EXPERT OPINION

informa healthcare

Buprenorphine and buprenorphine/naloxone soluble-film for treatment of opioid dependence

Michael Soyka
University of Munich, Psychiatric Hospital, Munich, Germany

Introduction: Opioid dependence is a chronic relapsing disorder that shows excess mortality and comorbidity with somatic and psychiatric disorders. Methadone and buprenorphine/naloxone are widely accepted and are used as first-line maintenance treatments for opioid dependence. Fatal intoxications with these agents, risk of diversion, and accidental intoxications, especially in children, are apparent risks and are of increasing public concern. Buprenorphine/naloxone sublingual tablet is an established treatment for opioid dependence. A novel buprenorphine/naloxone film has been developed with improved pharmacokinetics and a hopefully lower risk of diversion and accidental intoxications.

Areas covered: This review evaluates the available preclinical and clinical data on the novel buprenorphine/naloxone film for the treatment of opioid dependence. Literature was identified though a comprehensive PubMed search and data sources included official FDA information.

Expert opinion: This is an interesting new formulation of a well-established medication in opioid dependence. However, few data have been published on its safety and efficacy. In an experimental study, the new formulation suppressed symptoms of opioid withdrawal as expected. Results of an unpublished study made public by the FDA suggest a spectrum of adverse events similar to that of the conventional sublingual tablet. Some data show patients may prefer the novel film over the sublingual tablet. The estimated lower risk for diversion and especially for accidental poisoning in children cannot be assessed in clinical studies but requires data from emergency room visits.

Keywords: buprenorphine, buprenorphine film, naloxone, opioid dependence, opioid receptors, opioids, therapy

Expert Opin. Drug Deliv. (2012) 9(11):1409-1417

1. Introduction

Opioid dependence is a chronic medical disorder defined by a cluster of somatic, psychological, and behavioral symptoms. The non-medical use of opioids, including heroin, represents a major public health problem: the worldwide prevalence of opioid use disorders is 0.4% in individuals aged 15 – 64 years, with some 12 million heroin users worldwide [1,2]. In Europe, the average prevalence of problematic opioid use is estimated to be 3.6 – 4.4 cases per 1000 population aged 15 – 64 years [3]. This corresponds to approximately 1.35 million affected individuals in Europe. In the United States, the 12-month prevalence of drug abuse in general, with and without dependence, was recently estimated at 5.7% [4]. Approximately 3.7 million individuals have used heroin at least once in their lives, and 750,000 – 1,000,000 individuals are currently heroin dependent [5]. The World

10.1517/17425247.2012.729574 ISSN 1742-5247

Health Organization (WHO) estimates that the burden of harm from opioid use is 11.2 million disability-adjusted life-years (DALYs; [6]).

The endogenous opioid system has been extensively studied over the past decades but the exact neurobiological mechanisms underlying opioid dependence, compulsive drug use, and drug seeking are not entirely understood [7-9]. Three major classes of opioid receptors have been characterized – mu, kappa, and delta (μ, κ, and δ) [10]. Mu and kappa receptors are located in the gray matter of the spinal cord, limbic system, thalamus, ventral striatum, and brainstem and delta receptors throughout the whole gray matter of the telencephalon. Beta-endorphins are endogenous ligands for mu and delta receptors, enkephaline for delta receptors, and dynorphine predominantly, but not exclusively for kappa receptors [11-14].

Mu receptors play an essential role in mediating the analgesic and euphoric effects of opioids, in respiratory depression and also in physical dependence. There are at least two subtypes of mu receptors, μ1 and μ2. The μ1-receptor subtype mediates analgesia and euphoria, the μ2-subtype respiratory depression [7]. The opioid system is linked to other neurotransmitter systems, and opioids also modulate dopamine release in the mesolimbic system and nucleus accumbens, the key structure in addiction [15,16]. Trigo *et al.* [17] suggested a model in which enkephalinergic interneurons in the ventral tegmentum release enkephalins that act via presynaptic mu receptors on GABAergic neurons and indirectly induce dopamine release in the nucleus accumbens. In addition, experimental data indicate that opioids in the hypothalamus control dopamine levels in the nucleus accumbens [18].

Neuroimaging studies, in particular PET studies using opioid receptor ligands, have substantially increased our knowledge about the plasticity of the opioid receptor system, its relationship to reward processing [19] and how different drugs act at the opioid receptor. At clinical doses, buprenorphine occupies the mu-opioid receptor near maximum [20]. For buprenorphine, receptor occupancy of 50 – 60% is required to suppress the withdrawal symptoms [21]. PET studies indicate that mu-opioid receptor binding may predict the outcome not only of opioid but also of cocaine dependence [22].

