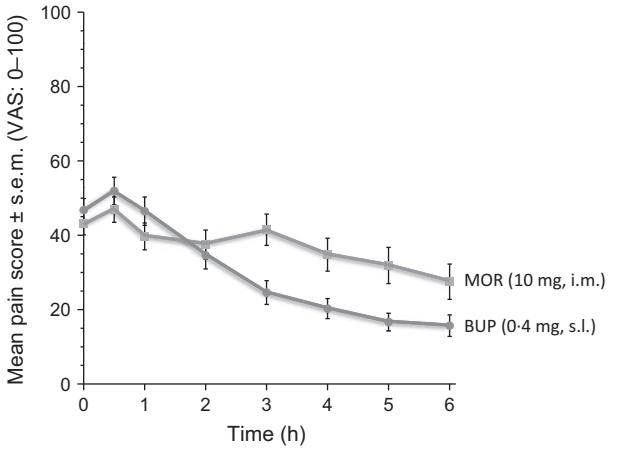

Fig. 2. The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of i.m. morphine (10 mg) in a randomized, double-blind study of post-op pain of 101 patients (mean age: 40–45 years). Pain was measured using a 10-cm pain scale (0 = none, 10 = as much as imaginable). Buprenorphine produced the same pain relief as did morphine during the first 2 h and modestly greater pain relief from 2 to 6 h. Redrawn from Edge *et al.*[22]

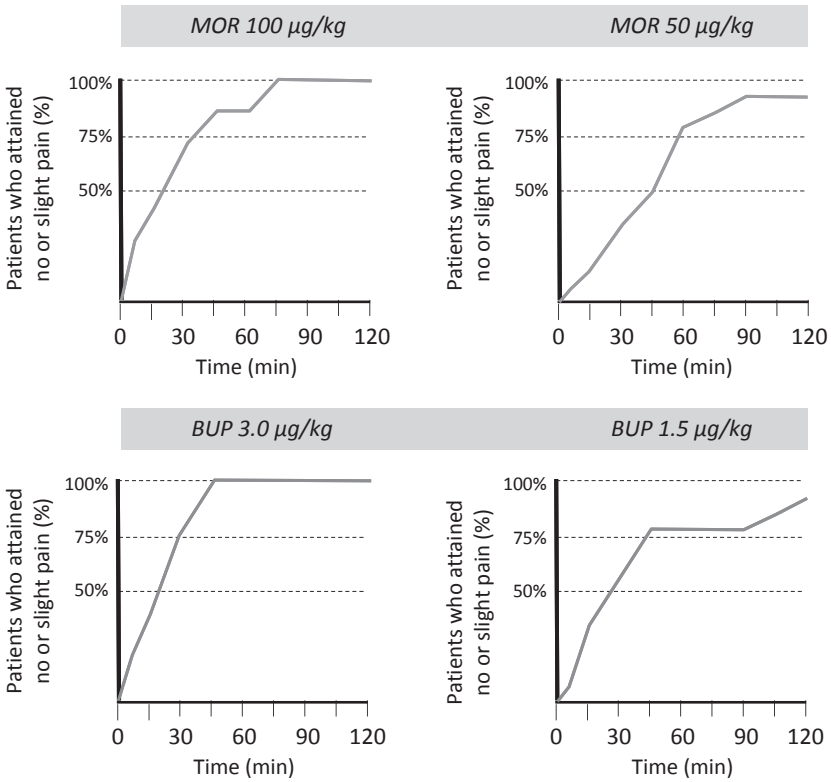

Fig. 3. The analgesic efficacy of i.v. buprenorphine (1·5 and 3·0 µg/kg) was compared to i.v. morphine (50 and 100 µg/kg) for post-operative pain in a double-blind trial involving 57 children (0·5–6 years) recovering from a scheduled lateral thoracotomy. Pain index (PI) values were assessed using a 9-point scale (0 = no pain, 1–3 = slight pain, 4 and 5 = moderate pain, 6–8 = severe pain, 9 = worst possible pain). Post-operatively, the patients received increments of 0·01 mL/kg of either buprenorphine or morphine every 5–15 min until the patient had a PI = 0 or 1 for more than 15 min. The higher doses of buprenorphine and morphine both produced a pain-free response. Redrawn from the data in Maunuksela *et al.*[25]

randomized, double-blind study of 34 patients following major abdominal surgery (Figure S12)[29]; in a double-blind, randomized study of 57 patients after Caesarean section (Figure S13)[30]; a double-blind study of 40 patients following major orthopaedic surgery (Table 1)[31]; and in a double-blind study of 50 patients after abdominal surgery (Figure S14).[32]

