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Safety and Efficacy of Buprenorphine Patch in the Management of Chronic Pain

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ABSTRACT: A transdermal formulation of buprenorphine was introduced in 2001, which reignited interest in this medication for the treatment of chronic moderate-to-severe pain. This review presents the evidence published since November 2011, focusing on issues of safety and efficacy, and providing evidence-based guidance on clinical applications of transdermal buprenorphine. Medical literature were identified by searching databases, including Medline, EMBASE, PsychINFO, AMED, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Methodology Register, the Health Technology Assessment, and the NHS Economic Evaluation Database. All randomized controlled trials in adults diagnosed with chronic non-malignant moderate-to-severe pain were included.

KEYWORDS: buprenorphine, transdermal, lower-dose, non-malignant pain, chronic pain, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, efficacy, safety, topical administration

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Introduction

Buprenorphine was introduced in parenteral and sublingual formulations over 30 years ago, but was not regularly used in the management of pain because of underestimation of the potency of its analgesic effect.[1] A transdermal formulation was introduced in 2001, which reignited interest in this medication for the treatment of chronic moderate-to-severe pain.[2] Table 1 lists the formulations of buprenorphine that are currently available. A 20-µg/hour dose equates to a dose of 0.48 mg buprenorphine per 24 hours.[3]

Buprenorphine is a semisynthetic derivative of the opium alkaloid thebaine, which can be found in the poppy *Papaver somniferum*.[1] It acts centrally as an analgesic by binding to the mu-opioid receptor, for which it has very high affinity and is not easily displaced, thus being highly potent. In addition, it dissociates slowly from the receptor, resulting in an analgesic action of long duration.[4] Research suggests that buprenorphine acts as a partial agonist at the mu receptor and as an antagonist at the kappa receptor.[5–9] Expected agonist effects at the mu receptor are supraspinal analgesia, respiratory depression, miosis, decreased gastrointestinal motility, and euphoria. The antagonist action at the kappa receptor may be associated with buprenorphine's fewer psychotomimetic effects,[10,11] and potentially antidepressant and antipsychotic effects.[12–14] There

Table 1. Available formulations of buprenorphine.

BRAND NAME	ROUTE OF ADMINISTRATION	STRENGTHS	CLINICAL INDICATIONS
BuTrans® (Europe and US)	Transdermal 7-day patch	5, 7.5, 10, 15, 20 mcg/hr	Chronic moderate – severe pain
Norspan® (Australia)	Transdermal 7-day patch	5, 10, 20 mcg/hr	Chronic moderate – severe pain
Transtec® (Europe)	Transdermal 3-day patch	35, 52.5, 75 mcg/hr	Chronic moderate – severe pain
Temgesic®	Sublingual tablet	200 mcg	Acute pain
Subutex®	Sublingual tablet	400 mcg, 2 mg, 8 mg	Opioid dependence
Suboxone®	Sublingual film (combination buprenorphine/naloxone)	2 mg/500 mcg, 8 mg/2 mg	Opioid dependence
Temgesic®	Intravenous solution	300 mcg/mL	Acute pain

is a demonstrated ceiling effect with respect to respiratory depression.[2,15,16] This ceiling effect is unique to partial opioid agonists, and is in contrast to full opioid agonists that demonstrate increasing (and potentially fatal) respiratory depression with escalating doses.[15,17–19] It is noted that preclinical studies suggest that this effect varies between substantially different opioids.[20] It is very lipophilic, with an octanol:water partition coefficient of 1217, and has a low molecular weight of 468 g/mol, making it ideal for transdermal formulations.[21]

Several authors have previously conducted systematic reviews on the use of transdermal buprenorphine in chronic pain,[22–24] with the most recent being the work of Plosker, who reviewed the literature in November 2011.[25] This review is an update and aims to present the evidence published since then, focusing on issues of safety and efficacy, and providing evidence-based guidance on clinical applications of transdermal buprenorphine. Data from previous systematic reviews are summarized where no new research has been published since 2011.

Pharmacokinetics and pharmacodynamics. Buprenorphine diffuses from the patch through the stratum corneum and forms a reservoir in the subcutaneous tissue. From there, it undergoes systemic circulation and gradually increases in concentration in the plasma over the first 48 hours before reaching a plateau. The type of patch system used is a matrix system, where the drug is incorporated into an adhesive polymer and distributed evenly throughout the patch. This means that the amount of drug released depends on the mass of drug within the matrix and the surface area of the skin over which the patch is applied. Steady-state plasma levels are achieved with the application of the first patch within 24–48 hours, with terminal half-life of 12 hours, and remain relatively constant with the reapplication of a new patch every seven days. Onset of analgesic action is after 48 hours. The drug is approximately 96% bound to plasma proteins and has a large volume of distribution. After the patch is removed, plasma levels decrease by half in the first 10–24 hours and then more slowly after that, with an estimated terminal half-life of 26 hours.[25]