2. Overview of the market

A number of psychosocial approaches and therapies with the goal of abstinence from opioids have proven efficacy in opioid dependence, but the overall abstinence rates are low and hardly exceed 20% [23].

Long-term studies among opioid-dependent individuals indicate a low abstinence and high mortality rate [24-29]. A recent comprehensive review by Degenhardt *et al.* [28] of 58 prospective studies reporting mortality rates from opioid-dependent samples found an overall all-cause mortality of 2.09 per 100 person years. Other studies estimate the mortality of untreated heroin dependence at 1 – 3% per year and thus 13 times higher than for the general population [19]. Termorshuizen *et al.* [17] reported follow-up data of a large sample of opioid users and demonstrated that at least 27% (probably 38%) of them had died within 20 years after starting regular drug use. Similar data (37.8% fatal outcome over 20 years) have been published for Norway, with an estimated standard mortality rate of 23.6 [25], and from other European studies [24]. The European Monitoring Centre for Drugs and Drug Addiction [3] concluded that problem drug users have a 10 to 20 times higher mortality risk than their peers.

Maintenance treatment with full or partial opioid agonists has proven efficacy in reducing opioid consumption, criminal behavior, and psychosocial and medical morbidity, including rates of HIV and hepatitis B virus (HBV) infections, as indicated by many studies and meta-analyses [30-33], and has changed the therapeutic options for opioid-dependent individuals dramatically over the past two decades. Methadone is a full agonist at the mu-opioid receptor. A very substantial body of literature has shown that methadone increases retention rates and social functioning in opioid addicts [30,33-37]. Numerous long-term studies indicate that methadone and buprenorphine reduce opioid use and its associated harms [32,38]. Still, there are persistent concerns about diversion of methadone, concomitant drug use, and especially mortality in opioid-maintained patients [39].

3. Introduction to the compound

Search strategy method: Medline and PubMed were used to identify possible publications (buprenorphine film only two hits). In addition, an internet search via Google was performed using the term "buprenorphine film" and finally the manufacturer Reckitt Benckiser was addressed for additional or unpublished material. In addition some researchers were addressed directly for further information.

Numerous studies have proven the efficacy of buprenorphine or its combination with naloxone in reducing substance use and improving social and clinical functioning in opioid-dependent individuals [36,40-42]. All major treatment guidelines [5,37,42-45] and reviews [34,35,46-48] recommend both methadone and buprenorphine as effective and first-line medications in the treatment of opioid dependence. In addition, there is some evidence that buprenorphine is effective in reducing comorbid cocaine use [49]. Misuse and diversion of buprenorphine and the buprenorphine/naloxone combination are still matters of concern [50-52], although Cicero *et al.* [53] pointed out that the misuse potential of buprenorphine is lower than that of methadone, oxycodone, and hydrocodone, and that it is rarely the primary drug of abuse. Post-marketing surveillance has provided some evidence that the combination is less commonly injected, by opioid users, than the pure buprenorphine form [54].

Buprenorphine has poor bioavailability in its present sublingual form. The tablets may require several minutes to fully dissolve. The usual dosages for maintenance therapy

are 8 – 16 mg [30]. A possible advantage of buprenorphine is that cessation of treatment results in less severe withdrawal symptoms than cessation of methadone [32]. Direct buprenorphine/naloxone induction is a safe and effective strategy in opioid dependence, as demonstrated in experimental studies [55].

3.1 Rationale for development of a new formulation for buprenorphine

There have been persistent safety concerns about the increasing number of emergency department visits because of intoxications with prescription drugs, especially opioids such as methadone, oxycodone, and hydrocodone [56] but also buprenorphine. Specifically, the risk for children to be exposed to buprenorphine has apparently increased. In the United States, the number of children exposed to buprenorphine increased from 53 in 2004 to 907 in 2008, with a total of 1786 children exposed in the 2000 – 2008 period [57]. For 2009, 1262 cases were recorded by the American Association of Poison Control Centers. Alternate forms might reduce this risk of diversion also in adults. Although buprenorphine overdoses are generally well tolerated, children appear to be at risk for respiratory depression and central nervous system reactions [58]. In addition, the risk of diversion of the sublingual tablet form has been linked to difficulties in supervising its consumption [59].

In addition to improving safety, the absorption and dissolution time of buprenorphine might be improved by using a film. The buprenorphine film may adhere firmly to the mucosa and dissolve more quickly than the conventional sublingual tablet. Also, the aim is to achieve more complete absorption from the film than from the tablet.

