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REVIEW ARTICLE

Treating Chronic Pain: An Overview of Clinical Studies Centered on the Buprenorphine Option

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Abstract

The buprenorphine receptor binding profile is unique in that it binds to all three major opioid receptors (mu, kappa, delta), and also binds to the orphan-like receptor, the receptor for orphanin FQ/nociceptin, with lower affinity. Within the mu receptor group, buprenorphine analgesia in rodents is dependent on the recently discovered arylepoxamide receptor target in brain, which involves a truncated 6-transmembrane mu receptor gene protein, distinguishing itself from morphine and most other mu opioids. Although originally designed as an analgesic, buprenorphine has mainly been used for opioid maintenance therapy and only now is increasingly recognized as an effective analgesic with an improved therapeutic index relative to certain potent opioids. Albeit a second-, third-, or fourth-line analgesic, buprenorphine is a reasonable choice in certain clinical situations. Transdermal patches and buccal film formulations are now commercially available as analgesics. This review discusses buprenorphine pharmacodynamics and pharmacokinetics, use in certain populations, and provides a synopsis of systematic reviews and randomized analgesic trials. We briefly discuss postoperative management in patients receiving buprenorphine maintenance therapy, opioid equivalence to buprenorphine, rotations to buprenorphine from other opioids, and clinical relevance of buprenorphine-related QTc interval changes.

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Buprenorphine Analgesia: Key Points

The buprenorphine receptor binding profile is unique in that it binds to all three major opioid receptors (mu, kappa, delta), with much less affinity to the orphan-like receptor (ORL-1).

There is high first-pass clearance requiring administration by routes other than oral administration.

Buprenorphine is metabolized to the active metabolite norbuprenorphine through cytochrome 450 (CYP) 3A4 and CYP3C8, but its rate-limiting metabolism is through multiple conjugases.

Clearance is independent of renal function and is not removed by dialysis, making it a preferred analgesic in renal failure.

Clearance is also not influenced by mild to moderate liver failure.

Analgesia is equivalent to other opioids, but with a dose-related ceiling effect on respiratory depression, less constipation, and less hypogonadism, thus having a better therapeutic index than other potent opioids.

The evidence for buprenorphine analgesia is moderate and more direct comparisons between buprenorphine and other opioids are needed.

1 Introduction

Opioid therapy for chronic pain involves, for the most part, potent opioids such as morphine, oxycodone, fentanyl, hydrocodone, and hydromorphone. In recent years, these opioids have been marketed for chronic non-cancer pain and have been modified into tamper-resistant formulations in response to the opioid epidemic. A large part of the efforts and finances pharmaceutical companies have invested have been in this direction; however, these formulations do not address addiction risk and remain susceptible to illicit route conversion. They are not tamper-proof. Other side effects occur with these opioids, including hypogonadism, falls risks, infections, sleep-disordered breathing immunosuppression, poor wound healing, and mortality [1].

Buprenorphine was synthesized from thebaine in 1966, and, approximately 12 years later, Donald Jasinski issued the following statement: "In conclusion, buprenorphine has a unique pharmacology with immediately obvious therapeutic applications as an analgesic of low abuse potential" [2]. When first released, buprenorphine was a schedule III analgesic. Injectable buprenorphine became commercially available in 1981, with the least restrictions for a potent opioid in the US (with the exception of nalbuphine). In the US, low-dose transdermal buprenorphine is available in 5, 7.5, 10, 15, and 20 μg/h doses (Butrans™; Purdue Pharma LP, Stamford, CT, USA), and in Europe in 35, 52.5 and 70 μg/h doses (Transtec™; Napp Pharmaceuticals Ltd, Cambridge, UK). Sublingual buprenorphine is available in several formulations. The generic buprenorphine/naloxone combination comes in 2/0.5 mg and 8/2 mg doses, and as buprenorphine without naloxone in 2 mg and 8 mg doses. The buprenorphine/naloxone brand name Suboxone™ (Reckitt Benckiser, Slough, UK) comes in 2/0.5 mg, 4/1 mg, and 8/2 mg tablets, and Subutex™ (Reckitt Benckiser) as 2 mg and 8 mg. The newer sublingual combination tablets with greater bioavailability come in 1.4/0.36 mg and 5.7/1.4 mg (Zubsolv™; Orexo, Morristown, NJ, USA). A buccal film comes in 2.1/0.3 mg, 4.2/0.7 mg, and 6.3/1 mg doses (Bunavail™; BioDelivery Sciences International, Inc., Raleigh, NC, USA), and as a buprenorphine patch (BioDelivery Sciences International, Inc.) in 75, 150, 300, 450, 600, 750, and 900 μg doses (Belbuca™).

Transdermal buprenorphine became available when various transdermal delivery systems were being developed in the 1990s. It reduced even further the potential risk of misuse in its matrix form, and has been noted to have even fewer side effects than sublingual buprenorphine with or without naloxone [3]. The advantages of buprenorphine include a ceiling on the euphoriant effects and on respiratory depression, but not on analgesia at doses up to 32 mg/day [4, 5]. As a result, unlike other potent opioids, a dose-related improved therapeutic index has been noted. Buprenorphine has less physical dependence, as seen with milder withdrawal with abrupt abstinence. Buprenorphine is not associated with falls risks and hypogonadism and is not an immunosuppressant [1].

The pharmacokinetics of buprenorphine are quite stable in renal failure and doses do not have to be altered in mild to moderate hepatic impairments (Child–Pugh class A and B). Transdermal buprenorphine (5–20 μg/h) is an excellent step II analgesic, and is preferred to tramadol since it is not associated with seizures or falls in the elderly. Compliance has improved as the patch is only changed once in 7 days. Furthermore, buprenorphine has fewer drug–drug interactions than tramadol as the rate-limiting metabolizing enzymes are conjugases and not mixed-function oxidases (cytochromes) [1, 3, 6, 7].

2 Pharmacodynamics of Buprenorphine

The buprenorphine receptor binding profile is unique in that it binds with high affinity to all three major opioid receptor classes (mu, kappa, delta), and with lower affinity to the orphan-like receptor (ORL-1), the receptor for orphanin FQ/

nociceptin [8–11]. It is a partial agonist at traditional mu receptors (potentially contributing to its ceiling effect on respiratory depression), an inverse agonist at the kappa receptor, and an antagonist at delta receptors [12]. However, its affinity for a recently discovered structurally distinct subtype of mu receptor involved in its analgesia that truly distinguishes buprenorphine [12, 13]. Both morphine and methadone act through traditional full-length mu receptors. In contrast, buprenorphine analgesia also depends on the arylepoxamide receptor (AEAr) target in brain, which includes a truncated 6-transmembrane protein from the mu opioid receptor gene (*Oprm1*). Mice lacking this protein displayed no buprenorphine analgesia, while showing normal responses to morphine. This unique receptor selectivity may account for its incomplete analgesic cross-tolerance. Similar to buprenorphine, both nalbuphine and butorphanol are dependent on the AEAr and have a ceiling effect on respiratory depression.

Although buprenorphine is a partial agonist at traditional mu receptors, it has high affinity for mu receptors, which is likely responsible for its slow dissociation [11, 14–16]. Buprenorphine is far more potent than either morphine (sevenfold) or fentanyl (fourfold) in stimulating [^{35}S]GTPγS binding (Table 1) [17].

The inverse agonist activity at the kappa receptor may explain buprenorphine-associated antihyperalgesic activity, as hyperalgesia is likely the result of dynorphin upregulation [12, 18, 19]. It is also a reason why there is less sedation and dysphoria with buprenorphine. Finally, kappa receptor antagonism is associated with antidepressant activity, which may be one reason why buprenorphine has been found to reduce depression and suicide ideation [20–23].

Biased signaling, in which opioids differentially activate various transduction systems, has proven to be important in understanding opioid pharmacology. Analgesia is associated with G-protein pathways, while arrestin recruitment is associated with many of the opioid-related adverse effects. Unlike traditional opioids such as morphine, fentanyl and methadone, buprenorphine does not recruit β-arrestin to the receptor. As a result, buprenorphine does not downregulate mu receptors on neuron surfaces, and in fact increases mu receptor expression in a chaperone effect [16]. The lack of morphine–β-arrestin interactions results in diminished analgesic tolerance, respiratory depression, and constipation in animals [24–27]. Administered together with a traditional mu opioid, buprenorphine antagonizes β-arrestin activity, which explains why morphine-induced receptor phosphorylation and desensitization is blocked when administered with buprenorphine [28, 29]. This may account for the superadditive effects when combining low-dose buprenorphine with fentanyl, oxycodone, and morphine [30–33].

Although it has been mentioned in the literature that buprenorphine has a ceiling effect on analgesia due to its partial agonist activity at the ORL-1 receptor, this has recently been questioned [10, 16, 34, 35]. The affinity of buprenorphine for ORL-1 is 500-fold less than for the mu receptor. Analgesic ceiling effects have only been noted in animal studies, while analgesic ceiling doses have not been noted in humans at doses up to 32 mg/day [4, 10, 36, 37].

Buprenorphine analgesia is largely mediated through mu receptors in the dorsal horn. However, there is a second supraspinal site that is not blocked by naloxone, pertussis toxin, or ORL-1 blockers, but selectively blocked by naloxonazine [38]. This is different than morphine and fentanyl [8]. Another unique feature of buprenorphine antinociception is that the Ser/Thr phosphatase inhibitor Okadaic acid blocks buprenorphine antinociception in animals in low doses, but potentiates it at high doses. Okadaic acid does not influence morphine or fentanyl antinociception [8].

Buprenorphine in animals at ultra-low doses facilitates thermal and mechanical hyperalgesia by activating spinal serotonergic neurotransmission through the serotonin receptor 5HT-2 [38]. Buprenorphine also blocks voltage-gated sodium channels and has been combined with local anesthetics in regional blocks [39, 40].

The synthetic opioids tramadol, tapentadol, methadone and dextromethorphan, as well as the lipophilic opioid meperidine, block serotonin and norepinephrine reuptake. These opioids are associated with the serotonin syndrome when combined with antidepressants, while fentanyl and oxycodone are also associated with the serotonin syndrome, presumably by a mechanism independent of monoamine reuptake inhibition. Buprenorphine neither blocks monoamine reuptake nor is it associated with the serotonin syndrome [41].

Buprenorphine has a unique receptor interaction, as demonstrated by modeling interactions with the mu receptor, which also explains its long dwell-time on mu receptors. The cyclopropyl methyl group prevents deep binding within the receptor pocket, which favors a high position within the receptor pocket located more toward the extracellular surface. However, a greater number of interactions in the pocket occur between the ligand and receptor than occurs with other

Table 1 Dose at which 50% G-protein activation occurs, as measured by [^{35}S]GTPγS, and β-arrestin recruitment occurs in HEK293 cells [17]

Opioid	[^{35}S]GTPγS binding EC_{50} (nM)	β-arrestin recruitment (nM)
Morphine	97.5 ± 28.5	322 ± 44
Methadone	87.2 ± 42.2	2110 ± 999
Fentanyl	56.6 ± 31.2	210 ± 42
Buprenorphine	14.5 ± 5.1	Not active
Norbuprenorphine	1.7 ± 0.7	84.6 ± 12

EC50 half maximal effective concentration

opioids and the metabolite norbuprenorphine, accounting for its slower dissociation from the receptor [42]. The cyclopropyl methyl group also provides some antagonism toward receptor activation, accounting for the lower intrinsic efficacy of buprenorphine. These interactions produce a conformation that prevents receptor phosphorylation, β-arrestin interactions, and receptor downmodulation (Table 1) [17, 43]. Despite being classified as a partial agonist, buprenorphine produces analgesia with only 5–10% of receptors occupied [44]; one can add a potent opioid to buprenorphine and anticipate analgesia [45–48].