It is recommended that patches be sited over non-hairy areas of skin such as the top of the outer arm, upper chest, and back and side of the chest, as studies have shown that application over these areas does not cause large differences in plasma levels.[26] If a hairless site cannot be found, a sensitive and careful discussion should be had with the patient about shaving an area of skin for patch placement. Absorption is also affected by repeated use of the same application site, with some studies showing that buprenorphine exposure can be doubled. Therefore, it is recommended that patch sites should be rotated, with sites not to be reused for 21 days.[27,28]

Buprenorphine is metabolized in the liver via the cytochrome P450 enzyme 3A4 to norbuprenorphine, the only known active metabolite, and via UDP-glucuronosyltransferase to buprenorphine 3-O-glucuronide. Norbuprenorphine also undergoes glucuronidation. The metabolites are excreted via the biliary and renal systems. Clearance is 55 L/hour.[27,28] In all, 70% of the drug is eliminated in the feces.[29]

There appear to be few clinically relevant pharmacokinetic drug interactions. Although buprenorphine is metabolized by the cytochrome P450 system, specifically CYP3A4, it has been shown that there is no clinically significant effect on the peak concentration of the drug when administered with ketoconazole, known to strongly inhibit CYP3A4.[27,28,30] Studies have, however, demonstrated increases in peak plasma concentrations of buprenorphine and norbuprenorphine when sublingual buprenorphine was coadministered with atazanavir and ritonavir, both of which are antiretroviral drugs of the protease inhibitor class, used to treat HIV/AIDS and also known to inhibit CYP3A4.[27,28] There has been little examination of the interactions between buprenorphine and drugs that induce CYP3A4, such as carbamazepine, however patients receiving drugs known to induce CYP3A4 activity, such as phenytoin, rifampicin, glucocorticoid, or modafinil, concomitantly with buprenorphine should be monitored for reduced analgesic efficacy.[25] Buprenorphine appears to have a favorable interaction profile compared to methadone.[30] *In vitro* studies, however, have demonstrated an association between some serotonin reuptake inhibitors, such as fluoxetine and fluvoxamine, and decreased metabolism of methadone and buprenorphine, which could result in increased plasma concentrations.[30] While buprenorphine appears to be associated with less

QT-interval prolongation than methadone,[31] it is important to bear in mind if the patient is also taking other medications that are associated with QT prolongation.

Ceiling effect with regard to analgesia. While the characteristic ceiling effect of a partial agonist is observed with regard to respiratory depression,[2,16,17] some small studies have suggested there is no ceiling effect with regard to analgesia at usual analgesic doses.[16,32] The analgesic response with high-dose buprenorphine (eg, >4 mg per day) remains unclear, and more research is needed to examine whether there is a ceiling analgesic effect with higher doses of buprenorphine.

Combination of buprenorphine with other opioids. It is thought that at clinical doses used for analgesia, buprenorphine is considered to act as a full agonist[33] and can, therefore, be safely combined with other opioids. A small prospective, open-label feasibility study by Lundorff and colleagues in 2013[34] aimed to evaluate whether cancer-related pain, well controlled by pure agonist opioids, could be adequately controlled using transdermal buprenorphine. It also investigated whether breakthrough pain episodes could be controlled with the same dose of breakthrough pure agonist opioid medication when patients were using transdermal buprenorphine as opposed to pure agonist opioids. A total of 18 patients, who were receiving between 150 and 517 mg of morphine per day, were switched to transdermal buprenorphine doses of between 52.5 and 140 µg/hour, titrated to effect. No difference in pain severity was observed before and after the switch, and the patients did not require additional breakthrough pain medication, with the pure opioid agonist medication able to be combined safely with buprenorphine and being as effective after as before the switch. No antagonist effects were observed during the switch from pure agonist to buprenorphine. The authors do caution, however, that the dose conversion should be tailored for each individual patient.

Dose equivalence of opioid medications. Based on the few studies that are available, relative potency of transdermal buprenorphine to oral morphine has been suggested to be between 75:1 and 110:1, with considerable variability between patients.[35,36] When switching from one opioid to another, because of the incomplete cross-tolerance, it is recommended that clinicians commence patients on 50–75% of the calculated equianalgesic dose and titrate to clinical effect.[35]