Other and minor objectives for developing a film are better taste and obtaining a formulation that may deter crushing and snorting.

Buprenorphine/naloxone sublingual film was introduced in Australia in 2011 as an alternative to tablets, with the aim of reducing the inconvenience and cost of supervised dosing, and to reduce diversion and misuse [70]. The Australian regulatory agency is requiring the removal of the target formulation within 2 years due to the superior characteristics of the film formulation.

4. Chemistry

Buprenorphine is a semisynthetic derivative of thebaine and a partial mu-opioid receptor agonist that has been extensively studied and is widely used for the maintenance treatment. Buprenorphine is a mixed opioid agonist-antagonist that produces a less than maximal or partial agonist effect at the mu-opioid receptor and is an antagonist at the kappa-opioid receptor [60,61]. Steady-state drug concentrations for a 16-mg dose of buprenorphine are reached after 7 days [62]. There are data showing a ceiling on the respiratory but not analgesic effect of buprenorphine [63]. Buprenorphine is basically metabolized by CYP3A4 (60%) and CYP2D6 isoenzyme (30%) [58]. It has a ceiling effect at the opioid receptor and probably a somewhat lower risk for fatal intoxications [37,64]. Buprenorphine has been marketed in most European countries and the United States since 2000 (2002 for the buprenorphine/naloxone combination) for the treatment of opioid dependence. Like methadone, buprenorphine has an abuse potential and a substantial risk for diversion [33,60]. A combination with naloxone in a fixed 4:1 ratio has been developed to avoid IV administration and diversion of buprenorphine. Naloxone is inactive when administered orally but can rapidly precipitate opioid withdrawal when injected and is therefore believed to discourage patients from parenteral misuse [47]; for this reason it is currently the preferred form in the United States. Experimental studies have shown that intramuscular injection of buprenorphine/naloxone precipitates withdrawal in opioid-dependent individuals [65,66]. Induction of buprenorphine/naloxone is generally considered to be easy and safe [66]. The addition of naloxone does not affect the efficacy of buprenorphine as a maintenance drug [61]. One of the advantages of buprenorphine over methadone is the absence of the cardiac risk of QT prolongation or Torsade de pointes [67].

5. Pharmacodynamics

No studies with the novel film have been published in this area.

6. Pharmacokinetics and metabolism

The pharmacokinetic profile of the buprenorphine/naloxone film was studied in open-label studies comparing sublingual doses in healthy adult volunteers not using opioids (n = 16). Each administration was performed under a naltrexone block. Data indicate that the pharmacokinetics of the buprenorphine/naloxone sublingual film is similar to those of the sublingual tablet, although not all doses and dose combinations met bioequivalence criteria [68]. A single-dose, cross-over pharmacokinetic study with buprenorphine 2 mg/naloxone 0.5 mg (n = 39) and 8 mg/2 mg (n = 44) buprenorphine film and tablet showed a small, clinically not relevant increase in buprenorphine levels with the film (see **Figures 1** and **2**).

As expected, opioid agonist ceiling effects were observed in a double-blind, parallel-group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 3, 8, 16, and 32 mg), placebo, and a full agonist control at various doses. In each case, a dose was reached that produced no further effect [68].

The dissolution times of the buprenorphine/naloxone film were compared with those of the tablet in 42 healthy volunteers (buprenorphine/naloxone dose combinations: 2/0.5, 4/1, 8/2, 12/3 mg). The dissolution time of the film was lower than that of the tablet at all dosages (see **Figures 3** and **4**) [68].

7. Clinical efficacy

Strain *et al.* [69] studied the feasibility of induction with a buprenorphine/naloxone soluble film in a clinical setting