3 Pharmacodynamics of Buprenorphine Metabolites

Norbuprenorphine, derived from the catabolism of buprenorphine through cytochrome P450 (CYP) 3A4, is a mu receptor agonist with high affinity for kappa and delta receptors. It triggers mu receptor G-protein binding to a greater extent than buprenorphine, as measured in vitro by [^{35}]S-GTPγS binding (Table 1), and, paradoxically, has only 1/50th the analgesic potency of buprenorphine [49]. Norbuprenorphine is a substrate for the efflux pump P-glycoprotein, whereas buprenorphine is not [50]. The brain-to-plasma norbuprenorphine ratio in mice with intact efflux pumps (wild-type MDR-1) and expression of P-glycoprotein is 0.1, indicating significant efflux from the central nervous system (CNS). A P-glycoprotein blocker such as PSC 833 will markedly increase norbuprenorphine plasma and brain leading to respiratory depression. Furthermore, P-glycoprotein influences gut norbuprenorphine absorption, which is the reason for increased plasma levels with PSC 833 [51]. Norbuprenorphine also has a high affinity and activates β-arrestin; interactions with β-arrestin are associated with opioid adverse effects, as demonstrated with morphine [52]. In part, norbuprenorphine accounts for the constipation and respiratory depression seen with buprenorphine [51, 53–57], and blocking the formation of norbuprenorphine may theoretically reduce buprenorphine toxicity [58].

Both buprenorphine and norbuprenorphine are glucuronidated to 3-glucuronides. Buprenorphine 3-glucuronide has affinity for mu and delta receptors, while norbuprenorphine 3-glucuronide has high affinity for kappa, but not delta, opioid receptors. Both glucuronides cause mild respiratory depression and antinociception in animals [54]. Little is known about the contribution of glucuronide metabolites to buprenorphine analgesia or adverse effects, however the general assumption is that the glucuronide metabolites are likely to contribute little to buprenorphine pharmacology. A reason for this assumption is that norbuprenorphine 3-glucuronide is also a P-glycoprotein substrate [59].

4 Pharmacokinetics

Buprenorphine oral bioavailability is 10–15%, largely due to high first-pass hepatic clearance [60–62]. Sublingual, buccal, and illicit conversion to intranasal buprenorphine bypasses first-pass hepatic clearance. On average, sublingual tablet bioavailability is 50%, relative to parenteral buprenorphine [61, 63, 64]. Time to analgesia from the time of parenteral injection ranges between 10 and 30 min, with an average duration of analgesia ranging from 6 to 8 h [65]. Pharmacokinetics are best described in a three-compartment model with first-order elimination [66, 67]. Peak plasma concentrations with sublingual tablets occur at around 90 min, whereas peak concentrations with parenteral buprenorphine occur between 2 and 3 min [68]. The plasma half-life of sublingual buprenorphine is 4–5 h. Brain levels exceed plasma levels because buprenorphine is very lipophilic and is not subject to P-glycoprotein efflux [44]. Half-life in the CNS is 155 min, and receptor dissociation time is 8.8 min, as opposed to seconds with fentanyl [67]. The time from onset to offset of analgesia is largely dependent on distribution within the CNS [69–72]. Clearance from the CNS is slower than plasma clearance, which accounts for the difference between plasma half-life of the drug and the duration of analgesia [73, 74]. Penetration through the blood–brain barrier occurs more rapidly, with slower migration to opioid receptor sites [49]. The duration of receptor occupancy has been measured using radiolabeled carfentanil in heroin-dependent volunteers administered a single 16 mg dose of sublingual buprenorphine. Seventy percent of receptors were occupied at 4 h, 50% at 24 h (the critical percentage occupancy necessary to inhibit craving), and 18% at 76 h [75]. Similar to methadone, craving can be checked by a single or twice-daily dose, whereas analgesia will likely require multiple daily doses.

Buprenorphine is 96% bound to α1-acid glycoprotein. The volume of distribution is quite large, at 430 L, reflecting its lipophilic characteristic, extensive penetration into tissues, and high protein binding. Cerebrospinal fluid is only 15–25% of the plasma levels, which does not reflect buprenorphine CNS levels [76].

There is a recognized slower decline in buprenorphine plasma levels after 6 h that is related to enterohepatic recirculation [77–79]. Buprenorphine 3-glucuronide is excreted in bile, deconjugated by bacterial glucuronidase in the colon, and subsequently reabsorbed [78, 80].

The newly developed and commercially available buccal buprenorphine film provides a greater bioavailable dose than sublingual buprenorphine tablets or film. The back layer of the film directs buprenorphine unidirectionally to the buccal surface, and much less is lost in the oral

cavity and swallowed [81]. The single-layer sublingual film does not have the bioerodible mucoadhesive structure of the buccal film, and bioavailability of the sublingual film is the same as sublingual tablets. Conversion from sublingual tablets or film to buccal patches approximates 2–1; a buccal patch dose of 4.2/0.7 is the equivalent of 8/2 mg of sublingual tablets. The buccal patch is associated with reduced constipation relative to sublingual tablets, thought to be due to reduced norbuprenorphine plasma levels with the buccal film [82].

Sublingual buprenorphine plasma levels are dose proportional from 1 to 32 mg; sublingual absorption is not limiting. Buprenorphine plasma half-life is longer with sublingual administration than parenteral administration, related to slow release from buccal fat, which may act as a local depot [83, 84]. A new buprenorphine/naloxone tablet with greater sublingual buprenorphine bioavailability was approved by the US FDA in July 2013 for maintenance therapy. There is 30% greater buprenorphine bioavailability per milligram of buprenorphine relative to the generic formulation [85]. The new 5.7/1.4 mg dose (buprenorphine/naloxone) tablet produces similar buprenorphine levels as the generic 8/2 mg dose, and dissolves at a faster rate [86], while the sublingual film dissolves even faster than the newer buprenorphine/naloxone tablets (173 s on average, vs. 242 s) [87].

The buccal patch comes as 75, 150, 300, and 450 µg doses and is administered every 12 h. Steady state is reached at 72 h and the mean plasma elimination half-life is 22.6 h. Absolute bioavailability ranges between 46 and 65% [88]. The 150 µg twice-daily dose produces plasma levels similar to the 10 µg/h transdermal patch, and the 300 µg/h dose is equivalent to the 20 µg/h patch [89].

The 35, 52.5, and 70 µg/h transdermal buprenorphine patches are not available in the US but are available in multiple European countries. The 3-day transdermal formulation produces half maximum plasma concentrations (C_{max}) at 12–24 h, with C_{max} reached at 60 h. Drug release, as measured by plasma concentrations over 72 h, is 'dome'-shaped, with concentrations diminishing after 60 h [90, 91].

The 7-day low-dose transdermal buprenorphine patch has a time to C_{max} (T_{max}) of 72 h. There is a 70% variance in peak to trough plasma concentrations over the 1-week period, and there are consistent dose to plasma concentrations with each patch if placed properly. Over a 3-week period, the 10 µg/h dose produces a minimum plasma concentration that ranges between 108 and 112 pg/mL [92]. The drug half-life after removing the patch is reported to be between 12 and 36 h [60, 92]. Absolute bioavailability of the low-dose transdermal buprenorphine patch is 15% compared with parenteral injection [76]. If patches are placed at the same site with each application, there is an increase in drug absorption, therefore patches should be rotated between the subclavicular, upper back, and upper deltoid regions. Drug absorption is 26% greater if patches are placed on the upper back as opposed to the sides of the chest [93].

Intranasal buprenorphine is not commercially available but is a route of abuse. The generic sublingual buprenorphine and buprenorphine/naloxone tablets are not tamper-resistant and can be crushed and intranasal insufflated or 'snorted'. The intranasal bioavailability of buprenorphine is 38–44%, with a T_{max} of 35–40 min, which is shorter than if administered sublingually. Naloxone is 24–30% bioavailable, which is much higher than when administered by mouth or sublingually, i.e. 2–3% [94]. The subjective 'high' is modest and transient withdrawal symptoms occur when the combination is snorted [95]. Transient withdrawal is due to the naloxone which has a short half-life relative to buprenorphine.

5 Metabolism

Buprenorphine is metabolized to the active metabolite norbuprenorphine through CYP3A4 and CYP2C8 [77, 80, 96]. The rate-limiting step to buprenorphine metabolism is glucuronidation; the parent drug is glucuronidated through UGT1A1, UGT1A3, UGT2B7, and UGT2B17, while norbuprenorphine is metabolized through UGT1A1 and UGT1A3 [97]. Analgesia is influenced by certain CYP3A4 and UGT single nucleotide polymorphisms [98, 99]. Depending on CYP3A4 activity, norbuprenorphine plasma levels may exceed buprenorphine, and conjugated buprenorphine and norbuprenorphine exceed unconjugated buprenorphine levels [100]. Glucuronidated metabolites undergo biliary and renal excretion, with biliary excretion leading to enterohepatic recirculation [80].

Buprenorphine has fewer drug–drug interactions than observed with other opioids metabolized through CYP3A4. If CYP3A4 is blocked, norbuprenorphine is not formed but buprenorphine is metabolized through glucuronidation. Ketoconazole, a strong inhibitor of CYP3A4, does not influence buprenorphine plasma clearance, as measured by the area under the curve of timed plasma levels [76, 101, 102]. Drugs such as atazanavir, which block both CYP3A4 and UGT1A1, increase buprenorphine levels [76], while drugs that induce CYP3A4, such as the classical antiseizure medications carbamazepine and rifampin, increase clearance and can lead to poor pain control [103, 104].

6 Issues Related to Special Populations

6.1 Children

Transdermal buprenorphine is not approved for children, while the parenteral form is used frequently in the perioperative setting. Premature infants and neonates experience

significant delays in clearing buprenorphine due to delays in expression of CYP3A4 [68, 105, 106]. In addition, glucuronidation is also delayed in premature and low-birthweight babies, contributing to delayed clearance [107–110]. By age 4–7 years, clearance rates are threefold greater than in adults [111, 112].

6.2 Elderly

A consensus group reported buprenorphine is an important opioid to be used in the elderly for safety and efficacy reasons [113]. Buprenorphine clearance does not change with age [114]; individuals over the age of 70 years, compared with younger individuals (average age of 32 years) receiving transdermal buprenorphine 10 μg/h, had the same clearance rate after the patch was removed [115].