Method

Literature search. Medical literature (including gray literature) were identified by searching databases, including Medline, EMBASE, PsychINFO, AMED, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, the Cochrane Methodology Register, the Health Technology Assessment, and the NHS Economic Evaluation Database. The search terms were
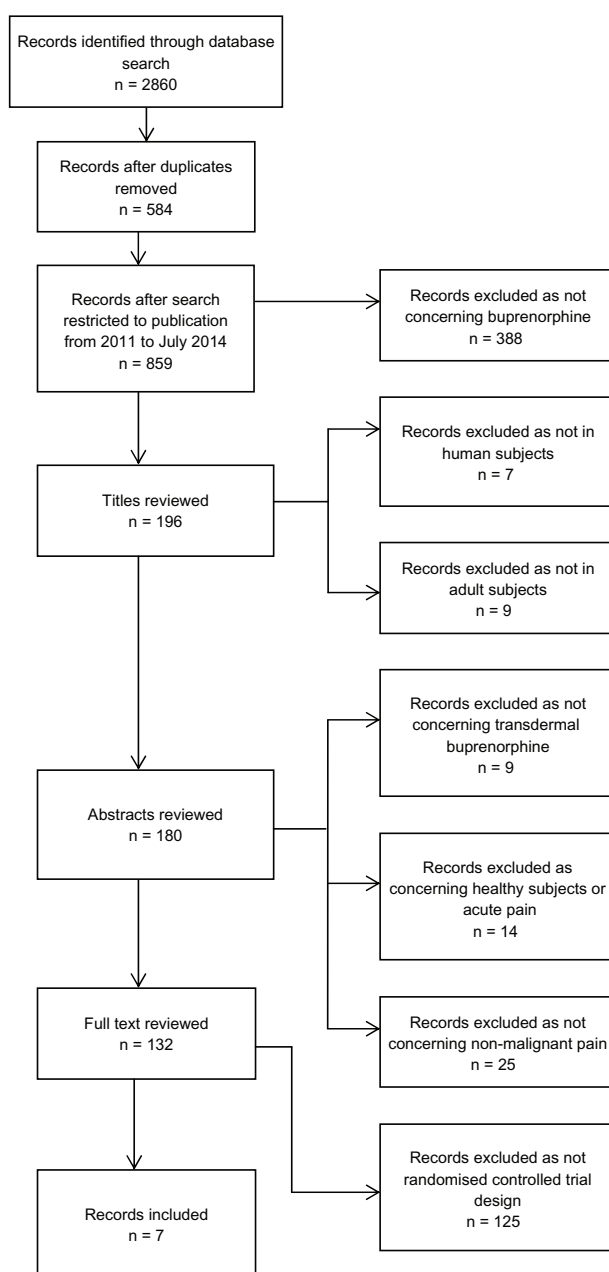
Figure 1. Flow chart describing search strategy.

buprenorphine or *bup** and *patch* or *transdermal* or *transdermal patch* or *administration, topical* or *transdermal drug administration*. The searches were restricted to results from 2011 to July 2014 to obtain studies published since Plosker's review, which included literature up to November 2011. Two authors (AY and AD) reviewed the titles, abstracts, and full text of potentially eligible studies. Figure 1 provides further detail on the search strategy. Searches were last updated on July 25, 2014.

Eligibility criteria. Randomized controlled trials in adult human men or women diagnosed with chronic non-malignant moderate-to-severe pain because of any cause, comparing transdermal buprenorphine with placebo, oral, or transdermal non-opioids (eg, acetaminophen,

Table 2. Study design and patient demographics of included randomized controlled trials.

AUTHOR, YEAR	STUDY DESIGN	DIAGNOSIS	STUDY LENGTH	MEAN AGE (YEARS)	% FEMALE
Yarlas et al., 2013[37] Steiner et al., 2011a[38]	Enriched double blinded	Lower back pain, opioid naïve	4 weeks run-in period + 12 weeks double-blinded phase	49	52
Mitra et al., 2013[39]	Open label	Lower back pain, opioid naïve	12 months	49	52
Miller et al., 2013[40] Steiner et al., 2011b[41]	Enriched double blinded plus open label extension phase	Lower back pain, opioid experienced	3 weeks run-in period + 7 weeks double-blinded phase + 52 week extension phase	50	48
Ripa et al., 2012[42]	Enriched double blinded	Osteoarthritis	1 week run-in period + 2 weeks double-blinded phase	57	63
Conaghan et al., 2011[43]	Open label	Osteoarthritis	12 weeks	72	66

non-steroidal anti-inflammatory drugs (NSAIDs)); weak opioids (eg, codeine); or strong opioids (eg, oxycodone, fentanyl), since 2011 are listed in Tables 2 and 3. Studies utilizing open-label or blinded designs were included, as were studies utilizing an enriched design. Outcomes examined included clinical outcomes such as measurements of pain, associated symptoms such as fatigue or anxiety, requirements for increases in dose or lack of treatment effect, patient-reported outcomes such as quality of sleep and quality of life, and safety outcomes such as overdose, respiratory depression, abuse and dependence, hyperalgesia, immunosuppression, driving, hormonal effects, and use in older adults and those with renal or hepatic impairment. Studies were excluded if they were not randomized controlled trials, were not conducted with patients diagnosed with chronic pain, or were published prior to 2011.