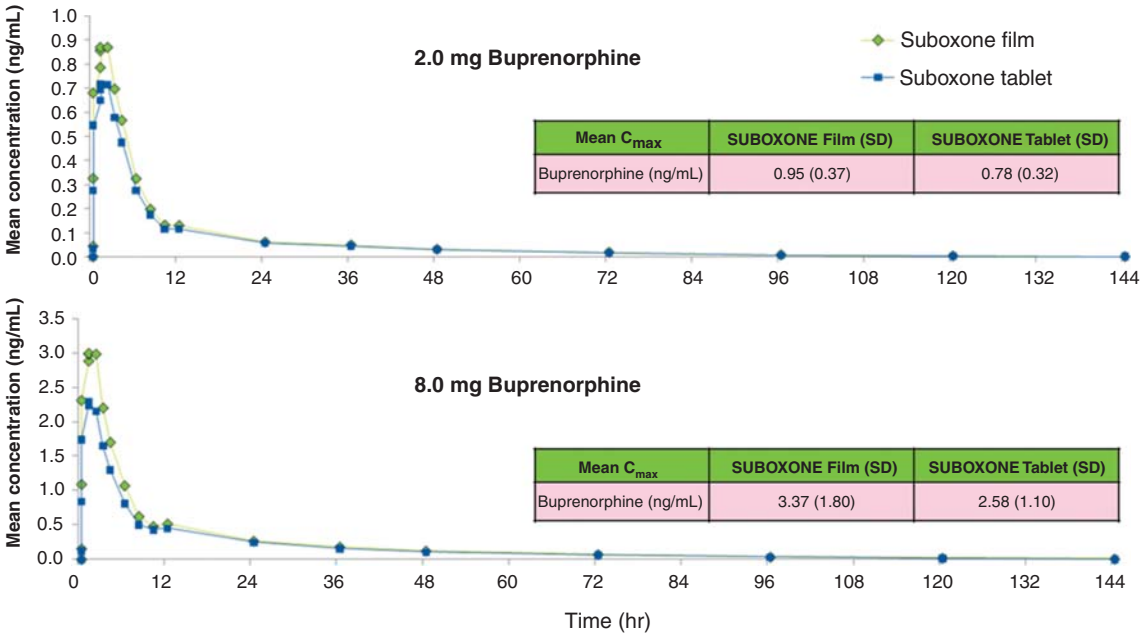

Figure 1. Comparison of absorption rate of buprenorphine 2 and 8 mg film versus tablet: no statistical differences.
*Mean C_{max} = The mean maximum drug concentration in plasma determined directly from individual concentration-time data. Data on file. Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.

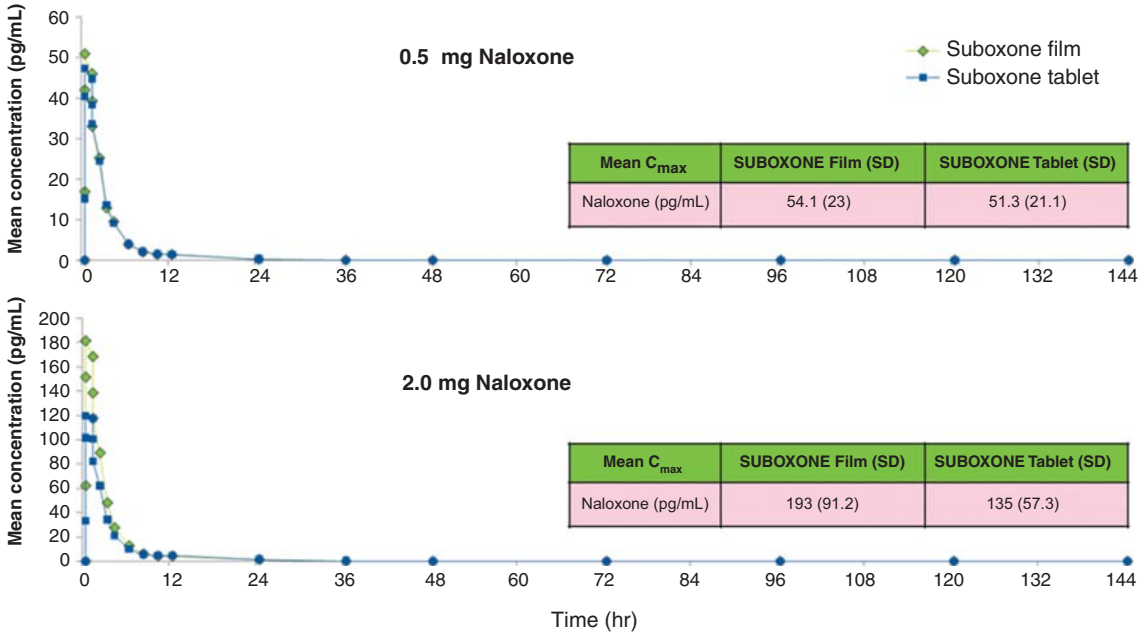

Figure 2. Rate and Extent of absorption of 0.5 and 2 mg naloxone in buprenorphine film and tablet: no statistical differences.
*Mean C_{max} = The mean maximum drug concentration in plasma determined directly from individual concentration-time data. Data on file. Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.

and performed a randomized study comparing the ability of buprenorphine and buprenorphine/naloxone films to suppress spontaneous withdrawal in 34 opioid-dependent volunteers (18 in the buprenorphine, 16 in the buprenorphine/naloxone group), most of whom were IV heroin users but some of whom inhaled heroin. Participants were maintained on morphine and underwent challenge sessions to confirm sensitivity to naloxone-induced opioid withdrawal.