Comparisons to strong analgesics other than morphine also have been made. In a randomized, single-blind study of 60 patients recovering from unilateral thoracotomy, PCA buprenorphine was equi-analgesic to PCA fentanyl (Fig. 4).[33] In a randomized study of 79 patients experiencing post-operative pain after general surgery, sublingual buprenorphine (0·4 mg) produced analgesia equal to that produced by dihydrocodeine (60 mg) for the first 2 h and greater effect thereafter (to 6 h) (Figure S15).[34] And in an exploratory multiple-comparisons study involving 258

Table 1. Pain intensity difference (PID) and sum of pain intensity difference (SPID) scores (mean and range) in a double-blind controlled study that compared epidural morphine (MOR) (4 mg) with epidural buprenorphine (BUP; 0·3 mg) in 40 patients (20M/20F; 16–69 years) after major orthopaedic surgery

Pain measure	MOR	BUP	*P*
PID	1·90 (0·0–4·0)	2·0 (0·0–4·0)	>0·05
SPID	2·60 (0·16–9·0)	3·30 (0·16–12·0)	>0·05

Pain intensity was assessed by the patient on a 0–4 scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain and 4 = intolerable pain) prior to drug administration and 10, 20, 30 and 60 min after injection. There was no significant difference ($P > 0·05$) in analgesic efficacy as measured by the pain intensity difference (PID) after 30 min and the sum of pain intensity difference (SPID) across all time points between the two drugs. Data from Wolff *et al.*[31]

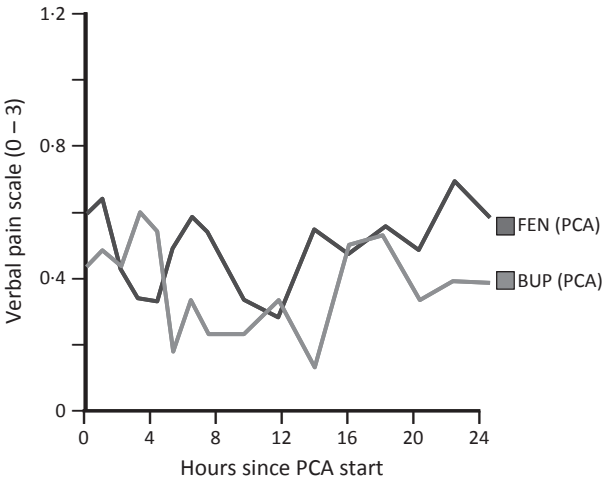

Fig. 4. The analgesic efficacy of patient-controlled analgesia (PCA) buprenorphine (demand dose 80 µg) was compared with that of PCA fentanyl (demand dose 34 µg) in patients recovering from elective thoracotomy (29/11F; average age: 55–65 years). Buprenorphine was equi-efficacious with fentanyl throughout 24 h. Redrawn from Lehmann *et al.*[33]

with cancer pain, transdermal buprenorphine was equi-analgesic with transdermal fentanyl, oral morphine or oral oxycodone (Table 2).[35] In a study of chronic cancer pain patients, in which 16 were switched from transdermal buprenorphine to transdermal fentanyl and 16 were switched from transdermal fentanyl to transdermal buprenorphine, buprenorphine produced the same level of analgesia as did fentanyl over the subsequent 3 weeks (Figure S16).[36] A more detailed analysis of transdermal buprenorphine trials is available.[14]

