**Buprenorphine- an atypical opioid: all you need to know**

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Abstract: The profile of buprenorphine is described, with a focus on its unique properties and clinical niche. The pharmacological principles determining the action, side effects and uses in best practice are explained, including those for special populations, namely children, the elderly and in pregnancy. Advice for safe use for chronic pain, as well as for opioid substitution therapy is provided. Counselling strategies to support concordance and safety are given.

Key Words: buprenorphine, opioid pharmacology, opioid dependence, chronic pain management

Key Points:

Buprenorphine is efficacious in treating chronic pain, with additional advantages for the elderly and for those with renal disease. Its well-recognised plateau characteristics, even at higher doses, allows safer pain relief with an improved addiction, tolerance and withdrawal profile, compared to other opioid interventions. Newer evidence supports the kinetic and dynamic properties which make it suitable for the treatment of opioid dependence, including during pregnancy (off-label). It can be used by injection for paediatric pain management in infants above 6 months old. Supportive and individual counselling is recommended.

There are no conflicts of interest.

Buprenorphine is a semi-synthetic opioid with unique properties and clinical applications. Its analgesic role is primarily for long-acting pain relief, which is reinforced by useful patch and lozenge formulations. The unusual pharmacology of buprenorphine confers advantages regarding tolerance, withdrawal and reduced respiratory depression risk, all of which are particularly beneficial for long-term opioid use. Elements of this profile also lend themselves to use in opioid addiction management.

**How do opioids work?**

All opioid compounds used clinically have some commonality in how they work, because pain relief is primarily activation of the mu opioid receptor located on brain and spinal cord neurons. This is an agonist action, because the mu receptor normally responds to binding of endogenous peptides, such as endorphins, to provide natural pathways forpain relief. The opioid drugs are ‘switching on’ this mechanism. It is noteworthy that peripheral nervous system opioid receptors are abundant, as well as widespread throughout the gastro-intestinal tract, mediating the constipating effects. Those located on afferent peripheral nerves display some analgesic response to opioid agents. However, this response is unreliable, and therefore peripheral nerves are not the pharmacological or clinical target.

**Opioid mechanism of action**

Once activated, the mu opioid receptor stabilises the neuronal membrane via inhibitory G protein messengers. Reduced nerve excitability makes action potential generation more difficult, suppressing the transmission of pain signals. There are differing levels of attraction for the mu receptor, as well as differences in the strength of action once bound, giving each member of the opioid drug family distinctive properties, including the level of pain relief and duration of action.

**Buprenorphine Pharmacology and Therapeutics**

Buprenorphine is synthesised from poppy seed derivatives, making it a semi-synthetic opioid. It is highly lipid soluble, hence its suitability for transdermal preparations. This also affords a high volume of distribution of up to 335 litres (i.v) (Drugbank). Despite a partial agonist action at the mu receptor, buprenorphine is up to eighty times more potent than morphine (Sittl et al 2006; MIMS 2012) with a more durable analgesic effect. This makes it ideal for chronic pain and palliative care. The low oral bioavailability for buprenorphine favours sub lingual (s.l.) and patch formulations for chronic use, while intramuscular and intravenous delivery can provide pain cover peri-operatively. The sub-lingual and intramuscular formulations are licensed for premedication (BNF 72).

Protein binding predominantly to α- and β-globulins is high at 96%, but the wide therapeutic index of buprenorphine, combined with the unlikely displacement of drugs such as warfarin from albumin, means this is not clinically relevant (SPC). Hepatic metabolism is by glucuronidation and via CPY3A4 mediated oxidation to 3 active metabolites, including norbuprenorphine. Seventy percent of the drug is excreted in faeces, and the remainder is excreted in urine. This means that the dose does not need adjustment in renal impairment, which makes buprenorphine particularly safe in the elderly (Hand et al 1990; Filitz et al 2006)

Pharmacokinetics are reported as stable in mild to moderate hepatic deficiency (Foster et al 2013), but severe liver disease could permit elevated plasma concentrations, potentiating adverse reactions (SPC). Drugs that are known to inhibit or induce CYP3A4 have the potential to diminish or enhance buprenorphine metabolism, with associated clinical consequences (see Table 2).