6.3 Renal Impairment

The pharmacokinetics of transdermal buprenorphine in patients with severe renal failure receiving hemodialysis have demonstrated that plasma clearance is not altered by renal failure, and is unchanged by dialysis. Buprenorphine is not associated with post-dialysis pain [116]. Norbuprenorphine does not accumulate in renal failure, even though, in part, clearance is dependent on renal function. Moreover, uremia is associated with reduced CYP3A4 activity and hence less norbuprenorphine formation [117, 118]. Dialysis improves CYP3A4 activity, therefore levels may vary depending on the effectiveness of dialysis [119]. Accumulation of glucuronidated metabolites is possible, and drug elimination is unchanged with parenteral injection [120, 121]. Buprenorphine is one of the safer opioids to use in renal failure.

6.4 Liver Impairment

Mild to moderate liver impairment (Child–Pugh A and B) does not impair clearance and dose adjustments are not necessary. However, naloxone bioavailability may markedly increase in hepatic failure, such that the combination formulations should not be used in moderate to severe hepatic failure [122]. Patients with severe liver failure and portal hypertension will have increased buprenorphine bioavailability [123]; however, glucuronidation is better preserved than mixed-function oxidases, which may modulate bioavailability [123–125]. On the other hand, certain glucuronidases can be reduced in severe liver disease. Overall preservation is related to upregulation of multiple UGTs in the remaining hepatocytes and significant extrahepatic glucuronidation [125, 126]. Buprenorphine is bound to α1-acid glycoprotein, which is not as reduced by liver disease [125]. It also has more predictable pharmacokinetics than fentanyl or methadone in liver failure, which are subject to mixed-function oxidases; morphine and hydromorphone will have the same relative pharmacokinetics [96]. At the onset of hepatorenal syndrome, buprenorphine may be preferred because of its stable pharmacokinetics in renal failure and ceiling effect on respiratory failure [127]. More studies are needed in this important area.

7 Systematic Reviews of Clinical Studies

We conducted an informal systematic review of buprenorphine analgesic studies using the PubMed electronic database to select representative trials and articles on various important topics regarding buprenorphine use as an analgesic. We initially focused on systematic reviews, then on randomized and non-randomized trials of transdermal buprenorphine and buccal buprenorphine (summarized in Tables 2, 3, and 4). We then briefly reviewed representative studies of buprenorphine as a postoperative analgesic, and comparisons of analgesia between sublingual buprenorphine and buprenorphine/naloxone. We also reviewed equivalence and methods of rotating from potent opioids to buprenorphine. Finally, we reviewed barriers to using sublingual buprenorphine as an analgesic when it is not licensed as such.

Several studies have compared fentanyl, morphine, and buprenorphine analgesia and adverse effects as primary outcomes, with one review encompassing 14 randomized and quasi-randomized comparisons [128]. Buprenorphine in this limited comparison reduced pain intensity to a greater extent than morphine (mean difference − 16.2 on a 0–100 visual analog scale [VAS]; 95% confidence interval [CI] − 28.9 to − 3.5). Morphine was associated with higher rates of constipation (odds ratio [OR] 7.5, 95% CI 1.4–38.8, and patients discontinued morphine more often (OR 5.8, 95% CI 1.17–20.1). Transdermal fentanyl caused more nausea than transdermal buprenorphine (OR 4.7, 95% CI 1.07–20.4) and had a higher discontinuation rate (OR 5.9, 95% CI 1.8–19.9). There was a non-significant difference in pain control between the two transdermal opioids. The authors concluded that buprenorphine has a better therapeutic index than morphine and fentanyl; however, the wide CIs for effect sizes in this review suggest a great deal of variability between studies, which weakens the conclusions.

Two years later, the same authors published a systematic review of the adverse effects of transdermal fentanyl and transdermal buprenorphine [129]. Randomized and non-randomized trials, and direct and indirect comparisons were included. A total of 49 unique studies found that fentanyl caused higher rates of constipation and had a greater number of serious adverse events. There were no differences in the frequency of dizziness, somnolence, nausea, or treatment discontinuation (which differed from the first review).

Table 2 Randomized trials of transdermal buprenorphine

Reference	Type of pain (no. of patients)	Buprenorphine dose	Comparator	Outcomes	Adverse events	Comments
Sittl et al. [136]	Uncontrolled chronic pain [157]	35, 52.5, 70 µg/h	Placebo	Good to complete pain relief: 43.5% BUP 32.5% Placebo Reduction in rescue doses: 56.7 vs. 8%	78%, mild to moderate, largely CNS, GI	–
Conaghan et al. [138]	Osteoarthritis (219)	5–25 µg/h	Codeine plus acetaminophen	Same pain control at 12 weeks	81–86%. Largely mild to moderate, erythema at the patch site 27%. Attrition in both arms was high	No difference in laxative use
Poulain et al. [137]	Cancer (289), opioid tolerant [morphine 90–150 mg/day]	70 µg/h	Placebo	Responder < 5 NRS: 74.5% BUP, 50% Placebo	–	Attrition 100/289
Steiner et al. [139]	Chronic LBP (541)	10–20 µg/h	Enriched enrollment randomized withdrawal	BUP reduced pain −0.58 (NRS 0–10)	55% BUP and 52% Placebo	–
Landau et al. [141]	Chronic LBP (267)	10–20 µg/h	Enriched enrollment randomized withdrawal	Ineffective analgesia, BUP 57.2% vs. 65% Placebo, NNT 7.2 OR ineffective analgesia Placebo 1.79 (95% CI 1.09–2.95)	Most AEs were with titration- pruritus at the patch site, headache 3.9%, somnolence 2.3%	Opioid-naive
Gordon et al. [142]	Chronic LBP [78]	10–40 µg/h	Placebo	VAS 45.3 BUP vs. 53.1 Placebo Improved sleep	Nausea, dizziness, somnolence, dry mouth	Constipation not different from Placebo
Steiner et al. [140]	Chronic LBP (443), opioid-tolerant receiving morphine 30–80 mg	5 and 20 µg/h	Oxycodone 40 mg/day	Decreased pain − 0.67 (20 vs. 5) and − 0.75 (oxycodone vs. 5) [0–10 NRS]	77% BUP 20 73% oxycodone	BUP 20 µg/h = oxycodone 40 mg/day
Mitra et al. [143]	Chronic non-cancer pain [46]	Transdermal buprenorphine	Transdermal fentanyl	At 12 months, 16/46 remain on study Sleep: BUP > Fentanyl Mood: BUP > Fentanyl	Fentanyl > BUP	High attrition

LBP low back pain, *BUP* buprenorphine, *NRS* numerical rating scale, *NNT* number needed to treat, *CI* confidence interval, *VAS* visual analog scale, *CNS* central nervous system, *GI* gastrointestinal, *AEs* adverse events

Table 3 Non-randomized transdermal buprenorphine trials

Reference	Type of pain (no. of patients)	Buprenorphine dose	Design	Outcome	Adverse effects	Comment
Muriel et al. [144]	Non-cancer 82.4% (1212)	35, 52.5, 70 µg/h	Open-label	Good to very good pain control at 1 month, 63%	42.5%, most commonly nausea and vomiting, constipation 2%	56% completed 3 months
Griessinger et al. [145]	Non-cancer 72% (3690)	35, 52.5, 70 µg/h	Postmarketing	Good to very good relief, 80%	22%, treatment-associated 16% Attrition for lack of efficacy 5%	
Gianni et al. [146]	Elderly, non-cancer (93)	35, 52.5, 70 µg/h: patch cut for lower doses	Observational	Reduced pain at 1 month, 56% Improved sleep, reduced rescue, improved depression and ADLs	47%, 37% stopped,12.5% stopped for AEs – nausea, constipation, sleepiness, skin rash	
Sittl et al. [147]	Cancer (496) and non-cancer (380)	35, 52.5, 70 µg/h	Retrospective Fentanyl comparator	Mean dose escalation Fentanyl > BUP		Fentanyl/morphine 1:85–89 BUP/morphine 1:80–81
Likar et al. [148]	Non-cancer (239) and cancer (134)	35, 52.5, 70 µg/h		90% satisfaction with pain control, 66% required < + 1 rescue dose	9.2% nausea, 4.6% dizziness, 4.2% vomiting, 3.8% constipation, 12% erythema and 10% pruritus at the patch site, duration of treatment 7.5 months	
Przeklasa-Muszynska et al. [155]	Cancer (80.7%) and non-cancer (4030)	35, 52.5, 70 µg/h		VAS baseline 62.5 mm to 16.5 mm at 3 months, 88.7% good to very good pain control	137 stopped due to lack of efficacy, 33 stopped for AEs, most commonly nausea	
Yoon et al. [150]	Non-cancer (119)	5–40 µg/h		Baseline NRS 6.2–2.64 at 12 weeks, improved sleep and QOL	78%, nausea 39.5%, constipation 31.6%, dizziness 27.2%, somnolence 19.3%, vomiting 16.7%, 50 stopped Bup	Opioid-naive
Lesen et al. [151]	Non-cancer (7053)	5–20 µg/h		Duration average on BUP 260 days, low-dose escalation from 11 to 15 µg/h		Only 4% remained on BUP at 2 years

ADLs activities of daily living, *VAS* visual analog scale, *NRS* numerical rating scale, *QOL* quality of life, *AEs* adverse events, *BUP* buprenorphine

Table 4 Buccal buprenorphine analgesic trials

Reference	Patient (n) and Pain	Buccal dose	Comparator	Outcome	Adverse effects	Comments
Rauck et al. [152]	CLBP (749)—opioid-naive	150–450 μg q12 h	Placebo-enriched Enrollment Randomized Withdrawal	Between-group differences pain severity −0.61 by NRS. Reduced pain by 30% (63% vs. 47%)	10% nausea 4% constipation	Similar AEs to placebo
Gimbel et al. [153]	CLBP (511)—opioid-tolerant 30–160 mg morphine daily	150–900 μg q12 h	Placebo-enriched Enrollment Randomized Withdrawal	Between-group differences pain severity −0.98 NRS	Vomiting on BUP 5% vs. 2%, no other differences with Placebo	
Hale et al. [154]	CLBP (445)	150–900 μg q12 h	Single-arm, long-term follow-up	158/435 on BUP at 48 weeks. Dose unchanged in 86%	22% with titration, 14% long-term Discontinuation for AEs 2.8%, most commonly nausea, headache, constipation	

AEs adverse events, *BUP* buprenorphine, *NRS* numerical rating scale, *q12h* every 12 h, *CLBP* chronic low back pain

The authors felt that transdermal buprenorphine should be favored over transdermal fentanyl in patients with renal impairment, the elderly, and those immunosuppressed; however, there were no direct comparisons in these populations, therefore the conclusions require validation in randomized trials.