In a study of 60 patients who were randomly assigned either i.m. buprenorphine (0·3 mg) or epidural sufentanil (50 μg) following orthopaedic surgery, buprenorphine produced less analgesia over the first 2 h, but greater analgesia from 2 to 8 h (Figure S17).[37] In only one identified study, did the analgesic effect of buprenorphine not attain that produced by morphine. In a double-blind study of patients with post-operative (N = 128) or chronic cancer (N = 8) pain, sublingual buprenorphine (0·8 mg) produced the same level of analgesia as did 8 mg of i.m. morphine, but less than that produced by 16 mg morphine (Figure S18).[38] The study was designed to determine the relative potency of the two drugs, so higher doses of buprenorphine were not tried. In regard to the question of using higher doses of buprenorphine in order to achieve full analgesic effect, two studies are particularly noteworthy. In a case report of a terminally ill pancreatic cancer patient with kidney and liver failure suffering from severe pain, buprenorphine was given (i.v. and transdermal) in increasing doses over the final 15 days until the patient reported adequate pain relief (Fig. 5).[39] And in an informative study of 50 patients who underwent elective Caesarean section and were administered i.v. buprenorphine in the immediate post-operative period at doses titrated against the response of each patient in order to obtain complete freedom from pain.[40] A graph of the data reveals a dose-related effect, with 100% of the patients attaining complete pain relief (Fig. 6).

Table 2. The analgesic efficacy of transdermal buprenorphine (BUP) was compared with oral morphine (MOR), oral oxycodone (OXY) and transdermal fentanyl (FEN) in a retrospective, exploratory observational analysis involving 258 post-operative patients (147M/111F; average age 65 years) who had advanced metastatic cancer and persistent pain

Group	MOR	OXY	FEN	BUP	P
AP (PID ≥ 30%)					
No	30·0	28·6	28·6	29·3	>0·05
Yes	70·0	71·4	68·2	70·7	>0·05
AP (PID stable or worsening)					
No	77·5	83·9	94·1	94·5	>0·05
Yes	22·5	16·1	15·9	15·5	>0·05
WP (PID ≥ 30%)					
No	52·5	37·5	45·5	37·1	>0·05
Yes	47·5	62·5	54·5	62·9	>0·05
WP (PID stable or worsening)					
No	85·0	83·9	72·7	83·6	>0·05
Yes	15·0	16·1	27·3	16·4	>0·05

Worst pain (WP), actual pain, least pain and average pain (AP) were assessed using an 11-point numerical score (0 = no pain; 10 = worst pain) over a 3-week period. There was no significant difference (P > 0·05) in analgesic efficacy among the drugs. Data from Corli *et al.*[35]

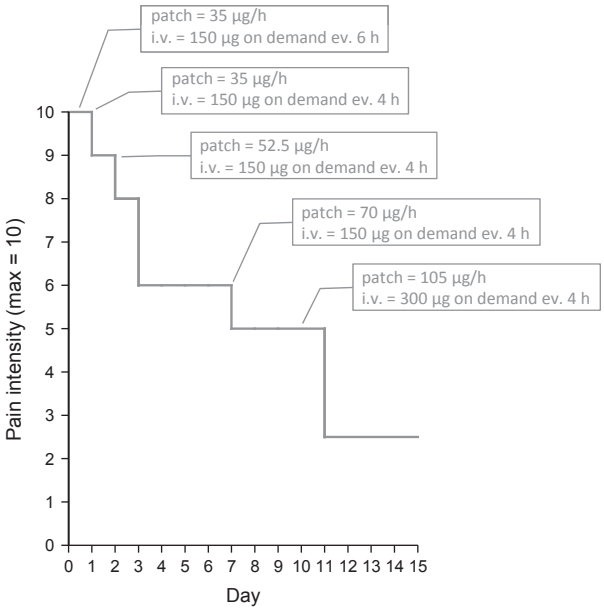

Fig. 5. Progressive increase in pain relief with increasing dose of buprenorphine in a terminally ill cancer patient with liver failure. Drawn based on the narrative in Ciccozzi *et al.*[39]