As a lipophilic compound, buprenorphine can access the CNS rapidly but, unlike fentanyl, cannot act immediately. This is because, although there is high affinity for the mu receptor, there is very slow association and disassociation from the receptor site. The slow onset limits the ‘high’, while the long offset contributes to prolonged pain relief. The protracted inaccessibility of the receptors to other endogenous and opioid agents may confer some level of antagonism. Thus, the relatively low intrinsic activity at the mu receptor is thought to bestow a partial agonist effect. It is argued that this may not translate to limitations in analgesic potential (Dahan et al 2006).

Conversely, the lower risk of respiratory depression is attributed to this ‘ceiling effect’ at the mu receptor (Dahan et al 2005), which is evident even at higher doses (NICE 2007). Respiratory complications are unlikely to reach clinical significance in normal dose ranges (Reisine and Bell, 1993; Walsh et al 1994), but this remains a potentially life-threatening event for which vigilance is important. This is particularly relevant where there is a lack of studies pertinent to the newer patch formulations. It is noteworthy that compromised patients e.g., those with respiratory disease, the elderly, those with co-morbidities, and those on CNS depressants, remain at greater risk of respiratory depression.

**Pharmacodynamics**

The pharmacology of buprenorphine is further complicated by mixed agonist and antagonist actions at the kappa and delta receptors. The delta receptor is the natural target for enkephalins, producing analgesia and mood enhancement (Neito et al 2005), whereas antagonism could offset opioid addiction and tolerance (Shippenberg et al 2009). Buprenorphine binds to, but does not act at the delta receptor, whereas the metabolite norbuprenorphine is a full agonist. Thus, the drug opposes itself, making the clinical relevance difficult to interpret. Such complex receptor interactions may account for some of the benefits for treating narcotic addiction.

Kappa opioid receptor activation by its natural ligand dynorphin, is associated with a stress response, producing low mood, anxiety, increased appetite and increased sensitivity to pain. Kappa receptor antagonism by buprenorphine (Richards and Sadee 1985) counteracts the dysphoric effects of dynorphin, which have been shown to be enhanced bychronic opioid use/abuse (Bruijnzeel 2009). Higher levels of dynorphin, when unopposed by the withdrawal of euphorigenic opioids is suggestedas beingone reason for the depressant effects of narcotic withdrawal (Land et al 2008). The antagonism by buprenorphine may offset negative emotional states from withdrawal reactions, improving the compliance and relapse rates in users (Ford et al 2011).

More recently, the opioid receptor-like 1 (ORL-1/NOP receptor) has been linked with buprenorphine, which is thought to be a full ORL-1 agonist (Chiou et al, 2007). The natural agonist is nociceptin, the role of which is to modulate pain and induce hyperalgesia. As such, agonism of ORL-1 is also associated with opposing the dopaminergic reward system. It is speculated that the notorious ‘ceiling’ effect and the partial agonist status of buprenorphine is related to the opposing forces of its dual action at the mu and ORL-1 receptors (Lufty et al 2003). This would produce the effect of analgesia, with less reward response. This corresponds with the clinical profile of buprenorphine, which is associated with muted euphoria and is known to support opiate abuse management.

**Long-term pain management**

Chronic pain is a common problem, as distinct from cancer-related pain, with a recent systematic review placing the UK prevalence at up to half of the total adult population, equating to approximately 28 million people (Fayaz et al, 2016). Buprenorphine use is placed at the upper point of step 2 (e.g BuTrans low dose patch) or above, using the World Health Organisation (WHO) analgesic ladder, as intervention is likely to be for persisting or increasing pain (WHO 2003, CKS 2017a AQ3). With a long duration of action, a wide dose range, a safer respiratory and renal profile and less constipation than traditional opioids, buprenorphine is an attractive option.

The BuTrans patch is licensed for non-malignant pain at 4 different strengths (5,10,15, and 20 micrograms per 1 hour). The requirement for escalation to the use of moderate to strong opioid drugs is common, and buprenorphine is used in the pain management of conditions such as arthritis (James et al, 2010) and chronic pain syndromes (Wolff et al, 2012). Hapoctasin provides a higher strength patch licensed for severe pain (non-malignant and malignant), delivering up to 70 micrograms per 1 hour (BNF 72). It is of interest that a buccal film formulation of buprenorphine with superior bioavailability and extended release properties has been licensed in the United States (Belbuca), indicated for chronic pain.