A more recent comparison of transdermal buprenorphine with transdermal fentanyl involved 18 prospective, retrospective comparisons and systematic reviews [130]. In prospective comparisons at the landmark time of 90 days on therapy, there were no differences in the opioid dose escalation index that had been observed in retrospective studies. In retrospective studies, dose escalation was less with buprenorphine. By indirect comparison, the sum of the pain intensity differences (SPID) and response defined by a 30% reduction in pain intensity were similar between the two opioids; however, fewer patients were rotated off buprenorphine. The authors concluded that analgesia produced by these two opioids was similar and that patients developed less analgesic tolerance, although this was only observed in retrospective comparisons.

A systematic review of sublingual buprenorphine for cancer pain included studies published from 1979 through 2013 [131]. Of the 10 trials, all but one was observational and low quality, with a high risk of bias. The average pain reduction was 2.3 points on a 0- to 10-point numerical rating scale (NRS).

A second systematic review of sublingual buprenorphine included trials published between 1979 and 2012 [132]. All studies were observational and hence at significant risk for bias. In one study, 0.2–0.4 mg of sublingual buprenorphine produced similar analgesia as 5–20 μg/h of transdermal buprenorphine. Pain intensity decreased from a baseline severity of 5.9 (0–10 NRS) to 3.1. The average reduction in pain was between 2.1 and 2.3 points on a 0–10 NRS. Adverse effects, including nausea, vomiting, and dizziness, were worse with sublingual than transdermal buprenorphine.

A systematic review of buprenorphine for cancer pain included eight studies of transdermal buprenorphine; five studies involved sublingual tablets, two studies involved intramuscular buprenorphine, and one study involved subcutaneous buprenorphine [133]. Ten of 16 studies were small, with < 100 individuals. In the eight transdermal trials, comparisons were with placebo or morphine. The relative risk (RR) for pain reduction favored buprenorphine (1.35, 95% CI 1.14–1.59), which was equivalent to a number needed to treat (NNT) to produce a pain response better than the comparator of 4.9. Insufficient data were available for sublingual and parenteral buprenorphine. Adverse effects were less with buprenorphine (RR 0.38, 95% CI 0.2–0.71), while CNS adverse effects were similar to placebo in one study and hydromorphone in a second study. Similar to the previously reviewed study, sublingual buprenorphine had greater adverse effects than transdermal buprenorphine. Sublingual buprenorphine related to nausea and vomiting was similar to pentazocine, while CNS adverse effects were similar to both tramadol and pentazocine. Withdrawal because of adverse effects was similar to placebo and tramadol.

A Cochrane Database systematic review focused on buprenorphine for neuropathic pain [134]. Of the 10 trials, none met the criteria of a randomized trial of 2 weeks' duration, which the authors felt was the minimal criteria needed to gauge clinical efficacy. The authors felt that randomized trials are needed to assess the benefits of buprenorphine in neuropathic pain.

On 16 January 2017, the Canadian Agency for Drugs and Technologies in Health published a summary of all studies to date that involved buprenorphine in the management of chronic pain [135]. This summary included four systematic reviews, two Cochrane Database systematic reviews, and two systematic reviews with meta-analysis. The number of trials in systematic reviews was low, which subsequently biased the results. There were six randomized, double-blind trials, four randomized, open-label trials, and four enriched enrollment randomized withdrawal studies. Comparators to buprenorphine were placebo, tramadol, transdermal fentanyl, codeine and oxycodone. All but two randomized trials were sponsored by pharmaceutical companies. Patients in these studies had pain from osteoarthritis, low back pain, neuropathic pain, musculoskeletal pain, and AIDs. The review found that tramadol, codeine, and buprenorphine produced similar analgesia in osteoarthritis, while fentanyl and buprenorphine produced similar analgesia in those with neuropathic pain and pain from AIDs. Transdermal buprenorphine 20 µg/h was equivalent to oxycodone 40 mg daily when treating low back pain. A network meta-analysis concluded that morphine was better for chronic low back pain. Buprenorphine was superior to placebo in all comparison trials, with similar adverse effects to placebo, but fewer dropouts.

A review of transdermal buprenorphine trials, both randomized and non-randomized, and buccal buprenorphine are available in Tables 2, 3, and 4, respectively [136–155].

8 Miscellaneous but Important Topics

8.1 Postoperative Pain Management in Buprenorphine-Tolerant Patients

In an early study involving patients with postoperative pain, 0.2 mg of parenteral buprenorphine was administered every 3–15 min until pain control was achieved. Doses required for analgesia ranged widely, from 0.2 to 7 mg. The cohort of young women in this study had few comorbidities and, predictably, better tolerated this dosing strategy than those with multiple comorbidities. The duration of analgesia post-titration averaged 14.2 h with loading, and was directly related to dose. Despite doses as high as 7 mg, respiratory depression did not occur [156].

Transdermal buprenorphine has been used for postoperative pain. Doses between 5 and 20 µg/h produce similar analgesia as tramadol 150–300 mg/day for single-level spinal surgery [157].

Parenteral buprenorphine by patient-controlled analgesia (PCA) has been compared with morphine analgesia by PCA for lung surgery [158]. Buprenorphine 25 µg/h with PCA demand dosing was compared with morphine 0.83 mg/h. The time to activation of PCA was longer for buprenorphine and there was less hyperalgesia around the incision site with buprenorphine. In a second PCA study involving patients undergoing spinal surgery, the demand doses were actually more frequent with buprenorphine in the first 6 h after surgery, which differed from the first study; however, after 6 h, the number of rescue doses was the same as with PCA morphine [159].

There are a multitude of other studies in the postoperative setting that have been published but are not reviewed here as this could be a separate review. However, one unique feature of buprenorphine is that it is a voltage-gated sodium channel blocker and has been combined with local anesthetics in perineural blocks for regional postoperative analgesia [40, 160–162].

8.2 Is Sublingual Buprenorphine/Naloxone Objectively and Subjectively Equivalent to Sublingual Buprenorphine Alone? Buprenorphine Equivalents

Buprenorphine bioavailability is slightly greater with generic buprenorphine/naloxone compared with sublingual buprenorphine without naloxone [163]. Technically, the differences are small and not clinically significant, and clinicians should consider them equivalent, milligram for milligram. The addition of naloxone does not influence buprenorphine bioavailability. In fact, some authors have claimed that perhaps naloxone attenuates some of the buprenorphine adverse effects [164]. However, patients subjectively experience a difference when switching from buprenorphine to the combination. In one study, 50% of patients who switched to the combination experienced adverse effects that they did not experience while receiving generic sublingual buprenorphine tablets [165]. This was more evident in those who were opioid-dependent. Eighty percent of patients who switched to the combination described it as a bad experience, however there may be an explanation for this. Both naloxone and buprenorphine are glucuronidated and compete for metabolism by the same conjugases. Buprenorphine causes substrate inhibition at UGT2B7, which also metabolizes naloxone. At the enzyme site, buprenorphine concentrations of 0.3 nM will prevent naloxone metabolism through UGT2B7, which may make naloxone more systemically bioavailable [166]. Although buprenorphine bioavailability remains the same, naloxone bioavailability may increase with doses, such that, particularly in opioid-dependent patients, subjective adverse effects may be experienced.

Table 5 lists the equivalence between sublingual, parenteral, and transdermal buprenorphine, as published in the palliativedrugs.com newsletter dated November/December 2006.

Table 5 Buprenorphine equivalents, sublingual, parenteral and transdermal[a]

Sublingual buprenorphine (μg)	Subcutaneous buprenorphine (μg)	Transdermal buprenorphine (μg/h)
240	120	5
480	240	10
960	480	20
1680	840	35
2520	1260	52.5
3360	1680	70

[a]From the palliativedrugs.com newsletter, November/December 2006

Table 6 Oral morphine to transdermal buprenorphine equivalents[a]

Oral morphine (mg/day)	Transdermal buprenorphine (μg/h)
12	5
24	10
48	20
84	35
126	52.5
168	70

[a]From the palliativedrugs.com newsletter, November/December 2006

8.3 Buprenorphine Equivalents to Other Opioids

Some direct comparisons of analgesic equivalents have been published, but equivalent studies are sparse. Many equianalgesic estimates are indirect through a third opioid, which is likely to have inaccuracies. Equivalents compared across select populations (chronic low back pain, neuropathic pain, postoperative pain, and cancer pain) may not be generalizable. With this in mind, the buprenorphine to morphine equianalgesic ratio ranges between 1:60 and 1:100 [167–172]. Sublingual buprenorphine 0.4 mg is equivalent to 30 mg of immediate-release morphine, while parenteral buprenorphine is 30–40 times more potent than parenteral morphine, such that 0.3 mg of buprenorphine is equivalent to 10 mg of morphine [173]. Table 6 lists the equivalents of oral morphine to transdermal buprenorphine. In two studies involving patients with chronic cancer pain, buprenorphine 0.8 mg was equivalent to 60 mg of oral morphine and 35 μg/h of transdermal buprenorphine [171, 172].

In another study, transdermal buprenorphine 20 μg/h produced the same degree of analgesia as 40 mg of oxycodone in patients with chronic low back pain [139]. In the postoperative setting, 5–20 μg/h of transdermal buprenorphine produced similar analgesia as tramadol 150–300 mg/day [157]. In a small series of patients with cancer, the equivalence between parenteral fentanyl and buprenorphine is reported to be 6:8, such that fentanyl 25 μg/h is equivalent to 35 μg/h of buprenorphine, which in turn is equivalent to 1 mg/h of parenteral morphine [172, 174].

8.4 Can Buprenorphine be Combined with Other Potent Opioids?

Because buprenorphine has a high affinity and long dwell time on mu receptors, it would seem rational that it would produce subadditive analgesia when combined with other opioids, and vice versa, such that potent opioids combined with around-the-clock buprenorphine would also be subadditive. In the postoperative setting, at usual analgesic doses, buprenorphine did not impair morphine analgesia. Buprenorphine 0.4 μg/kg as an infusion, and 0.15 μg/kg as the demand dose, did not prevent morphine analgesia [175]. Cancer patients with breakthrough pain receiving transdermal buprenorphine doses ranging from 35 to 70 μg/h responded well to morphine. The investigators used an oral morphine to transdermal buprenorphine ratio of 75:1 and converted the equivalent parenteral morphine dose using a ratio of 1:3 (parenteral to morphine) [176].

The most controversial area is in the perioperative setting when patients are receiving high-dose buprenorphine for maintenance therapy. Some recommend keeping buprenorphine in the perioperative period if the risk of pain from the procedure is low, but recommend switching to methadone prior to surgery when the risk of pain in the perioperative setting is high. Once the surgical pain has resolved, patients are switched back to buprenorphine [177, 178]. This is undertaken because mu receptor affinity is about the same between methadone and morphine, therefore one would anticipate an analgesic response to morphine. This approach is based on a theoretical understanding of buprenorphine pharmacology that is rational. However, clinical retrospective studies of patients receiving buprenorphine maintenance therapy found that morphine responses were not different compared with methadone-maintained individuals [47, 179]. These authors felt that buprenorphine-maintained individuals do not need to be switched off their maintenance opioid, an approach that has also been advocated by others [180].