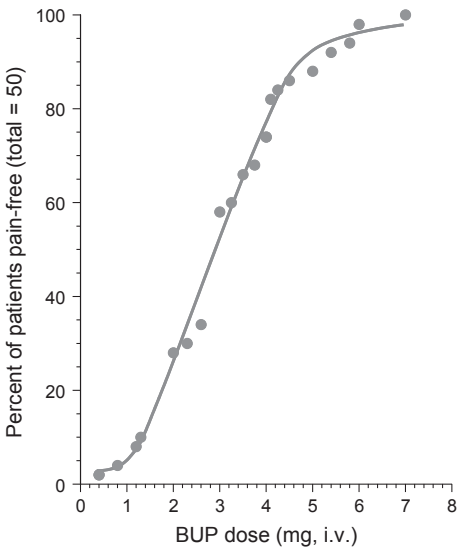

Fig. 6. The analgesic efficacy of i.v. buprenorphine was studied over a 24-h period in post-operative pain relief involving 50 patients (average age = 27·5 years) recovering from elective Caesarean section. Post-operatively, patients received buprenorphine in aliquots of 0·2 mg over 3–15 min, until the pain was relieved. Pain was assessed by its presence or absence at frequent intervals. All of the patients achieved complete analgesic effect with 0·4–7·0 mg of buprenorphine. Drawn based on data reported in Budd.[40]

WHAT IS NEW AND CONCLUSION

Despite buprenorphine's partial agonist characterization *in vitro*, in 23 of the 24 identified studies in the current review, buprenorphine produced the same level of analgesic effect or even greater analgesic effect than did the generally accepted full agonists morphine, fentanyl, sufentanil and oxycodone. These studies included pain designated as severe. In addition, in two studies in which a maximal-possible analgesic effect was designated, buprenorphine produced 100% effect.[25,40] This is consistent with PET scans of human brains showing that at clinically analgesic doses of buprenorphine, there remains a reserve of unoccupied μ-opioid receptors.[41] Based on these results, buprenorphine has full analgesic efficacy in clinical pain practice.

Then should buprenorphine continue to be called a partial agonist? There are reasons it might (*and some counterarguments*): one is that buprenorphine does not produce full effect in several *in vitro* assays (*but in the same assays, neither does morphine*)[13]; another is that buprenorphine produces an 'inverted-U' dose–response curve in some animal pain models (i.e., the antinociceptive effect reaches a maximum then declines at higher doses)[5] and healthy pain-free volunteers[42] (*but this does not occur in most pain models*[43] *and to our knowledge has never been reported in pain patients, even at doses at least an order of magnitude higher than those commonly used*)[40]; and another is that buprenorphine can precipitate withdrawal in a patient taking, or abusing, a strong opioid (*but, even if true, such an effect can be due to a mechanism other than partial agonism*). The fact that buprenorphine appears to be a true partial agonist on the endpoint of respiratory depression, with a ceiling effect,[42,44] cannot be generalized to analgesia, because the ability to be a partial agonist on one endpoint and a full agonist on another endpoint is mechanistically possible and easily explained.[45] Perhaps the answer lies in the multimechanistic pharmacology of buprenorphine. Its overall analgesic action is likely mediated by a combination of receptors. Thus, partial agonism at a specific receptor subtype is not particularly relevant and probably does not apply to its overall analgesic action. Thus, buprenorphine can be a partial agonist *in vitro,* yet its analgesic efficacy can equal or exceed other opioids due to its ability to act through additional targets, making its partial agonism *in vitro* a poor predictor of its overall analgesic effect.

In conclusion, despite some preclinical data predicting that buprenorphine might not produce analgesic effect equal to full agonist analgesics such as morphine, fentanyl or oxycodone, the published clinical data demonstrate that it does.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 The analgesic efficacy of i.m. buprenorphine (0·6 mg) was compared with that of i.m. morphine (15 mg) for postoperative pain in a double-blind trial involving 58 women (average age 25–30 years) recovering from elective Caesarian section.

Figure S2 The analgesic efficacy of i.m buprenorphine (0·20 or 0·40 mg) was com-pared with that of i.m morphine (5 or 10 mg) for postoperative pain in a randomized, double-blind, parallel study involving 133 patients (age range: 17–70 years) who had undergone a major abdominal, orthopedic, or thoracic surgery, and i.m buprenorphine (0·15 or 0·30 mg) with i.m morphine (5 or 10 mg) in a second study that involved 69 patients.