There remains a lack of evidence to support opioids in the long-term management of pain (Chou et al 2015) yet harms such as overdose and adverse drug reactions are recognised (SIGN 2013). In view of this, use for chronic pain should be accompanied by careful counselling, regular and vigilant reviews, and skilled support (Box 1)

It is notable that many of the chronic pain states are related to auto-immune disorders with associated immune defects and may require corticosteroid therapy, incurring further immune suppression. Some opioids, such as morphine, when used long-term, are mooted as harmful to the immune system (Eisenstein and Hilburger, 1998; Wang et al, 2008). The mechanism remains unclear, but T and B lymphocytes express all opioid receptor sub-types, with greater ambiguity over effects on other lymphocyte populations and macrophages (Liang et al 2016). In contrast, buprenorphine use has not been associated with immune-suppression or interference with hypothalamic-pituitary axis function (Gomez-Flores and Weber, 2000).

**Palliative care**

Buprenorphine may form one component of an array of analgesic interventions in cancer pain management. The approach is also based upon the WHO pain ladder (WHO 2003), but buprenorphine is positioned at step 3 in palliative care as the licensed preparations are targeted at moderate to severe cancer pain. At the higher doses, it is considered a strong opioid (SIGN 2013). One role for buprenorphine is as an alternative to oral medication with traditional opioids such as morphine (WHO, 2003). A recent Cochrane Review evaluated the role of buprenorphine for cancer pain in adults and children and reported its position to be fourth in line after morphine, oxycodone and fentanyl, of value when used via sublingual and injectable routes (Schmidt-Hansen et al, 2015) (See Table 2 for use in children)

Because of the extensive mu receptor binding properties of buprenorphine, there has been clinical concern that rescue medication will not be effective. In view of the persistent and widespread binding properties of buprenorphine, this is understandable. However, the clinical picture has not supported this scenario, and other opioids have been found to be effective for the management of breakthrough pain (Budd and Collett, 2003).

**Pain management for those taking buprenorphine for opioid dependence**

Those on long-term buprenorphine (or methadone) as addiction therapy do not necessarily have analgesic level cover (depending on how recently the drug was taken, and the presence/absence of opioid induced hyperalgesia), so if acute pain management is required, additional measures must be initiated. This is made more complicated by the belief (byboth clinicians and patients) that any opioid administered could cause addiction relapse (not proven), (Savage et al 2008) and that the pain requirement may be exaggerated, as part of drug seeking behaviour. This scenario requires expertise and an individualised approach. Issues to be considered should include how long the pain relief is needed for, and whether the person is on a buprenorphine/naloxone combination. There are guidelines available to support decision making, such as the CKS section in opioid dependence on managing acute and chronic pain, (CKS 2017c) and additional details are also provided by the Department of Health (2007a).

**Managing Addiction**

Sub-lingual buprenorphine (with and without naloxone) is approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA), for the management of opioid dependence. While currently second in line to methadone in the UK (CKS 2017b), buprenorphine has seen growing popularity in this arena, particularly since the generic version has reduced cost (Table 3). The ability to attenuate the effects of morphine and heroin has made buprenorphine an attractive alternative to methadone for the management of opioid dependence.

The widespread receptor binding provides sufficient opioid stimulation to offset craving, but with minimal euphoria (Ford et al 2011). Achieving extensive receptor occupation requires higher doses, but is advantageous because this limits the prospect of overcoming dependence treatment by seeking a “high” with another opioid. It is of interest that the FDA have recently approved an implant (Probuphine), which delivers continual low dose buprenorphine for six months, for those on a suitable substitution programme (FDA 2016).

Methadone remains the first line agent to treat opioid addiction in the UK (SEE TABLE 3). It has an established evidence base, it is economical and its sedative effects can be helpful in alleviating the anxiety associated with withdrawal (CKS 2017b, Department of Health 2007a). However, buprenorphine is less sedating (BNF 72), allowing a more normal lifestyle. It is also associated with a reduction in abusive behaviours, for reasons outlined above, as well as because of the full agonist action on the ORL-1 receptor.