Table 3. Treatment details and primary outcomes of included randomized controlled trials.

AUTHOR, YEAR	TRANSDERMAL BUPRENORPHINE DOSE	COMPARATOR	SAMPLE SIZE	PRIMARY OUTCOMES
Yarlas et al., 2013[37] Steiner et al., 2011a[38]	10–20 mcg/hr (n = 1027 for run-in period, n = 256 in double-blinded phase)	Placebo (n = 283)	1027 for run-in period, 539 for double-blinded phase	Health-related quality of life (SF-36v2 self-report survey) Pain Interference score of Brief Pain Inventory Short Form Average pain over last 24 hours (numerical rating scale)
Mitra et al., 2013[39]	5 mcg/hr then titrated to effect (n = 22)	Transdermal fentanyl 12 mcg/hr then titrated to effect (n = 24)	46	Effectiveness of medication on pain levels (visual analog scale) Comparison of fentanyl and buprenorphine doses with equipotent dose of morphine for gaining pain relief Physical activity, additional rescue medication, additional healthcare visits, sleep quality, mood, side effects (self-rated scales)
Miller et al., 2013[40] Steiner et al., 2011b[41]	5 mcg/hr (n = 222), 20 mcg/hr (n = 219)	Oral immediate release oxycodone 10 mg QID (n = 221)	1160 for run-in period, 662 for double-blinded phase and extension phase	Health-related quality of life (SF-36v2 self-report survey) Average pain over the last 24 hours score
Ripa et al., 2012[42]	Titratable 10–20 mcg/hr (n = 101), fixed-dose 20 mcg/hr (n = 103)	Oral acetaminophen/ hydrocodone variable doses (n = 274)	274 for run-in period, 204 for double-blinded phase	Completion of double-blind phase
Conaghan et al., 2011[43]	5–25 mcg/hr plus acetaminophen 1 g QID (n = 110)	Oral codeine/ acetaminophen 16 mg/1 g QID or 60 mg/1 g QID (n = 110)	220	Average pain score (self-rated) Amount of rescue medication Quality of sleep (Medical Outcomes Study Sleep Scale) Pain, stiffness, ability to perform daily activities (Western Ontario and McMaster Universities OA Index) Patient satisfaction (questionnaire) Quality of life (EQ-5D and General Wellbeing Index)

Efficacy

It is important when assessing the efficacy of treatments for chronic pain to take a multidimensional approach and consider not just pain severity but also pain-related impairment, including aspects such as quality of life, sleep, mobility, and function.[44]

Lower back pain. Since the publication of Plosker's review in 2011,[25] one randomized controlled trial utilizing an enriched design has demonstrated that transdermal buprenorphine is better than placebo for control of pain severity in patients with chronic lower back pain.[37,38] The study population in this trial was prospectively selected by positive response to the drug under study during a run-in period, in order to increase ability to detect an effect size.[45] One other trial, also utilizing an enriched design, has also demonstrated that control of pain severity is better with higher (20 µg/hour) as opposed to lower (5 µg/hour) doses, suggesting a dose–response relationship.[40,41] These studies also reported that improvements in quality of life, sleep quality, function, and ability to perform activities of daily living were found to be as good as or better than placebo. One open-label trial[39] designed as a feasibility study for a larger, prospective long-term evaluation of transdermal buprenorphine compared to transdermal fentanyl found, however, that control of pain severity was not able to be maintained after six months of treatment, with only 11% of patients on buprenorphine and 13% of patients on fentanyl experiencing maintenance of pain relief at six months. No new studies comparing transdermal buprenorphine with morphine or oxycodone, or with another partial agonist were identified. More randomized controlled studies comparing transdermal buprenorphine with other active treatments would be needed, however, to provide stronger evidence of efficacy.

Osteoarthritis. One open-label study by Conaghan and colleagues[43] demonstrated that transdermal buprenorphine is as effective as acetaminophen/codeine for control of pain severity in osteoarthritis. Another study by Ripa and colleagues in 2012[42] randomized 198 patients to switch from oral acetaminophen/hydrocodone to either a titratable dose of 10–20 or a fixed dose of 20 µg/hour of transdermal buprenorphine and showed that the majority of patients achieved adequate control of pain severity with buprenorphine, with only three patients reporting lack of therapeutic effect. No new studies comparing transdermal buprenorphine with morphine or oxycodone, or with another partial agonist were identified.