8.5 Rotating to Buprenorphine from Other Opioids and the Risk of Withdrawal

Buprenorphine causes withdrawal in a 'stop/start' strategy when used in opioid rotation for patients receiving high doses of potent opioids. There are several factors that predict this occurrence: [1] the dose of buprenorphine; [2] the time interval between stopping the potent opioid and starting buprenorphine; [3] the patients' accumulated

physical dependence [181]; and [4] the dose of potent opioid prior to rotation. Withdrawal is unlikely if individuals receive ≤ 60 mg/day of morphine or methadone ≤ 30 mg. Several approaches use a gap between stopping the potent opioid and initiating buprenorphine. In one study, the potent opioid was stopped for 12 h (excluding methadone, which required a longer gap) and sublingual buprenorphine 1 mg was initially administered, followed by 2 mg 45 and 90 min later for persistent pain. Titration thereafter was based on analgesia. Buprenorphine was also titrated if patients experienced withdrawal off their potent opioid [182]. This approach illustrates a common strategy when rotating off high-dose opioids to buprenorphine (exclusive on methadone); a 12- to 24-h gap and relatively small but frequent sublingual doses were initiated at the first sign of withdrawal.

A second study involved patients receiving 60–200 mg/day of oral morphine equivalents (excluding methadone at > 80 mg/day). Patients stopped their opioid and sublingual buprenorphine 2 mg was initiated at the onset of withdrawal, and 2–4 mg was administered as needed thereafter for pain or if withdrawal symptoms from abstinence occurred. The next day, 2 mg was administered every 4 h as needed for pain, and 4 mg was administered at night. On the second day, buprenorphine was administered as 4 mg every 8 h, and 2–4 mg every 4 h as needed [183].

A third approach involved stopping all opioids and starting sublingual buprenorphine 8 mg 24 h later (48 h later if receiving methadone) at the onset of withdrawal. An 8 mg dose was repeated 1 h later for pain or persistent withdrawal symptoms. Clonidine was also provided to blunt abstinence. Total daily doses were limited to 32 mg. Doses were adjusted to analgesia 1 week later [184, 185].

An overlap approach has been previously published in a randomized trial. Patients receiving 80–220 mg of oral morphine equivalents had their opioid dose reduced by half, while buprenorphine was added at half the equivalent doses using an equianalgesic ratio of buprenorphine (buccal) to oral morphine of 1:100. For example, if a patient was receiving 160 mg/day of sustained-release morphine, the dose was reduced to 40 mg twice daily and buccal buprenorphine 300 µg was added twice daily. Of 35 participants, only two experienced mild withdrawal [186]. Presumably, a completed rotation could be accomplished through further reductions in the potent opioid and simultaneous buprenorphine titration, although this was not part of the study.

8.6 Can Sublingual Buprenorphine Be Used as an Analgesic Without the Training and Registration Required for Addiction?

Suboxone™ (Actavis Elizabeth, LLC, Elizabeth, NJ, USA) and Subutex™ (Roxane Laboratories, Columbus, OH, USA) are licensed by the FDA for opioid maintenance therapy, but not as analgesics. Sublingual buprenorphine tablets were approved for office-based addiction therapy established by the Drug Addiction Treatment Act of 2000. Prescribers who explicitly use buprenorphine for detoxification and maintenance therapy must register with the Center for Substance Abuse Treatment of the Substance Abuse and Mental Health Services Administration and undergo special training for certification. However, the FDA permits the use of Suboxone™ and Subutex™ as an off-label analgesic. The requirements involve registering with the Drug Enforcement Administration as a prescriber of schedule III medications. Registration as a prescriber for maintenance therapy and training are otherwise not required. It is important that prescribers using sublingual buprenorphine as an analgesic note on their prescriptions that it is explicitly being used for pain, otherwise pharmacies will not fill the prescription if the prescriber is not registered as a maintenance prescriber. Some insurance companies attempt to limit sublingual buprenorphine to addiction and maintenance only. We refer to Heit and Covington's open letter to the FDA as a reference in an appeal for covering the medication for analgesia [187].

8.7 Buprenorphine and QTc Intervals

Buprenorphine mildly inhibits cardiac repolarization and prolongs QTc intervals. Its affinity for the potassium repolarization channel is 100-fold less than methadone. Clinically, patients have been rotated from methadone to buprenorphine as a result of a prolonged QTc interval, with resolution of the prolonged QTc interval [188–194]. However, due to the prolonged QTc intervals noted at doses > 20 ug/h, the transdermal buprenorphine ceiling dose in the US is 20 µg/h. Transdermal doses of 10 µg/h had no effect on QTc intervals, whereas the 40 and 80 µg/h doses increased QTc by 12–14 ms. Interestingly, naltrexone eliminated the prolonged QTc interval [195]. Despite this finding, this has not been a concern in the maintenance literature, nor has there been a need to monitor buprenorphine with serial ECGs on maintenance therapy, as has been suggested with methadone [196, 197]. Buprenorphine has not been associated with arrhythmias or Torsades de pointe [195].

On the other hand, when buprenorphine is combined with medications that prolong the QTc interval, there may be concern. QTc intervals are prolonged when buprenorphine is combined with certain antiretroviral medications (delavirdine and ritonavir), but prolongation does not occur if these drugs are not combined, and, although the clinical significance is uncertain, physicians should be cautious [198]. Some clinicians suggest avoiding buprenorphine in patients who already have a prolonged QTc interval and a genetically related prolonged QT syndrome, or who are

receiving antiarrhythmic medication that prolongs the QTc interval, such as amiodarone [199].

9 Status of Buprenorphine as an Analgesic

There is increased interest in using buprenorphine as an analgesic, with a growing number of formulations. Buprenorphine formulations for maintenance therapy can be used off-label for analgesia but it must be clearly marked on the prescription that the intent is analgesia. Buprenorphine may be preferred in patients who have renal failure or mild to moderate liver failure, those in whom standard opioids have not worked or those who have difficulty swallowing, the elderly, or those who wish to remain sexually active while receiving opioid therapy [1]. The generic formulations are less expensive than most sustained-released and transdermal potent opioid commercial products. Buprenorphine is an important opioid in the 'tool box' of analgesics, for which clinicians should be knowledgeable.

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Compliance with Ethical Standards

Conflicts of interest M. P. Davis, G. Pasternak and B. Behm all declare that they have no relevant conflicts of interest.

References

1. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012;10(6):209–19.
2. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. Arch Gen Psychiatry. 1978;35(4):501–16.
3. Henningfield JE, Sun WZ. Concluding statement—neuropharmacological basis and clinical rationale for control of transdermal buprenorphine as a step II analgesic. Acta Anaesthesiol Taiwan. 2015;53(2):77–9.
4. Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32.
5. Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. Br J Anaesth. 2005;94(6):825–34.
6. Pergolizzi JV Jr, Scholten W, Smith KJ, Leighton-Scott J, Willis JC, Henningfield JE. The unique role of transdermal buprenorphine in the global chronic pain epidemic. Acta Anaesthesiol Taiwan. 2015;53(2):71–6.
7. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Sympt Manag. 2005;29(3):297–326.
8. Ding Z, Raffa RB. Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine. Br J Pharmacol. 2009;157(5):831–43.
9. Khroyan TV, Wu J, Polgar WE, Cami-Kobeci G, Fotaki N, Husbands SM, et al. BU08073 a buprenorphine analogue with partial agonist activity at mu-receptors in vitro but long-lasting opioid antagonist activity in vivo in mice. Br J Pharmacol. 2015;172(2):668–80.
10. Lutfy K, Cowan A. Buprenorphine: a unique drug with complex pharmacology. Curr Neuropharmacol. 2004;2(4):395–402.
11. Negus SS, Bidlack JM, Mello NK, Furness MS, Rice KC, Brandt MR. Delta opioid antagonist effects of buprenorphine in rhesus monkeys. Behav Pharmacol. 2002;13(7):557–70.
12. Grinnell SG, Ansonoff M, Marrone GF, Lu Z, Narayan A, Xu J, et al. Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. Synapse. 2016;70(10):395–407.
13. Majumdar S, Grinnell S, Le Rouzic V, Burgman M, Polikar L, Ansonoff M, et al. Truncated G protein-coupled mu opioid receptor MOR-1 splice variants are targets for highly potent opioid analgesics lacking side effects. Proc Natl Acad Sci USA. 2011;108(49):19778–83.
14. Traynor JR, Nahorski SR. Modulation by mu-opioid agonists of guanosine-5′-O-(3-[35S]thio)triphosphate binding to membranes from human neuroblastoma SH-SY5Y cells. Mol Pharmacol. 1995;47(4):848–54.
15. Fantozzi R, Mullikin-Kilpatrick D, Blume AJ. Irreversible inactivation of the opiate receptors in the neuroblastoma x glioma hybrid NG108-15 by chlornaltrexamine. Mol Pharmacol. 1981;20(1):8–15.
16. Zaki PA, Keith DE Jr, Brine GA, Carroll FI, Evans CJ. Ligand-induced changes in surface mu-opioid receptor number: relationship to G protein activation? J Pharmacol Exp Ther. 2000;292(3):1127–34.
17. McPherson J, Rivero G, Baptist M, Llorente J, Al-Sabah S, Krasel C, et al. mu-opioid receptors: correlation of agonist efficacy for signalling with ability to activate internalization. Mol Pharmacol. 2010;78(4):756–66.
18. Vanderah TW, Gardell LR, Burgess SE, Ibrahim M, Dogrul A, Zhong CM, et al. Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance. J Neurosci. 2000;20(18):7074–9.
19. Ossipov MH, Lai J, Malan TP Jr, Porreca F. Spinal and supraspinal mechanisms of neuropathic pain. Ann N Y Acad Sci. 2000;909:12–24.
20. Stanciu CN, Glass OM, Penders TM. Use of Buprenorphine in treatment of refractory depression: a review of current literature. Asian J Psychiatr. 2017;26:94–8.
21. Karp JF, Butters MA, Begley AE, Miller MD, Lenze EJ, Blumberger DM, et al. Safety, tolerability, and clinical effect of low-dose buprenorphine for treatment-resistant depression in midlife and older adults. J Clin Psychiatry. 2014;75(8):e785–93.
22. Bodkin JA, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. J Clin Psychopharmacol. 1995;15(1):49–57.
23. Falcon E, Browne CA, Leon RM, Fleites VC, Sweeney R, Kirby LG, et al. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. Neuropsychopharmacology. 2016;41(9):2344–51.
24. Bohn LM, Lefkowitz RJ, Gainetdinov RR, Peppel K, Caron MG, Lin FT. Enhanced morphine analgesia in mice lacking beta-arrestin 2. Science. 1999;286(5449):2495–8.
25. Raehal KM, Schmid CL, Groer CE, Bohn LM. Functional selectivity at the mu-opioid receptor: implications for understanding opioid analgesia and tolerance. Pharmacol Rev. 2011;63(4):1001–19.