In pregnancy, methadone or buprenorphine (unlicensed) may be used as substitution therapy to achieve stability and both are considered safe (CKS 2017d) (Table 2). Both drugs can cause neonatal abstinence syndrome, although neonatal withdrawal may be milder following maternal buprenorphine use (CKS 2017d) Both drugs are excreted in breast milk, with poor oral absorption of buprenorphine a potential advantage for the infant (Ford 2011, CKS 2017d) (lactation unlicensed use) (Table 2).

While the overdose risk is six times less than for methadone (Marteau et al 2015), the high lipid solubility of buprenorphine allows the conversion of the lozenge formulation, to an injectable powder. This incurs some abuse potential (CKS 2017b). To overcome this, the buprenorphine lozenge can be combined with naloxone, which has little effect when takenorally. If injected, the naloxone blocks opioid receptor stimulation, triggering an unpleasant withdrawal reaction. This is a considerably more expensive option (see table 3).

Further information on dosages and switching protocols are available in the BNF (Joint Formulary Committee 2017), CKS (2017b,c) and NICE (2007) guidelines.

Table 1. Buprenorphine Profile: adult use

|  |  |
| --- | --- |
| Characteristic | **Buprenorphine** |
| Mu receptor | Partial agonist (traditional concept) |
| Affinity  | Binds strongly to mu receptor/long duration action |
| Onset of action | i.v 5-10 minsi.m 10-20 minss.l tablet approx. 100 mins patches 12-24 hours  |
| Duration of action | i.v/i.m 2-6 hours (t ½ 5 hours)s.l 6-8 hours (t ½ mean 32 hours)x1 bu-trans patch-up to 7 days’ pain relief x1 transtec patch- up to 4 days’ pain relief(patch t ½ 26-30 hours) \* |
| Potency | x20-80 more potent than morphine § |
| Addiction potential | Weak  |
| Formulations | s.l,i.m slow i.vpatch (range strengths) |
| Dose Range | Pain (s.l) 200-400microgram every 6-8hrsPatches 5-20 micrograms/houri.m/slow i.v 300-600microgram every 6-8 hrsDependence (s.l)0.4mg-24mg (max 32mg) |
| Common adverse drug reactions e.gSerious adverse drug reactions e.g | Anorexia, fatigue, confusion, depression, tremor, abdominal painPsychiatric disorder(s), angina, respiratory depression, anaphylactoid reactionNB: NOT full list |
| Withdrawal  | Milder than for morphine  |
| Renal | Relatively safe |
| Hepatic | Caution CYP 3A4 interactions |
| Respiratory depression | Rare at clinical doses  |
| Overdose | Partial reversal by naloxone |
| Controlled drug classification | Class C schedule 3 |
| Drug-Drug Interactions (DDI) | Can precipitate withdrawal if used with other opioids (BNF 72)Enhanced sedative effect if used with alcohol, anaesthetics, benzodiazepines, tricyclic antidepressants etc (BNF 72)Monoamine oxidase inhibitorsCYP3A4 inhibitors e.g ritonavir,clarithromycin, itra/fluconazole,cimetidine; grapefruit juice,verapamil:increased buprenophrine plasma concentration (SPC, Department of Health (b) 2007)CYP3A4 inducers e.g rifampicin, St John’s Wort and anti-epileptic drugs such as phenytoin: use with caution as there is limited information (SPC, Department of Health (b)2007) |

SPC: summary product characteristics

BNF 72 (2017)

Drugbank

Department of Health (b)

\*SPC; Vadivelu and Hines (2008)

§ Sittl et al (2006)

NOTE: variation in terminal half-lives for different formulations thought to be related to deposition of the drug in local tissues, e.g oral muscosa (Kuhlman et al 1996)