Neuropathic pain. No new randomized controlled trials evaluating the use of transdermal buprenorphine in neuropathic pain were identified. There is, however, evidence from animal models[46] and experimental studies of humans that transdermal buprenorphine may be efficacious in the treatment of neuropathic pain,[47] and a growing literature of case studies report on the successful treatment of several conditions with neuropathic pain, including trigeminal neuralgia,[48] radicular pain,[48] post-herpetic neuralgia,[49] AIDS-related neuropathic pain,[50] cancer-related pain,[51] and central pain syndrome.[52] One

open-label study in 2008 of 30 patients with chronic painful neuropathy did demonstrate meaningful pain relief with the use of transdermal buprenorphine.[53] There is, however, a lack of evidence from large randomized placebo-controlled trials supporting efficacy in terms of relieving pain severity as well as improvements in other dimensions such as quality of life, sleep, mobility, and function.

Peripheral vasculopathy. One small randomized trial by Aurilio and colleagues in 2009[54] showed that transdermal buprenorphine can improve pain control in patients suffering from peripheral vasculopathy. A group of 86 patients suffering from peripheral vasculopathy was randomized to receive either transdermal buprenorphine with a peridural infusion of morphine and ropivacaine or peridural infusion of morphine and ropivacaine infusion alone. Those who received transdermal buprenorphine reported better pain control, increased hours of sleep, and fewer side effects than those who received only the peridural infusion.

Long-term outcomes. Two randomized controlled trials identified by this review studied long-term outcomes. The study by Mitra and colleagues,[39] designed as a feasibility study for a larger investigation into long-term outcomes, randomized 46 patients to receive either transdermal buprenorphine or transdermal fentanyl over a 12-month period. There was a very high dropout rate before the completion of the study period, with 41% of patients receiving buprenorphine and 38% of patients receiving fentanyl withdrawing from the study prior to 12 months because of unacceptable side effects, mostly local skin reactions such as itching, redness, swelling, and blisters in the group receiving buprenorphine and nightmares, nausea, and increased drowsiness in the group receiving fentanyl. Of the participants who remained, there was no significant difference in control of pain intensity between the two groups at 12 months, and only a small proportion of the groups (11% in the buprenorphine group and 13% in the fentanyl group) were still obtaining good pain control at the 12-month period. The authors caution, however, that a larger study is required to determine long-term outcomes. The study by Miller and colleagues[40] followed the progress of the participants in that of Steiner and colleagues[41] after a 52-week open-label extension phase. The majority of the participants in this extension phase reported sustained improvements in quality of life. No new studies comparing transdermal buprenorphine with morphine or oxycodone, or with another partial agonist were identified.

Safety

Table 4 details the proportion of participants in each of the five randomized controlled trials identified by this updated review who did not complete the entirety of the trial because of adverse effects, and the most commonly reported adverse effects in each trial leading to discontinuation.

Nausea, vomiting, dizziness, application site reactions, and somnolence were reported consistently across all trials, indicating that it is a common reason for patients to stop

Table 4. Adverse effects leading to discontinuation.

AUTHOR, YEAR	DISCONTINUATION RATE DUE TO ADVERSE EFFECTS (%)	MOST COMMONLY REPORTED ADVERSE EFFECTS LEADING TO DISCONTINUATION
Yarlas et al., 2013[37] Steiner et al., 2011a[38]	Open label run-in: 239/1024 (23%) Active treatment: 40/256 (16%) Placebo: 20/283 (7%)	Run-in period: nausea, dizziness, headache Double-blind period: nausea, vomiting, dizziness, anxiety
Mitra et al., 2013[39]	Buprenorphine arm: 8/22 (41%) Fentanyl arm: 8/24 (38%)	Buprenorphine arm: application site reactions Fentanyl arm: nightmares, nausea, increased drowsiness
Miller et al., 2013[40] Steiner et al., 2011b[41]	Open label run-in: 144/1160 (12%) 5 mcg/hr arm: 14/222 (6%) 20 mcg/hr arm: 29/219 (13%) Oxycodone arm: 16/221 (7%)	Not specified for discontinued group, most commonly reported adverse effects overall: nausea, application site reactions, headache, vomiting, constipation, dizziness, somnolence
Ripa et al., 2012[42]	Titratable arm: 10/101 (10%) Fixed dose arm: 16/103 (16%)	Nausea, dizziness, vomiting, somnolence, application site erythema
Conaghan et al., 2011[43]	Buprenorphine arm (titration and assessment periods): 38/110 (35%) Codeine/acetaminophen arm (titration and assessment periods): 24/110 (22%)	Buprenorphine arm: nausea, constipation, vomiting, dizziness, somnolence, application site reactions Codeine/acetaminophen arm: constipation, nausea, lethargy

treatment with transdermal buprenorphine. The rates of discontinuation varied from 6% to 41%, which suggests that the adverse effects are intolerable for a significant proportion of patients, but are consistent with the rates of discontinuation reported in these trials for comparator opioids.