26. Raehal KM, Bohn LM. The role of beta-arrestin2 in the severity of antinociceptive tolerance and physical dependence induced by different opioid pain therapeutics. Neuropharmacology. 2011;60(1):58–65.
27. Reiter E, Ahn S, Shukla AK, Lefkowitz RJ. Molecular mechanism of beta-arrestin-biased agonism at seven-transmembrane receptors. Annu Rev Pharmacol Toxicol. 2012;52:179–97.
28. Yu Y, Zhang L, Yin X, Sun H, Uhl GR, Wang JB. Mu opioid receptor phosphorylation, desensitization, and ligand efficacy. J Biol Chem. 1997;272(46):28869–74.
29. Grinnell SG, Majumdar S, Narayan A, Le Rouzic V, Ansonoff M, Pintar JE, et al. Pharmacologic characterization in the rat of a potent analgesic lacking respiratory depression, IBNtxA. J Pharmacol Exp Ther. 2014;350(3):710–8.
30. Cowan A. Buprenorphine: the basic pharmacology revisited. J Addict Med. 2007;1(2):68–72.
31. Cowan A. Buprenorphine: new pharmacological aspects. Int J Clin Pract Suppl. 2003;133:3–8 **(discussion 23–4)**.
32. Kogel B, Christoph T, Strassburger W, Friderichs E. Interaction of mu-opioid receptor agonists and antagonists with the analgesic effect of buprenorphine in mice. Eur J Pain. 2005;9(5):599–611.
33. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. Eur J Pain. 2009;13(3):219–30.
34. Recker MD, Higgins GA. The opioid receptor like-1 receptor agonist Ro 64-6198 (1S,3aS-8-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one) produces a discriminative stimulus in rats distinct from that of a mu, kappa, and delta opioid receptor agonist cue. J Pharmacol Exp Ther. 2004;311(2):652–8.
35. Lewis JW, Husbands SM. The orvinols and related opioids–high affinity ligands with diverse efficacy profiles. Curr Pharm Des. 2004;10(7):717–32.
36. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R, et al. Current knowledge of buprenorphine and its unique pharmacological profile. Pain Pract. 2010;10(5):428–50.
37. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. Palliat Med. 2006;20(Suppl 1):s3–8.
38. Gerhold KJ, Drdla-Schutting R, Honsek SD, Forsthuber L, Sandkuhler J. Pronociceptive and antinociceptive effects of buprenorphine in the spinal cord dorsal horn cover a dose range of four orders of magnitude. J Neurosci. 2015;35(26):9580–94.
39. Schnabel A, Reichl SU, Zahn PK, Pogatzki-Zahn EM, Meyer-Friessem CH. Efficacy and safety of buprenorphine in peripheral nerve blocks: a meta-analysis of randomised controlled trials. Eur J Anaesthesiol. 2017;34(9):576–86.
40. Leffler A, Frank G, Kistner K, Niedermirtl F, Koppert W, Reeh PW, et al. Local anesthetic-like inhibition of voltage-gated Na(+) channels by the partial mu-opioid receptor agonist buprenorphine. Anesthesiology. 2012;116(6):1335–46.
41. Rickli A, Liakoni E, Hoener MC, Liechti ME. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: link to clinical reports of serotonin syndrome. Br J Pharmacol. 2018;175(3):532–43.
42. Sutcliffe KJ, Henderson G, Kelly E, Sessions RB. Drug binding poses relate structure with efficacy in the mu opioid receptor. J Mol Biol. 2017;429(12):1840–51.
43. Christopoulos A, El-Fakahany EE. Qualitative and quantitative assessment of relative agonist efficacy. Biochem Pharmacol. 1999;58(5):735–48.
44. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. Clin J Pain. 2008;24(2):93–7.
45. Sloan P. Buprenorphine for chronic pain management. J Support Oncol. 2012;10(6):220–1.
46. Macintyre PE, Huxtable CA. Buprenorphine for the management of acute pain. Anaesth Intensive Care. 2017;45(2):143–6.
47. Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care. 2013;41(2):222–30.
48. Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care. 2011;39(5):804–23.
49. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. J Pharmacol Exp Ther. 1995;272(2):505–10.
50. Tournier N, Chevillard L, Megarbane B, Pirnay S, Scherrmann JM, Decleves X. Interaction of drugs of abuse and maintenance treatments with human P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2). Int J Neuropsychopharmacol. 2010;13(7):905–15.
51. Alhaddad H, Cisternino S, Decleves X, Tournier N, Schlatter J, Chiadmi F, et al. Respiratory toxicity of buprenorphine results from the blockage of P-glycoprotein-mediated efflux of norbuprenorphine at the blood-brain barrier in mice. Crit Care Med. 2012;40(12):3215–23.
52. Raehal KM, Walker JK, Bohn LM. Morphine side effects in beta-arrestin 2 knockout mice. J Pharmacol Exp Ther. 2005;314(3):1195–201.
53. Webster LR, Camilleri M, Finn A. Opioid-induced constipation: rationale for the role of norbuprenorphine in buprenorphine-treated individuals. Subst Abuse Rehabil. 2016;7:81–6.
54. Brown SM, Holtzman M, Kim T, Kharasch ED. Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. Anesthesiology. 2011;115(6):1251–60.
55. Yassen A, Kan J, Olofsen E, Suidgeest E, Dahan A, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the respiratory depressant effect of norbuprenorphine in rats. J Pharmacol Exp Ther. 2007;321(2):598–607.
56. Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. J Pharmacol Exp Ther. 1997;281(1):428–33.
57. Strang J, Knight A, Baillie S, Reed K, Bogdanowicz K, Bell J. Norbuprenorphine and respiratory depression: Exploratory analyses with new lyophilized buprenorphine and sublingual buprenorphine. Int J Clin Pharmacol Ther. 2018;56(2):81–5.
58. Megarbane B, Marie N, Pirnay S, Borron SW, Gueye PN, Risede P, et al. Buprenorphine is protective against the depressive effects of norbuprenorphine on ventilation. Toxicol Appl Pharmacol. 2006;212(3):256–67.
59. Brown SM, Campbell SD, Crafford A, Regina KJ, Holtzman MJ, Kharasch ED. P-glycoprotein is a major determinant of norbuprenorphine brain exposure and antinociception. J Pharmacol Exp Ther. 2012;343(1):53–61.
60. Wang Y, Cipriano A, Munera C, Harris SC. Dose-dependent flux of buprenorphine following transdermal administration in healthy subjects. J Clin Pharmacol. 2016;56(10):1263–71.
61. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev. 2011;4(1):28–41.
62. Bullingham RE, McQuay HJ, Moore RA. Clinical pharmacokinetics of narcotic agonist-antagonist drugs. Clin Pharmacokinet. 1983;8(4):332–43.
63. Mendelson J, Upton RA, Everhart ET, Jacob P 3rd, Jones RT. Bioavailability of sublingual buprenorphine. J Clin Pharmacol. 1997;37(1):31–7.
64. Nath RP, Upton RA, Everhart ET, Cheung P, Shwonek P, Jones RT, et al. Buprenorphine pharmacokinetics: relative

bioavailability of sublingual tablet and liquid formulations. J Clin Pharmacol. 1999;39(6):619–23.
65. Downing JW, Leary WP, White ES. Buprenorphine: a new potent long-acting synthetic analgesic. Comparison with morphine. Br J Anaesth. 1977;49(3):251–5.
66. Yassen A, Olofsen E, Kan J, Dahan A, Danhof M. Animal-to-human extrapolation of the pharmacokinetic and pharmacodynamic properties of buprenorphine. Clin Pharmacokinet. 2007;46(5):433–47.
67. Yassen A, Olofsen E, Dahan A, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine and fentanyl in rats: role of receptor equilibration kinetics. J Pharmacol Exp Ther. 2005;313(3):1136–49.
68. Bullingham RE, McQuay HJ, Moore A, Bennett MR. Buprenorphine kinetics. Clin Pharmacol Ther. 1980;28(5):667–72.
69. Yassen A, Kan J, Olofsen E, Suidgeest E, Dahan A, Danhof M. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the respiratory-depressant effect of buprenorphine and fentanyl in rats. J Pharmacol Exp Ther. 2006;319(2):682–92.
70. Yassen A, Olofsen E, Romberg R, Sarton E, Danhof M, Dahan A. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the antinociceptive effect of buprenorphine in healthy volunteers. Anesthesiology. 2006;104(6):1232–42.
71. Koppert W, Ihmsen H, Korber N, Wehrfritz A, Sittl R, Schmelz M, et al. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005;118(1–2):15–22.
72. Ebling WF, Lee EN, Stanski DR. Understanding pharmacokinetics and pharmacodynamics through computer stimulation: I. The comparative clinical profiles of fentanyl and alfentanil. Anesthesiology. 1990;72(4):650–8.
73. Pontani RB, Vadlamani NL, Misra AL. Disposition in the rat of buprenorphine administered parenterally and as a subcutaneous implant. Xenobiotica. 1985;15(4):287–97.
74. Shiue CY, Bai LQ, Teng RR, Arnett CD, Dewey SL, Wolf AP, et al. A comparison of the brain uptake of *N*-(cyclopropyl[11C] methyl)norbuprenorphine ([11C]buprenorphine) and *N*-(cyclopropyl[11C]methyl)nordiprenorphine ([11C]diprenorphine) in baboon using PET. Int J Rad Appl Instrum B. 1991;18(3):281–8.
75. Greenwald M, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn M, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry. 2007;61(1):101–10.
76. Plosker GL. Buprenorphine 5, 10 and 20 mug/h transdermal patch: a review of its use in the management of chronic non-malignant pain. Drugs. 2011;71(18):2491–509.
77. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. Drugs. 1979;17(2):81–110.
78. Brewster D, Humphrey MJ, McLeavy MA. Biliary excretion, metabolism and enterohepatic circulation of buprenorphine. Xenobiotica. 1981;11(3):189–96.
79. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE. The metabolism and excretion of buprenorphine in humans. Drug Metab Dispos. 1984;12(5):577–81.
80. Picard N, Cresteil T, Djebli N, Marquet P. In vitro metabolism study of buprenorphine: evidence for new metabolic pathways. Drug Metab Dispos. 2005;33(5):689–95.
81. Sullivan JG, Webster L. Novel buccal film formulation of buprenorphine-naloxone for the maintenance treatment of opioid dependence: a 12-week conversion study. Clin Ther. 2015;37(5):1064–75.
82. Webster L, Hjelmstrom P, Sumner M, Gunderson EW. Efficacy and safety of a sublingual buprenorphine/naloxone rapidly dissolving tablet for the treatment of adults with opioid dependence: a randomized trial. J Addict Dis. 2016;35(4):325–38.
83. Kuhlman JJ Jr, Lalani S, Magluilo J Jr, Levine B, Darwin WD. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. J Anal Toxicol. 1996;20(6):369–78.
84. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44(7):661–80.
85. Gunderson EW, Hjelmstrom P, Sumner M, Study I. Effects of a higher-bioavailability buprenorphine/naloxone sublingual tablet versus buprenorphine/naloxone film for the treatment of opioid dependence during induction and stabilization: a multicenter, randomized trial. Clin Ther. 2015;37(10):2244–55.
86. Fischer A, Jonsson M, Hjelmstrom P. Pharmaceutical and pharmacokinetic characterization of a novel sublingual buprenorphine/naloxone tablet formulation in healthy volunteers. Drug Dev Ind Pharm. 2015;41(1):79–84.
87. Lintzeris N, Leung SY, Dunlop AJ, Larance B, White N, Rivas GR, et al. A randomised controlled trial of sublingual buprenorphine-naloxone film versus tablets in the management of opioid dependence. Drug Alcohol Depend. 2013;131(1–2):119–26.
88. Bai SA, Xiang Q, Finn A. Evaluation of the pharmacokinetics of single- and multiple-dose buprenorphine buccal film in healthy volunteers. Clin Ther. 2016;38(2):358–69.
89. Priestley T, Chappa AK, Mould DR, Upton RN, Shusterman N, Passik S, et al. Converting from transdermal to buccal formulations of buprenorphine: a pharmacokinetic meta-model simulation in healthy volunteers. Pain Med. Epub 29 Sep 2017. https://doi.org/10.1093/pm/pnx235.
90. Evans HC, Easthope SE. Transdermal buprenorphine. Drugs. 2003;63(19):1999–2010 **(discussion 1–2)**.
91. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. Expert Rev Neurother. 2005;5(3):315–23.
92. Kapil RP, Cipriano A, Friedman K, Michels G, Shet MS, Colucci SV, et al. Once-weekly transdermal buprenorphine application results in sustained and consistent steady-state plasma levels. J Pain Symp Manag. 2013;46(1):65–75.
93. Plosker GL, Lyseng-Williamson KA. Buprenorphine 5, 10 and 20 mug/h transdermal patch: a guide to its use in chronic non-malignant pain. CNS Drugs. 2012;26(4):367–73.
94. Middleton LS, Nuzzo PA, Lofwall MR, Moody DE, Walsh SL. The pharmacodynamic and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. Addiction. 2011;106(8):1460–73.
95. Walsh SL, Nuzzo PA, Babalonis S, Casselton V, Lofwall MR. Intranasal buprenorphine alone and in combination with naloxone: abuse liability and reinforcing efficacy in physically dependent opioid abusers. Drug Alcohol Depend. 2016;162:190–8.
96. Tegeder I, Lotsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clin Pharmacokinet. 1999;37(1):17–40.
97. Chang Y, Moody DE. Glucuronidation of buprenorphine and norbuprenorphine by human liver microsomes and UDP-glucuronosyltransferases. Drug Metab Lett. 2009;3(2):101–7.
98. Blanco F, Muriel C, Labrador J, Gonzalez-Porras JR, Gonzalez-Sarmiento R, Lozano FS. Influence of UGT2B7, CYP3A4, and OPRM1 gene polymorphisms on transdermal buprenorphine pain control in patients with critical lower limb ischemia awaiting revascularization. Pain Pract. 2016;16(7):842–9.
99. Sastre JA, Varela G, Lopez M, Muriel C, Gonzalez-Sarmiento R. Influence of uridine diphosphate-glucuronyltransferase 2B7 (UGT2B7) variants on postoperative buprenorphine analgesia. Pain Pract. 2015;15(1):22–30.
100. Moody DE, Slawson MH, Strain EC, Laycock JD, Spanbauer AC, Foltz RL. A liquid chromatographic-electrospray ionization-tandem mass spectrometric method for determination of buprenorphine, its metabolite, norbuprenorphine, and a