Table 2. Opioid Dependence Community Expenditures (England) in January 2017

|  |  |  |  |
| --- | --- | --- | --- |
|  | Substitution cost/day(non-proprietary except suboxone)  | Jan 2017 number of prescribed items by GP practices in England | January 2017 cost of prescribed items by GP practices in England |
| **Buprenorphine**  | s.l tablet 24mg/day £1.50/day(based on 8mg pack cost) | 59,895 items | £417,968 |
| **Buprenorphine HCL with naloxone** | Suboxone 8mg/2mg s.l tablet 24mg/day£8.16 | 2733 | £77,186 |
| **Methadone**  | Oral solution (120mg)£1.62/day (based on 500ml cost) | 149,106 | £981,542 |

(BNF 72(2017); *OpenPrescribing.net (2017)*

Table 3: Buprenorphine use in special populations

[See comment in PubMed Commons below](http://www.ncbi.nlm.nih.gov/pubmed/15966752#comments)

|  |  |
| --- | --- |
|  | **Buprenorphine** |
| **Elderly** | Uses: chronic pain and palliative care.Patch formulation helpful re slow release. |
| **Children** | Uses palliative cares.l tablets unlicensed for <6 years.injection unlicensed < 6 months.Patches unlicensed for children. |
| **Pregnancy and lactation** | Crosses placenta (SPC)Used but unlicensed for opioid dependence in pregnancy.Dose kept minimal during lactation, with neonates monitored for side-effects (poor oral absorption from breast milk expedient)§NOTE buprenorphine and naloxone combination also used \* |

BNF 72(2017)

§ Ford et al 2011

**\*** Jumah et al (2016)

**Box 1: Bullet points on recommended counselling**

* Conveying the potential risk of addiction is for everyone, not just certain ‘types’.
* Advising patients about, and monitoring for, potential serious adverse drug events, such as overdose.
* Recognizing and counselling patients about the potential for misuse, abuse, and addiction /patient risk assessment.
* Safe use of the drug, e.g not changing formulation by crushing or changing route of administration.
* Recognizing and reporting drug diversion from healthcare setting to the community.
* Check drug-drug interactions, as well as other the counter, herbal and recreational agents.
* Lifestyle considerations*,* e.g driving (guidance on informing the DVLA) and working.
* Potential withdrawal issues and symptoms.
* Common adverse drug reactions.
* Co-prescribing as required to improve concordance.
* Only use for the condition for which prescribed.
* Counselling patients about proper medication use, storage, and disposal especially risks to children at home.
* Agreed monitoring schedule (initially more intensive and when stable minimal biannual check up).

Clinical Knowledge Summaries (2017a,b,c)

SIGN (2013)

Royal College Anaesthetists: Faculty of Pain Medicine (2017)

Conclusions:

Opioid selection based on efficacy and tolerability is paramount, and insight into the respective properties of available agents should optimise clinical benefits.

Buprenorphine pharmacotherapy is efficacious for pain management and opioid dependence, while taking account of the potential hazards.

Safe use and concordance may be enhanced by appropriate counselling.

Judicious use of all opioids remains a key target, particularly in view of the problems associated with some non-opioid drug groups, namely NSAIDs.

**CPD questions**

Why does buprenorphine action last for a long time?

What are the properties which make buprenorphine suitable for opioid addiction management?

Where does intervention with buprenorphine start, on the WHO analgesic and cancer pain ladders?

In whom should buprenorphine not be used?

**References**

British National Formulary: Joint Formulary Committee. *British National Formulary* (online) London: BMJ Group and Pharmaceutical Press. <https://www.evidence.nhs.uk/formulary/bnf/current>. Accessed online June 2017

[Bruijnzeel](http://www.ncbi.nlm.nih.gov/pubmed/?term=Bruijnzeel%20AW%5Bauth%5D) AW (2009) Kappa-opioid receptor signaling and brain reward function

[Brain Res Rev. 62(1): 127–146.](http://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=19804796)

Budd K, Collett BJ (2003). Old dog--new (ma)trix.Br J Anaesth. 90(6):722-4.

Chiou LC, Liau YY, Fan PC, Kuo PH, Wang CH, Riemer C, Prinssen EP. (2007) Nociception/orphanin FQ peptide receptors: pharmacology and clinical implications. Curr Drug Targets ;8:117–35.

Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review. Annals of Internal Medicine 2015; 162: 276-286.