Overdose. No mention was made of overdose in any of the five randomized controlled trials identified. A large study by Coplan and colleagues in 2013[55] using a database of over 75,000 patients prescribing transdermal buprenorphine, extended-release morphine tablets, or transdermal fentanyl to compare rates of overdose found that the relative risk of overdose in those prescribed extended-release morphine compared to transdermal buprenorphine was 1.82 (95% CI 1.35–2.46) and in those prescribed transdermal fentanyl compared to transdermal buprenorphine was 1.42 (95% CI 1.01–2.00), supporting the hypothesis that as a partial mu receptor agonist, buprenorphine is associated with a lower risk of overdose than full mu receptor agonists.

Respiratory depression. Two of the studies[40,41,43] reported one case each of respiratory depression and dyspnoea.

Transdermal buprenorphine on its own is associated with a low risk of respiratory depression, because of the ceiling effect discussed previously, which has been demonstrated in both human and animal studies. However, this may not be the case if other central nervous system depressant drugs are co-administered.[1] It has also been demonstrated that buprenorphine-induced respiratory depression can be reversed completely with the use of naloxone, either using repeated doses or a continuous infusion; however, it should be noted that the administration of a single dose of naloxone will not be sufficient to induce a full, long-lasting reversal of narcotization – repeated doses or an infusion is needed due to the short-acting duration of effect of naloxone compared to the high affinity and long-acting duration of buprenorphine.[2]

Abuse and dependence. None of the five randomized controlled trials identified in this updated review assessed abuse and dependence liability of transdermal buprenorphine. As with all other centrally acting opioids, transdermal buprenorphine does have the potential to induce physical dependence, leading to withdrawal symptoms. These symptoms appear to be milder than those caused by full mu-opioid receptor agonists.[4,56] It has been proposed that buprenorphine's pharmacokinetic and pharmacodynamics properties, being slow to dissociate from the mu-opioid receptor and acting as a partial agonist, may reduce the risk of development of tolerance, dependence, and effects that might encourage misuse.[56] Owing to the now widely acknowledged concerns with the development of iatrogenic dependence with chronic opioid therapy, it is important that future studies on opioid analgesia collect data on development of aberrant medication behaviors, misuse, and dependence to inform this aspect of safety. Such studies may be able to establish if buprenorphine is associated with less risk of opioid use disorders compared to other opioids.

Hyperalgesia. None of the five identified trials reported on hyperalgesia. Both experimental and clinical research have suggested that pure mu-opioid receptor agonists can contribute to a hyperalgesic effect, namely, where an individual taking opioid medications for long term develops increasing sensitivity to noxious stimuli, which results in an increased pain response, and several different mechanisms have been proposed as to how this occurs.[2] In one study, 82 heroin-dependent participants were randomized to receive either methadone or buprenorphine and their experimental pain responses were compared to 21 control participants who were not heroin dependent. Hyperalgesia was demonstrated in the heroin-dependent group compared to placebo, and the effect continued after methadone or buprenorphine maintenance treatment.[57] In contrast, however, buprenorphine has been demonstrated in other human experimental pain models to have reduced

hyperalgesic effects compared to placebo.[47] It is thought that because agonist activity at kappa opioid receptors promotes hyperalgesic states,[58] buprenorphine's antihyperalgesic effects may be because of its kappa antagonism.[47] Further research into clarification as to the mechanism of action is needed.

Driving. One study[37,41] reported two patients being involved in motor vehicle accidents, one in the run-in phase and the other during the double-blind phase, but no further details were mentioned. Although opioids are associated with altered cognitive function and impaired psychomotor function, it is also known that these side effects decrease with long-term use. Studies in Germany comparing patients receiving stable doses of transdermal buprenorphine for chronic non-malignant pain with healthy volunteers in terms of driving ability using a computerized test showed that their driving ability was not inferior.[59–61] It is also important to bear in mind that buprenorphine can be associated with lethargy and sedation, especially early in treatment, and patients must be warned not to drive until they have stabilized on treatment. The impact of other drug interactions (eg, other sedative uses) could potentially affect performance and, hence, driving.