coformulant, naloxone, that is suitable for in vivo and in vitro metabolism studies. Anal Biochem. 2002;306(1):31–9.
101. Fihlman M, Hemmila T, Hagelberg NM, Kuusniemi K, Backman JT, Laitila J, et al. Voriconazole more likely than posaconazole increases plasma exposure to sublingual buprenorphine causing a risk of a clinically important interaction. Eur J Clin Pharmacol. 2016;72(11):1363–71.
102. Kapil RP, Cipriano A, Michels GH, Perrino P, O'Keefe SA, Shet MS, et al. Effect of ketoconazole on the pharmacokinetic profile of buprenorphine following administration of a once-weekly buprenorphine transdermal system. Clin Drug Investig. 2012;32(9):583–92.
103. Moody DE, Chang Y, Huang W, McCance-Katz EF. The in vivo response of novel buprenorphine metabolites, M1 and M3, to antiretroviral inducers and inhibitors of buprenorphine metabolism. Basic Clin Pharmacol Toxicol. 2009;105(3):211–5.
104. Moody DE, Fang WB, Lin SN, Weyant DM, Strom SC, Omiecinski CJ. Effect of rifampin and nelfinavir on the metabolism of methadone and buprenorphine in primary cultures of human hepatocytes. Drug Metab Dispos. 2009;37(12):2323–9.
105. Mahmood I. Prediction of clearance, volume of distribution, and half-life of drugs in extremely low to low birth weight neonates: an allometric approach. Eur J Drug Metab Pharmacokinet. 2017;42(4):601–10.
106. Ng CM, Dombrowsky E, Lin H, Erlich ME, Moody DE, Barrett JS, et al. Population pharmacokinetic model of sublingual buprenorphine in neonatal abstinence syndrome. Pharmacotherapy. 2015;35(7):670–80.
107. Vest M. Insufficient glucuronide formation in the newborn and its relationship to the pathogenesis of icterus neonatorum. Arch Dis Child. 1958;33(171):473–6.
108. Choonara I, Lawrence A, Michalkiewicz A, Bowhay A, Ratcliffe J. Morphine metabolism in neonates and infants. Br J Clin Pharmacol. 1992;34(5):434–7.
109. de Wildt SN, Kearns GL, Murry DJ, Koren G, van den Anker JN. Ontogeny of midazolam glucuronidation in preterm infants. Eur J Clin Pharmacol. 2010;66(2):165–70.
110. Hartley R, Green M, Quinn MW, Rushforth JA, Levene MI. Development of morphine glucuronidation in premature neonates. Biol Neonate. 1994;66(1):1–9.
111. Michel E, Anderson BJ, Zernikow B. Buprenorphine TTS for children: a review of the drug's clinical pharmacology. Paediatr Anaesth. 2011;21(3):280–90.
112. Michel E, Zernikow B. Buprenorphine in children. A clinical and pharmacological review [in German]. Schmerz. 2006;20(1):40–50.
113. Pergolizzi J, Boger RH, Budd K, Dahan A, Erdine S, Hans G, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract. 2008;8(4):287–313.
114. Vadivelu N, Hines RL. Management of chronic pain in the elderly: focus on transdermal buprenorphine. Clin Interv Aging. 2008;3(3):421–30.
115. Al-Tawil N, Odar-Cederlof I, Berggren AC, Johnson HE, Persson J. Pharmacokinetics of transdermal buprenorphine patch in the elderly. Eur J Clin Pharmacol. 2013;69(2):143–9.
116. Filitz J, Griessinger N, Sittl R, Likar R, Schuttler J, Koppert W. Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine. Eur J Pain. 2006;10(8):743–8.
117. Boger RH. Renal impairment: a challenge for opioid treatment? The role of buprenorphine. Palliat Med. 2006;20(Suppl 1):s17–23.
118. Yeung CK, Shen DD, Thummel KE, Himmelfarb J. Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. Kidney Int. 2014;85(3):522–8.
119. Nolin TD, Appiah K, Kendrick SA, Le P, McMonagle E, Himmelfarb J. Hemodialysis acutely improves hepatic CYP3A4 metabolic activity. J Am Soc Nephrol. 2006;17(9):2363–7.
120. Hand CW, Sear JW, Uppington J, Ball MJ, McQuay HJ, Moore RA. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. Br J Anaesth. 1990;64(3):276–82.
121. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. Anaesthesia. 1985;40(9):914.
122. Nasser AF, Heidbreder C, Liu Y, Fudala PJ. Pharmacokinetics of sublingual buprenorphine and naloxone in subjects with mild to severe hepatic impairment (child-pugh classes A, B, and C), in hepatitis C virus-seropositive subjects, and in healthy volunteers. Clin Pharmacokinet. 2015;54(8):837–49.
123. Furlan V, Demirdjian S, Bourdon O, Magdalou J, Taburet AM. Glucuronidation of drugs by hepatic microsomes derived from healthy and cirrhotic human livers. J Pharmacol Exp Ther. 1999;289(2):1169–75.
124. Hardwick RN, Ferreira DW, More VR, Lake AD, Lu Z, Manautou JE, et al. Altered UDP-glucuronosyltransferase and sulfotransferase expression and function during progressive stages of human nonalcoholic fatty liver disease. Drug Metab Dispos. 2013;41(3):554–61.
125. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147–61.
126. Elbekai RH, Korashy HM, El-Kadi AO. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. Curr Drug Metab. 2004;5(2):157–67.
127. Ciccozzi A, Angeletti C, Baldascino G, Petrucci E, Bonetti C, De Santis S, et al. High dose of buprenorphine in terminally ill patient with liver failure: efficacy and tolerability. J Opioid Manag. 2012;8(4):253–9.
128. Wolff RF, Aune D, Truyers C, Hernandez AV, Misso K, Riemsma R, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin. 2012;28(5):833–45.
129. Wolff RF, Reid K, di Nisio M, Aune D, Truyers C, Hernandez AV, et al. Systematic review of adverse events of buprenorphine patch versus fentanyl patch in patients with chronic moderate-to-severe pain. Pain Manag. 2012;2(4):351–62.
130. Ahn JS, Lin J, Ogawa S, Yuan C, O'Brien T, Le BH, et al. Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. J Pain Res. 2017;10:1963–72.
131. Cote J, Montgomery L. Sublingual buprenorphine as an analgesic in chronic pain: a systematic review. Pain Med. 2014;15(7):1171–8.
132. James IG, O'Brien CM, McDonald CJ. A randomized, double-blind, double-dummy comparison of the efficacy and tolerability of low-dose transdermal buprenorphine (BuTrans seven-day patches) with buprenorphine sublingual tablets (Temgesic) in patients with osteoarthritis pain. J Pain Symp Manag. 2010;40(2):266–78.
133. Naing C, Yeoh PN, Aung K. A meta-analysis of efficacy and tolerability of buprenorphine for the relief of cancer pain. Springerplus. 2014;3:87.