Clinical Knowledge Summaries 2017a: <http://cks.nice.org.uk/analgesia-mild-to-moderate-pain#!scenariorecommendation:27>. Accessed May 2017

Clinical Knowledge Summaries 2017b: Opioid Dependence

<https://cks.nice.org.uk/opioid-dependence#!scenario:2> Accessed May 2017

Clinical Knowledge Summaries 2017c: Opioid Dependence

<https://cks.nice.org.uk/opioid-dependence#!scenario:12> Accessed June 2017

Clinical Knowledge Summaries 2017d: Opioid Dependence

<https://cks.nice.org.uk/opioid-dependence#!scenario:10> Accessed July 2017

Dahan A, Yassen A, Bijl H, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M (2005) Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats.Br J Anaesth: 94(6):825-34.

Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M (2006) Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 96(5):627-32.

Department of Health (a): Drug misuse and dependence: UK guidelines on clinical management (2007).Section 7.8 <http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf> Accessed June 2017

Department of Health (b): Drug misuse and dependence: UK guidelines on clinical management (2007).Appendix 6 Drug Interactions <http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf> Accessed June 2017

Drugbank: <https://www.drugbank.ca/drugs/DB00921>. Accessed June 2017

Eisenstein TK, Hilburger ME(1998) Opioid modulation of immune responses: effects on phagocyte and lymphoid cell populations.*J Neuroimmunol.83(1-2):36-44.*

Fayaz A,Croft P,Langford RM,Donaldson LJ,Jones GT. (2016) Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*2016;**6:**e010364. doi: 10.1136/bmjopen-2015-010364

Filitz J, Griessinger N, Sittl R, Likar R, Schüttler J, Koppert W (2006) Effects of intermittent hemodialysis on buprenorphine and norbuprenorphine plasma concentrations in chronic pain patients treated with transdermal buprenorphine.Eur J Pain. 10(8):743-8.

Food and Drug Administration: Accessed June 2017 https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503719.htm

Ford C, Halliday K, Lawson E, Browne E (2011) Guidance for the use of substitute prescribing in the treatment of opioid dependence in primary care. <http://www.rcgp.org.uk/revalidation-and-cpd/~/media/Files/SMAH/RCGP-Guidance-for-the-use-of-substitute-prescribing-in-the-treatment-of-opioid-dependence-in-primary-care-2011.ashx>

Foster B, Twycross R, Mihalyo M, Wilcock A (2013). Buprenorphine. J Pain and Symptom Management. 45 (5)939-949.

Gomez-Flores R, Weber RJ (2000) Differential effects of buprenorphine and morphine on immune and neuroendocrine functions following acute administration in the rat mesencephalon periaqueductal gray.Immunopharmacology.48(2):145-56.

Hand CW, Sear JW, Uppington J, Ball MJ, McQuay HJ, Moore RA (1990) Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. Br J Anaesth. Mar; 64(3):276-82.

# James ICV, O’Brien CM, McDonald CJ. (2010) 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 and Symptom Management, 40(2);266-278

Jumah NA, Edwards C, Balfour-Boehm J, Loewen K, Dooley J, Gerber Finn L. (2016). Observational study of buprenorphine+naloxone in pregnancy in a rural and remote population. BMJ Open;6(10)e011774.doi10.1136/bmjopen-2016-011774.PMID:27799240

Kuhlman JJ Jr, Lalani S, Maqluilo J Jr, Levine B, Darwin WD. (1996) Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. J Anal Toxicol, 20, pp. 369–378

Land BB, Bruchas MR, Lemos JC, Xu M, Melief EJ, Chavkin C (2008)The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system.J Neurosci; 28(2):407-14.

Liang X, Liu R, Chen C, Ji F, Li T. (2016) Opioid System Modulates the Immune Function: A Review. Transl Perioper Pain Med. 1(1): 5–13.

Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ. (2003) Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors.J Neurosci. 23(32):10331-7.