Figure S3 The analgesic efficacy of i.m. buprenorphine (0·3 mg) was compared with that of i.m. morphine (10 mg) in a single-dose, double-blind, non-crossover study for pain after surgery (majority abdominal) in a randomized study of 50 patients (21M/29F, 20–80 years).

Figure S4 The analgesic efficacy of buprenorphine (0·3 mg i.m. followed by 0·4 mg every 6 h s.l.) was compared with i.m. morphine (10 mg intermittently) for 3 days of postoperative pain in a prospective randomized study involving 80 patients (40M/40F; 50–60 years) undergoing elective abdominal surgeries.

Figure S5 The analgesic efficacy of i.m. buprenorphine (0·2 or 0·4 mg) was compared with that of i.m. morphine (5 or 10 mg) in a double-blind, randomly-assigned evaluation for pain following surgery of 159 patients (41M/118F, 18–85 years).

Figure S6 The analgesic efficacy of s.l. buprenorphine (1·6 mg) was compared with that of i.v morphine (PCA) (72 mg) for postop pain relief in a randomized trial involving 52 males (age range: 52–82 years; average age: 72 years) following open prostatectomy.

Figure S7 The analgesic efficacy produced by i.v. buprenorphine (0·225–0·45 mg) was compared with that produced by i.v. morphine (7·5–15 mg) at the start of peritoneal closure at the end of elective abdominal hysterectomy or chol-ecystectomy in a randomized, double-blind study involving eighty patients (10M/70F; 16–67 years).

Figure S8 The analgesic efficacy of i.m. buprenorphine (0·3 mg) followed by i.v. bup-renorphine (0·6 mg then 0·35 mg as needed) was compared with that of i.m. morphine (10 mg) followed by i.v. morphine (20 mg then 3 mg + 0·5–6·0 mg/h as needed) for postoperative pain measured at rest and on coughing in a double-blind trial involving 13 patients (average age: 59–60 years) recovering from coronary bypass surgery.

Figure S9 The analgesic efficacy of PCA buprenorphine was compared with that of PCA morphine alone and in combination in a prospective, randomized, and double-blind four-arm trial with 120 patients (63M/57F; 21–80 years) during the first 12 postoperative hour following abdominal surgery.

Figure S10 The analgesic efficacy of i.v. buprenorphine (0·3 mg) was compared with that of i.v. morphine (10 mg) in a double-blind, between-patient study for pain after major abdominal surgery of 51 patients (25M/26F, mean age: 45–51 years).

Figure S11 The efficacy of epidural buprenorphine (60 μg) was compared with that of i.m. morphine (0·15 mg/kg) for pain relief in a prospective randomized trial involving 20 patients (6M/14F, 35–40 years) following spinal fusion surgery.

Figure S12 The analgesic efficacy of epidural buprenorphine was compared with that of epidural morphine in a randomized double-blind study of 34 patients (17M/ 17F, age 17–82 years) recovering from major abdominal surgery.

Figure S13 The analgesic efficacy of extradural buprenorphine (0·09 and 0·018 mg) was compared with that of extradural morphine (3 mg) for postoperative pain in a prospective double-blind randomized study involving 57 women (average age 25–30 years) after elective Caesarean section.

Figure S14 The analgesic efficacy of epidural buprenorphine (0·15 mg) was compared with that of epidural morphine (5 mg) in a double-blind study of 50 patients (22M/28F, average age 58–62 years) recovering from abdominal surgery. Pain was assessed using a 10-point VAS.

Figure S15 The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of oral dihydrocodeine (60 mg) in a randomized study of 79 postop patients (43M/36F, mean age: 45–48 year).

Figure S16 The analgesic efficacy of transdermal buprenorphine (BTDS) (52·5 μg/h) was compared with that of transdermal fentanyl (FTDS) (25 μg/h) for chron-ic cancer pain involving 32 patients (17M/15F; 42–78 year).