Application site reactions. Four out of five studies reported application site reactions as a common adverse effect and reason for participants to discontinue treatment.[37,38,40–43] A study by Wen and colleagues in 2013 showed that while the rates of application site reactions in patients using transdermal buprenorphine were higher than those using a placebo (16.6% versus 12.7%), this was still a comparable rate with rates of application site reactions in other transdermal medications around 17%. Rates of severe and inflammatory type reactions were low, and the most common reactions were pruritus, erythema, and rash.[62]

Use in kidney dysfunction. One study reported a case of acute renal failure as an adverse effect, but it was unclear as to whether this was because of the treatment or the patient's comorbid metastatic prostate cancer.[37,38] Studies in patients suffering from moderate-to-severe cancer pain concluded that transdermal buprenorphine is as safe, effective, and tolerable as fentanyl in patients with kidney dysfunction as compared to those without.[63] Doses do not require adjustment, as the pharmacokinetics of the medication are not affected by kidney dysfunction,[64] with the majority of the drug being excreted via the hepatic system.[65] Research has also demonstrated that transdermal buprenorphine can be used in patients undergoing intermittent hemodialysis, as this does not appear to affect plasma concentrations.[66–68]

Use in hepatic impairment. Few data are available with regard to the use of buprenorphine in patients with hepatic failure. A recent study evaluated the pharmacokinetic profile of buprenorphine (0.3 mg given intravenously) in subjects with mild-to-moderate chronic hepatic impairment and in healthy controls matched for age, weight, and sex. No differences between the groups were observed for most pharmacokinetic parameters (eg, steady-state volume of distribution, total clearance). However, the maximum plasma concentrations of buprenorphine and norbuprenorphine were 50% and 30% lower, respectively, in individuals with hepatic impairment. These subjects also had less nausea and vomiting compared to the controls. The results did not indicate the need for a buprenorphine dosage adjustment in individuals with mild-to-moderate chronic hepatic impairment.[69]

Use in older adults. None of the identified studies specifically investigated the use of transdermal buprenorphine in older adult subjects. When considering the use of any medication in older adults, it is important to consider the physiological changes that occur with ageing, particularly changes in body composition (increased body fat, decreased muscle mass, and total body water), respiratory function (increased chest wall rigidity, functional residual capacity, ventilation/perfusion mismatch, and decreased elastic recoil), gastrointestinal function (increased gastric transit time), hepatic function (decreased hepatocellular function and blood flow to the liver), and renal function (decreased blood flow and glomerular filtration rate), which can affect the pharmacokinetics of the drug.[70] Studies on the use of buprenorphine in specifically older adult populations have demonstrated that it is well tolerated, with good compliance rates, and improved quality of life and pain control.[71] As transdermal buprenorphine is a partial agonist, it is less likely to cause respiratory depression at therapeutic analgesic doses, and should theoretically be a safe choice for use in older adults. As previously discussed, buprenorphine doses do not need to be adjusted for patients with impaired renal or hepatic function. In addition, studies comparing the pharmacokinetics[72,73] and efficacy[74,75] of transdermal buprenorphine in younger versus older patient populations[72–75] conclude that no age-related dose adjustment is required. It is, however, important to bear in mind any potential drug–drug interactions between buprenorphine and a patient's other medications, as older adults are often on multiple different drugs, especially central nervous system depressants, drugs that affect CYP3A4 enzyme activity or reduce hepatic blood flow.[64] The safest approach is to start at a low dose, increase slowly, and titrate to effect.

Contraindications. Transdermal buprenorphine is contraindicated in patients with known hypersensitivity to buprenorphine or any of the contents contained in the patch, patients with severe impairment of respiratory function, patients receiving monoamine oxidase inhibitors or who have ceased taking them for less than 14 days, patients suffering from myasthenia gravis (because of the potentiation of opioids by cholinesterase inhibitors as well as concern over respiratory depression), patients suffering from delirium tremens, or patients known to be opioid dependent or who require opioid withdrawal treatment.[27,28]

Transdermal Buprenorphine in the Context of Other Treatments for Chronic Pain

Although arguments have been made for the inclusion of buprenorphine in the second step of a three-step analgesic

ladder along with codeine, tramadol, and tapentadol,[76–78] currently the World Health Organization classified buprenorphine as a step III opioid along with fentanyl, hydromorphone, methadone, morphine, and oxycodone in its three-step ladder of analgesia, originally developed for its recommendations first released in 1986 for the treatment of cancer-related pain and subsequently updated in 1996.[79] It is currently developing guidelines for the treatment of persistent pain in adults, with the release of a scoping document in 2012.[80] There is growing evidence for the efficacy of opioids in non-cancer pain, but attention to individual dose titration and consideration of tolerability must be considered for each individual patient.[81] Opioid management should be part of overall management using a multimodal and multidisciplinary approach. In general, prior to considering opioid therapy, clinicians should first consider whether a patient's condition could be more appropriately and effectively treated with non-pharmacological approaches or non-opioid therapies such as physiotherapy, psychological approaches, acetaminophen, and/or non-steroidal anti-inflammatory drugs.[79,82] If all other treatment options have been explored, a trial of an opioid analgesic can be considered. It is important to perform a comprehensive assessment of the patient before considering pharmacological treatments, including assessment of risk of misuse, impact of pain on function and quality of life, and the balance between potential therapeutic benefits and harms. Thorough assessment and explanation of potential adverse effects, potential for misuse, and agreement on strategies to monitor compliance, safety, and clinical response should take place.[82] In line with recommendations about treatment contracts (or similar), it should be explained to the patient that treatment with the opioid will cease if significant progress toward treatment goals has not been made.[82] Transdermal buprenorphine is a good choice for a first-line opioid analgesic in this context.