134. Wiffen PJ, Derry S, Moore RA, Stannard C, Aldington D, Cole P, et al. Buprenorphine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;(9):CD011603.
135. Buprenorphine for chronic pain: a review of the clinical effectiveness. Ottawa (ON); Canadian Agency for Drugs and Technologies in Health; 2017.
136. Sittl R, Griessinger N, Likar R. Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: a multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther. 2003;25(1):150–68.
137. Poulain P, Denier W, Douma J, Hoerauf K, Samija M, Sopata M, et al. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. J Pain Symp Manag. 2008;36(2):117–25.
138. Conaghan PG, O'Brien CM, Wilson M, Schofield JP. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomised trial. Osteoarthritis Cartilage. 2011;19(8):930–8.
139. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. J Pain. 2011;12(11):1163–73.
140. Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, et al. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manag. 2011;42(6):903–17.
141. Landau CJ, Carr WD, Razzetti AJ, Sessler NE, Munera C, Ripa SR. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clin Ther. 2007;29(10):2179–93.
142. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O'Mahony W, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clin Ther. 2010;32(5):844–60.
143. Mitra F, Chowdhury S, Shelley M, Williams G. A feasibility study of transdermal buprenorphine versus transdermal fentanyl in the long-term management of persistent non-cancer pain. Pain Med. 2013;14(1):75–83.
144. Muriel C, Failde I, Mico 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):451–62.
145. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice—a post-marketing surveillance study in 13,179 patients. Curr Med Res Opin. 2005;21(8):1147–56.
146. Gianni W, Madaio AR, Ceci M, Benincasa E, Conati G, Franchi F, et al. Transdermal buprenorphine for the treatment of chronic noncancer pain in the oldest old. J Pain Symptom Manag. 2011;41(4):707–14.
147. Sittl R, Nuijten M, Poulsen Nautrup B. Patterns of dosage changes with transdermal buprenorphine and transdermal fentanyl for the treatment of noncancer and cancer pain: a retrospective data analysis in Germany. Clin Ther. 2006;28(8):1144–54.
148. Likar R, Kayser 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):943–52.
149. Aalto M, Visapaa JP, Halme JT, Fabritius C, Salaspuro M. Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients. Nord J Psychiatry. 2011;65(4):238–43.
150. Yoon DH, Bin SI, Chan SK, Chung CK, In Y, Kim H, et al. Effectiveness and tolerability of transdermal buprenorphine patches: a multicenter, prospective, open-label study in Asian patients with moderate to severe chronic musculoskeletal pain. BMC Musculoskelet Disord. 2017;18(1):337.
151. Lesen E, Ericson L, Simonsberg C, Varelius R, Bjorholt I, Soderpalm B. Dose patterns among patients using low-dose buprenorphine patches. Pain Med. 2013;14(9):1374–80.
152. Rauck RL, Potts J, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. Postgrad Med. 2016;128(1):1–11.
153. Gimbel J, Spierings EL, Katz N, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. Pain. 2016;157(11):2517–26.
154. Hale M, Urdaneta V, Kirby MT, Xiang Q, Rauck R. Long-term safety and analgesic efficacy of buprenorphine buccal film in patients with moderate-to-severe chronic pain requiring around-the-clock opioids. J Pain Res. 2017;10:233–40.
155. Przeklasa-Muszynska A, Dobrogowski J. Transdermal buprenorphine in the treatment of cancer and non-cancer pain—the results of multicenter studies in Poland. Pharmacol Rep. 2011;63(4):935–48.
156. Budd K. High dose buprenorphine for postoperative analgesia. Anaesthesia. 1981;36(9):900–3.
157. Kim HJ, Ahn HS, Nam Y, Chang BS, Lee CK, Yeom JS. Comparative study of the efficacy of transdermal buprenorphine patches and prolonged-release tramadol tablets for postoperative pain control after spinal fusion surgery: a prospective, randomized controlled non-inferiority trial. Eur Spine J. 2017;26(11):2961–8.
158. Mercieri M, Palmisani S, De Blasi RA, D'Andrilli A, Naccarato A, Silvestri B, et al. Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial. Br J Anaesth. 2017;119(4):792–802.
159. Chang KY, Chang WK, Chang WL, Lin SM, Chan KH, Sung CS, et al. Comparison of intravenous patient-controlled analgesia with buprenorphine versus morphine after lumbar spinal fusion—a prospective randomized clinical trial. Acta Anaesthesiol Taiwan. 2006;44(3):153–9.
160. Williams BA, Butt MT, Zeller JR, Coffee S, Pippi MA. Multimodal perineural analgesia with combined bupivacaine-clonidine-buprenorphine-dexamethasone: safe in vivo and chemically compatible in solution. Pain Med. 2015;16(1):186–98.
161. Alemanno F, Westermann B, Bettoni A, Candiani A, Cesana BM. Buprenorphine versus tramadol as perineural adjuvants for postoperative analgesia in patients undergoing arthroscopic rotator cuff repair under middle interscalene block: a retrospective study. Minerva Anestesiol. 2014;80(11):1198–204.
162. Kosel J, Bobik P, Tomczyk M. Buprenorphine: the unique opioid adjuvant in regional anesthesia. Expert Rev Clin Pharmacol. 2016;9(3):375–83.
163. Strain EC, Moody DE, Stoller KB, Walsh SL, Bigelow GE. Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. Drug Alcohol Depend. 2004;74(1):37–43.
164. Weinhold LL, Bigelow GE, Preston KL. Combination of naloxone with buprenorphine in humans. NIDA Res Monogr. 1989;95:485.
165. Simojoki K, Vorma H, Alho H. A retrospective evaluation of patients switched from buprenorphine (Subutex) to the

buprenorphine/naloxone combination (Suboxone). Subst Abuse Treat Prev Policy. 2008;3:16.
166. Coffman BL, Rios GR, King CD, Tephly TR. Human UGT2B7 catalyzes morphine glucuronidation. Drug Metab Dispos. 1997;25(1):1–4.
167. Sittl R, Likar R, Nautrup BP. Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. Clin Ther. 2005;27(2):225–37.
168. Mok MS, Lippmann M, Steen SN. Multidose/observational, comparative clinical analgetic evaluation of buprenorphine. J Clin Pharmacol. 1981;21(7):323–9.
169. Tigerstedt I, Turunen M, Tammisto T, Hastbacka J. The effect of buprenorphine and oxycodone on the intracholedochal passage pressure. Acta Anaesthesiol Scand. 1981;25(2):99–102.
170. Wang RI, Johnson RP, Robinson N, Waite E. The study of analgesics following single and repeated doses. J Clin Pharmacol. 1981;21(2):121–5.
171. Mercadante S, Casuccio A, Tirelli W, Giarratano A. Equipotent doses to switch from high doses of opioids to transdermal buprenorphine. Support Care Cancer. 2009;17(6):715–8.
172. Mercadante S, Porzio G, Fulfaro F, Aielli F, Verna L, Ficorella C, et al. Switching from transdermal drugs: an observational "N of 1" study of fentanyl and buprenorphine. J Pain Symptom Manage. 2007;34(5):532–8.
173. Cuschieri RJ, Morran CG, McArdle CS. Comparison of morphine and sublingual buprenorphine following abdominal surgery. Br J Anaesth. 1984;56(8):855–9.
174. Skaer TL. Dosing considerations with transdermal formulations of fentanyl and buprenorphine for the treatment of cancer pain. J Pain Res. 2014;7:495–503.
175. Oifa S, Sydoruk T, White I, Ekstein MP, Marouani N, Chazan S, 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(3):527–41.
176. Mercadante S, Villari P, Ferrera P, Porzio G, Aielli F, Verna L, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symp Manag. 2006;32(2):175–9.
177. Stromer W, Michaeli K, Sandner-Kiesling A. Reply to: an alternative way of managing acute pain in patients who are in buprenorphine opioid substitution therapy programmes. Eur J Anaesthesiol. 2013;30(11):718–9.
178. Stromer W, Michaeli K, Sandner-Kiesling A. Perioperative pain therapy in opioid abuse. Eur J Anaesthesiol. 2013;30(2):55–64.
179. Huxtable CA, Macintyre PE. An alternative way of managing acute pain in patients who are in buprenorphine opioid substitution therapy programs. Eur J Anaesthesiol. 2013;30(11):717–8.
180. Leighton BL, Crock LW. Case series of successful postoperative pain management in buprenorphine maintenance therapy patients. Anesth Analg. 2017;125(5):1779–83.
181. Rosado J, Walsh SL, Bigelow GE, Strain EC. Sublingual buprenorphine/naloxone precipitated withdrawal in subjects maintained on 100 mg of daily methadone. Drug Alcohol Depend. 2007;90(2–3):261–9.
182. Malinoff HL, Barkin RL, Wilson G. Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther. 2005;12(5):379–84.
183. Rosenblum A, Cruciani RA, Strain EC, Cleland CM, Joseph H, Magura S, et al. Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: development and pilot test of a clinical protocol. J Opioid Manag. 2012;8(6):369–82.
184. Daitch D, Daitch J, Novinson D, Frey M, Mitnick C, Pergolizzi J Jr. Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. Pain Med. 2014;15(12):2087–94.
185. Daitch J, Frey ME, Silver D, Mitnick C, Daitch D, Pergolizzi J, Jr. Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. Pain Physician. 2012;15(3 Suppl):ES59–66.
186. Webster L, Gruener D, Kirby T, Xiang Q, Tzanis E, Finn A. Evaluation of the tolerability of switching patients on chronic full mu-opioid agonist therapy to buccal buprenorphine. Pain Med (Epub 25 Feb 2016).
187. Heit HA, Covington E, Good PM. Dear DEA. Pain Med. 2004;5(3):303–8.
188. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. Am J Addict. 2010;19(1):89–95.
189. Fareed A, Patil D, Scheinberg K, Blackinton Gale R, Vayalapalli S, Casarella J, et al. Comparison of QTc interval prolongation for patients in methadone versus buprenorphine maintenance treatment: a 5-year follow-up. J Addict Dis. 2013;32(3):244–51.
190. Stallvik M, Nordstrand B, Kristensen O, Bathen J, Skogvoll E, Spigset O. Corrected QT interval during treatment with methadone and buprenorphine: relation to doses and serum concentrations. Drug Alcohol Depend. 2013;129(1–2):88–93.
191. de Jong IM, de Ruiter GS. Buprenorphine as a safe alternative to methadone in a patient with acquired long QT syndrome: a case report. Neth Heart J. 2013;21(5):249–52.
192. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med. 2007;167(22):2469–75.
193. Krantz MJ, Garcia JA, Mehler PS. Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. Pharmacotherapy. 2005;25(4):611–4.
194. Darpo B, Zhou M, Bai SA, Ferber G, Xiang Q, Finn A. Differentiating the effect of an opioid agonist on cardiac repolarization from micro-receptor-mediated, indirect effects on the qt interval: a randomized, 3-way crossover study in healthy subjects. Clin Ther. 2016;38(2):315–26.
195. Harris SC, Morganroth J, Ripa SR, Thorn MD, Colucci S. Effects of buprenorphine on QT intervals in healthy subjects: results of 2 randomized positive- and placebo-controlled trials. Postgrad Med. 2017;129(1):69–80.
196. Mayet S, Gossop M, Lintzeris N, Markides V, Strang J. Methadone maintenance, QTc and torsade de pointes: who needs an electrocardiogram and what is the prevalence of QTc prolongation? Drug Alcohol Rev. 2011;30(4):388–96.
197. Russell L, Levine D. Methadone-induced Torsades de pointes. R I Med J (2013). 2013;96(8):20–1.
198. Baker JR, Best AM, Pade PA, McCance-Katz EF. Effect of buprenorphine and antiretroviral agents on the QT interval in opioid-dependent patients. Ann Pharmacother. 2006;40(3):392–6.
199. Kao DP, Haigney MC, Mehler PS, Krantz MJ. Arrhythmia associated with buprenorphine and methadone reported to the Food and Drug Administration. Addiction. 2015;110(9):1468–75.