Figure S17 The analgesic efficacy of i.m. buprenorphine (0·3 mg) was compared with that of epidural sufentanil (50 μg) for postoperative pain in a randomized study of patients (33M/26F), average age 40–45 year) after orthopedic surgery.

Figure S18 The analgesic efficacy of s.l. buprenorphine (0·2 mg; 0·4 mg; 0·8 mg) was compared with that of i.m. morphine (4, 8, 16 mg) for postoperative pain relief in a randomized, double-blind, multiple-dose, sequential twin crossover trial involving 140 patients (108 completed the study) in moderate to severe postoperative pain.

REFERENCES

1. Cowan A, Doxey JC, Harry EJ. The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Br J Pharmacol*, 1977;**60**:547–554.
2. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. *Drugs*, 1979;**17**:81–110.
3. Vadivelu N, Hines RL. Buprenorphine: a unique opioid with broad clinical applications. *J Opioid Manag*, 2007;**3**:49–58.
4. Budd K. Buprenorphine and the transdermal system: the ideal match in pain management. *Int J Clin Pract*, 2002;**133** (suppl.):9–14.
5. Cowan A. Buprenorphine: new pharmacological aspects. *Int J Clin Pract Suppl*, 2003;**113**:3–8; discussion 23–24.
6. Budd K, Raffa RB (Eds). *Buprenorphine – the unique opioid analgesic*. Stuttgart and New York: Thieme, 2005.
7. Pergolizzi J, Aloisi AM, Dahan A *et al.* Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract*, 2010;**10**:428–450.
8. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. *Curr Neuropharmacol*, 2004;**2**:395–402.
9. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol*, 2012;**10**:209–219.
10. Raffa RB, Tallarida RJ. 'Affinity': historical development in chemistry and pharmacology. *Bull Hist Chem*, 2010;**35**:7–16.
11. Maehle AH, Prull CR, Halliwell RF. The emergence of the drug receptor theory. *Nat Rev Drug Discov*, 2002;**1**:637–641.
12. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther*, 2001;**297**:688–695.
13. Traynor J. mu-Opioid receptors and regulators of G protein signaling (RGS) proteins: from a symposium on new concepts in mu-opioid pharmacology. *Drug Alcohol Depend*, 2012;**121**:173–180.
14. Raffa RB, Pergolizzi JVJ. Is buprenorphine a 'partial agonist'? preclinical and clinical evidence. *Pract Pain Manag*, 2013;**13**: 33–39.
15. Downing JW, Leary WP, White ES. Buprenorphine: a new potent long-acting synthetic analgesic. Comparison with morphine. *Br J Anaesth*, 1977;**49**:251–255.
16. Tigerstedt I, Tammisto T. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. *Acta Anaesthesiol Scand*, 1980;**24**:462–468.
17. Ouellette RD. Comparison of analgesic activity of buprenorphine hydrochloride and morphine in patients with moderate to severe pain postoperatively. *Surg Gynecol Obstet*, 1984;**159**:201–206.
18. Hovell BC, Ward AE. Pain relief in the post-operative period: a comparative trial of morphine and a new analgesic buprenorphine. *J Int Med Res*, 1977;**5**: 417–421.
19. Cuschieri RJ, Morran CG, McArdle CS. Comparison of morphine and sublingual buprenorphine following abdominal surgery. *Br J Anaesth*, 1984;**56**:855–859.
20. Dobkin AB, Esposito B, Philbin C. Double-blind evaluation of buprenorphine hydrochloride for post-operative pain. *Can Anaesth Soc J*, 1977;**24**:195–202.
21. Gaitini L, Moskovitz B, Katz E, Vaisberg A, Vaida S, Nativ O. Sublingual buprenorphine compared to morphine delivered by a patient-controlled analgesia system as postoperative analgesia after prostatectomy. *Urol Int*, 1996;**57**:227–229.
22. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia*, 1979;**34**:463–467.
23. Bradley JP. A comparison of morphine and buprenorphine for analgesia after abdominal surgery. *Anaesth Intensive Care*, 1984;**12**:303–310.
24. Rabinov M, Rosenfeldt FL, McLean AJ. A double-blind comparison of the relative efficacy, side effects and cost of buprenorphine and morphine in patients after cardiac surgery. *Aust N Z J Surg*, 1987;**57**:227–231.
25. Maunuksela EL, Korpela R, Olkkola KT. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain of children. *Br J Anaesth*, 1988;**60**:48–55.
26. Oifa S, Sydoruk T, White I *et al.* Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: a randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. *Clin Ther*, 2009;**31**:527–541.
27. Kay B. A double-blind comparison of morphine and buprenorphine in the prevention of pain after operation. *Br J Anaesth*, 1978;**50**:605–609.
28. Murphy DF, MacEvilly M. Pain relief with epidural buprenorphine after spinal fusion: a comparison with intramuscular morphine. *Acta Anaesthesiol Scand*, 1984;**28**:144–146.
29. Chrubasik J, Vogel W, Trotschler H, Farthmann EH. Continuous-plus-on-demand epidural infusion of buprenorphine versus morphine in postoperative treatment of pain. Postoperative epidural infusion of buprenorphine. *Arzneimittelforschung*, 1987; **37**:361–363.
30. Simpson KH, Madej TH, McDowell JM, MacDonald R, Lyons G. Comparison of extradural buprenorphine and extradural morphine after caesarean section. *Br J Anaesth*, 1988;**60**:627–631.
31. Wolff J, Carl P, Crawford ME. Epidural buprenorphine for postoperative analgesia: a controlled comparison with epidural morphine. *Anaesthesia*, 1986;**46**:77–79.
32. Zenz M, Piepenbrock S, Hubner B, Glocke M. A double-blind comparison of epidural buprenorphine and epidural morphine in postoperative pain (author's transl). *Anasth Intensivther Notfallmed*, 1981;**16**:333–339.
33. Lehmann KA, Grond S, Freier J, Zech D. Postoperative pain management and respiratory depression after thoracotomy: a comparison of intramuscular piritramide and intravenous patient-controlled analgesia using fentanyl or buprenorphine. *J Clin Anesth*, 1991;**3**:194–201.