How to Initiate and Cease Treatment

When initiating opioids for pain management, patients should initially commence transdermal buprenorphine at the lowest dose of 5 μg/hour. Doses should not be increased more frequently than every one or two weeks to allow for the drug to reach a steady state. If dose increases are indicated based on inadequate control of pain, the patch dose can be titrated upward to effect in increments of 5 mg every one to two weeks to the currently recommended maximum dose of 40 μg/hour (two patches of 20 μg/hour strength). Alternatively, a combination of patches, applied in separate locations, could be used. Short-acting supplemental analgesia may be required until analgesic efficacy with an appropriate dose of transdermal buprenorphine is achieved.[27,28] Breakthrough pain can be treated with short-acting opioids on a background of constant buprenorphine delivery. If the side effects of transdermal buprenorphine are not tolerated or the maximum dose limit is reached without efficacy, then switching to another opioid may be necessary.[35]

When switching to or rotating from another opioid, it is important to consider the tolerance and dependence of the patient to that opioid, as the commencement of buprenorphine can precipitate a withdrawal syndrome in patients who are highly tolerant of and dependent on full agonist opioids. Studies appear to suggest that patients taking opioids such as doses of 120 mg/day or less of parenteral morphine or 30 mg/day or less of oral methadone are less likely to precipitate withdrawal, and that this is dependent on the dose of buprenorphine given, dose of full agonist opioid, and time between administration of both medications.[3] Clinicians should, therefore, be mindful that precipitated withdrawal can occur even at low doses of full agonist opioids. It is generally difficult, however, to switch from a high dose of a strong opioid to transdermal form because of the relatively small dosage of the transdermal form. In terms of ceasing transdermal buprenorphine, a slow titration downward is also recommended, as is the usual practice with other opioid analgesics to reduce the risk of a withdrawal reaction.

Treatment Costs

Table 5 compares the wholesale costs and costs of approximate equianalgesic doses of several opioids to the patients in Australia, the latter subsidized by the government (Boughton, 2014, personal communication, November 2). It appears that an equipotent dose of transdermal buprenorphine is slightly more expensive than other opioids. While wholesale costs are broadly comparable in Australia, this may not be the case in other countries. Bearing in mind the complexity and variation of medication costs in different countries, discussion may have to be had with patients concerning treatment costs if buprenorphine is more expensive than other treatment options. This could also make it less attractive in countries where patients must bear the full cost of medications.

Table 5. Comparison of wholesale costs and costs of several opioids to the patients in Australia.

MEDICATION	NORSPAN (BUPRENORPHINE) TRANSDERMAL PATCH 10MCG/HR (2 PATCHES)	MS CONTIN (MORPHINE) TABLET 20MG (56 X 10MG TABLETS)	JURNISTA (HYDROMORPHONE) 4MG TABLET (14 TABLETS)	DUROGESIC (FENTANYL) TRANSDERMAL PATCH 12MCG/HR (5 PATCHES)
Wholesale price ($)	26.84	16.24	18.97	7.84
Maximum consumer price ($)	32.38	51.44	36.63	34.64

Summary

Buprenorphine's pharmacological properties make it ideal for a transdermal system of delivery, and studies suggest that it is a safe and efficacious choice for the management of several causes of chronic pain, and can be used in older adults and those with kidney dysfunction. Since the publication of Plosker's review in 2011, no new evidence has emerged from randomized controlled trials comparing buprenorphine to placebo/other opioids that demonstrated improvements in control of pain severity, quality of life, sleep quality, mobility, and function over a period of up to 15 weeks in patients with chronic lower back pain and osteoarthritis. More evidence is needed, however, on whether these outcomes are sustained in the long-term and in other chronic pain conditions. In addition, long-term limitations include skin reactions and limited dosing provided by the patch necessitating a switch to high-strength preparations or stronger opioids in response to development of tolerance and/or worsening pain from worsening of the primary pain condition or pathology.

Author Contributions

Analyzed the data: AY, AD, KEK, SN, NL. Wrote the first draft of the manuscript: AY. Contributed to the writing of the manuscript: AY, AD, KEK, SN, NL. Agree with manuscript results and conclusions: AY, AD, KEK, SN, NL. Jointly developed the structure and arguments for the paper: AY, AD, KEK, SN, NL. Made critical revisions and approved final version: AY, AD, KEK, SN, NL. All authors reviewed and approved of the final manuscript.

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