[Marteau](http://bmjopen.bmj.com/search?author1=Dave+Marteau&sortspec=date&submit=Submit), D; [McDonald](http://bmjopen.bmj.com/search?author1=Rebecca+McDonald&sortspec=date&submit=Submit), R;  [Patel](http://bmjopen.bmj.com/search?author1=Kamlesh+Patel&sortspec=date&submit=Submit) K. (2015)The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open 2015;5:e007629 doi:10.1136/bmjopen-2015-007629

MIMS (2012). Opioid Analgesics: Approximate Potency Equivalence with Oral Morphine : <http://www.mims.co.uk/opioid-analgesics-approximate-potency-equivalence-oral-morphine/pain/article/1146201>

National Institute for Health and Clinical Excellence (2007) Methadone and buprenorphine for the management of opioid dependence. TA114. Accessed via nice.org.uk on 6.6.2017

National Institute for Health and Clinical Excellence (May 2012) Opioids in Palliative Care. CG140. Accessed via www.nice.org.uk on 9.6.2017

Nieto MM, Guen SL, Kieffer BL, Roques BP, Noble F (2005) Physiological control of emotion-related behaviors by endogenous enkephalins involves essentially the delta opioid receptors.Neuroscience. 135(2):305-13.

* + Research

*OpenPrescribing.net, EBM DataLab, University of Oxford, 2017:*

<https://openprescribing.net/chemical/0410030C0/methadone>

<https://openprescribing.net/chemical/0410030A0/buprenorphine>

<https://openprescribing.net/chemical/0410030B0/buprenorphineHCL/naloxone>

Reisine, T. and Bell, G.I. (1993) Molecular biology of opioid receptors. *Trends Neurosci*.16: 506–510

Richards, M.L. and Sadée, W (1985) In vivo opiate receptor binding of oripavines to mu, delta, and kappa sites in rat brain as determined by an ex vivo labeling method. *Eur J Pharmacol*. 114: 343–353

Royal College of Anaesthetists: Faculty of Pain Medicine

<https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware/structured-approach-to-prescribing/long-term-prescribing>. Accessed July 2017

Savage SR, Kirsh KL, Passik SD. (2008) Challenges in using opioids to treat pain in persons with substance use disorders. Addict Sci Clin Pract.4:4-25.

Schmidt-Hansen M , Bromham N ,Taubert M , Arnold S, Hilgar JS. (2015). Buprenorphine for treating cancer pain. Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD009596. DOI: 10.1002/14651858.CD009596.pub4.

Shoblock JR. (2007) The pharmacology of Ro 64-6198, a systemically active, non- peptide NOP receptor (opiate receptor-like 1, ORL-1) agonist with diverse preclinical therapeutic activity. CNS Drug Rev;13:107–36.

Shippenberg TS, Chefer VI, Thompson AC (2009) Delta-opioid receptor antagonists prevent sensitization to the conditioned rewarding effects of morphine.Biol Psychiatry; 65(2):169-74.

SIGN 136. Management of Chronic Pain. December 2013. http://www.sign.ac.uk/pdf/SIGN136.pdf (accessed July 2017) <http://www.sign.ac.uk/assets/sign136.pdf>

Sittl R, Nuijten M, Nautrup BP (2006) 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. 28(8):1144-54.*

Summary Product Characteristics: Buprenorphine: <https://www.medicines.org.uk/emc/medicine/16787#INTERACTIONS> Accessed June 2017

# Vadivelu N, Hines RL. (2008) Management of chronic pain in the elderly: focus on transdermal buprenorphine. Clin Interven Aging; 3(3): 421–430

Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., and Bigelow, G.E. (1994) Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clin Pharmacol Ther*. 55: 569–580

Walsh SL, Preston KL, Bigelow GE, Stitzer ML (1995). Acute administration of buprenorphine in humans: partial agonist and blockade effects.*J Pharmacol Exp Ther. 274(1):361-72.*

Wang J, Barke RA, Ma J, Charboneau R, Roy S (2008) Opiate abuse, innate immunity, and bacterial infectious diseases.Arch Immunol Ther Exp (Warsz). 56(5):299-309.

WHO (2003) WHO's pain ladder. World Health Organization

Wolff RF,Aune D,Truyers C,Hernandez AV, Misso K, Riemsma R, Kleiinen J. (2012) [Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain](http://www.tandfonline.com/doi/abs/10.1185/03007995.2012.678938). [Current Medical Research and Opinion](http://www.tandfonline.com/toc/icmo20/28/5)Vol. 28 , (5) 833-845