34. Masson AH. Sublingual buprenorphine versus oral dihydrocodeine in post-operative pain. *J Int Med Res*, 1981;**9**:506–510.
35. Corli O, Montanari M, Deandrea S, Greco MT, Villani W, Apolone G. An exploratory analysis on the effectiveness of four strong opioids in patients with cancer pain. *Pain Med*, 2012;**13**:897–907.
36. Aurilio C, Pace MC, Pota V *et al.* Opioids switching with transdermal systems in chronic cancer pain. *J Exp Clin Cancer Res*, 2009;**28**:61.
37. Donadoni R, Rolly G. Epidural sufentanil versus intramuscular buprenorphine for postoperative analgesia. A double-blind comparative trial. *Anaesthesia*, 1987;**42**:1171–1175.
38. Wallenstein SL, Kaiko RF, Rogers AG, Houde RW. Clinical analgesic assay of sublingual buprenorphine and intramuscular morphine. *NIDA Res Monogr*, 1982;**41**:288–293.
39. Ciccozzi A, Angeletti C, Baldascino G *et al.* High dose of buprenorphine in terminally ill patient with liver failure: efficacy and tolerability. *J Opioid Manag*, 2012;**8**:253–259.
40. Budd K. High dose buprenorphine for postoperative analgesia. *Anaesthesia*, 1981;**36**:900–903.
41. Greenwald MK, Johanson CE, Moody DE *et al.* Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*, 2003;**28**:2000–2009.
42. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther*, 1994;**55**:569–580.
43. Christoph T, Kogel B, Schiene K, Meen M, De Vry J, Friderichs E. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *Eur J Pharmacol*, 2005;**507**:87–98.
44. Dahan A, Yassen A, Romberg R *et al.* Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*, 2006;**96**:627–632.
45. Raffa RB, Ding Z. Examination of the preclinical antinociceptive efficacy of buprenorphine and its designation as full- or partial-agonist. *Acute Pain*, 2007;**9**:145–152.