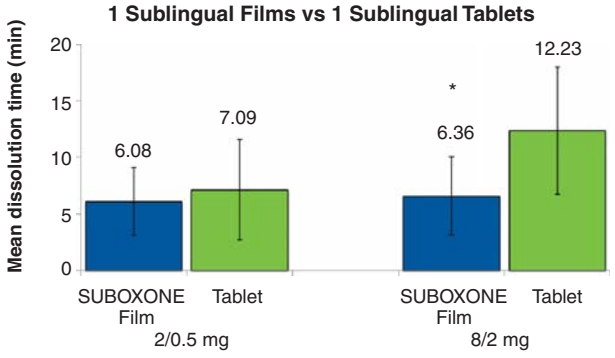

Figure 3. Dissolution times of 2 mg buprenorphine/0.5 mg naloxone and 8 mg burphenorphine/2 mg naloxone film versus tablets: lower dissolution times for the film.

*P < .0001; Vertical lines represent ± 1 standard deviation. Data on file. Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.

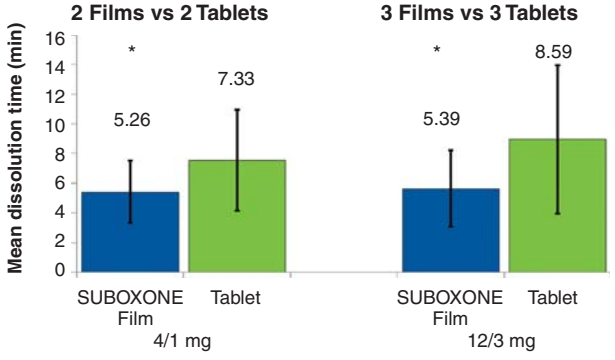

Figure 4. Dissolution times of buprenorphine 4 /1 mg naloxone and 12 /3 mg film versus tablets: lower dissolution times for the film.

*P < .0001; Vertical lines represent ± 1 standard deviation. Data on file. Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA.

Participants received either buprenorphine 16 mg or buprenorphine/naloxone film (16/4 mg) for a 3 – 5 day maintenance period. The primary outcome measure was the Clinical Opiate Withdrawal Scale (COWS) score and secondary measures were pupillometry, a visual analogue scale, and subjective rating scales. There was a significant reduction in the COWS score but no differences between the two groups. The most common adverse events were those consistent with opioid withdrawal. Four participants with high COWS scores (two in each group) dropped out. Four patients, again two in each group, had mild nonulcerous irritations of the oral mucosa not present at baseline; in three of the four, the irritation was attributed to teeth grinding or dental decay. Strain *et al.* [69] interpreted the findings as supporting the use of buprenorphine and buprenorphine/naloxone films as safe and effective delivery methods for opioid induction. Further, they concluded that the new film will not precipitate opioid withdrawal when taken sublingually. Advantages of the new formulation were seen as unit-dose packaging, thereby improving the ability to track a dose of the medication and also providing more child-resisting containment of the product [69].

Lintzeris *et al.* [70] performed a cross-over randomized clinical trial in Australia comparing the novel and conventional formulation on subjective dose effects and equivalence, through plasma levels, adverse events, patient satisfaction, supervised dosing time, and impact upon treatment outcomes (substance use, psychosocial function). The results have been presented at the recent CPDD meeting 6/2012. A total of 92 patients treated with the buprenorphine/naloxone tablets (mean dose 17 mg, mean duration of treatment 48 weeks) in an outpatient multisite double-blind double-dummy parallel group trial were included and randomized to either tablets or film, without dose changes over a 31-day period. No significant differences were detected between film and tablets on subjective ratings including craving and withdrawal, substance use, patient ratings dose adequacy (98% film, 89% tablet), psychosocial outcomes, adverse events, or plasma buprenorphine levels. There was a higher patient preference for film (59%) than tablets (23%). The authors concluded that film and tablets are comparable with respect to dose effects, clinical outcomes, and plasma levels and that the mucoadhesion of the film reduced time for supervised dosing which should enhance convenience, safety, and reduce diversion.

8. Safety and tolerability

An unpublished 12-week, open-label safety and tolerability study of buprenorphine/naloxone film in 194 patients transferred to buprenorphine/naloxone film from the tablet (same initial dosage) indicated an overall good tolerability, with 28% treatment-emergent adverse events (TEAEs), mostly mild in intensity [68]. The most common TEAE related to the film was oral hypesthesia, which was reported by two subjects (1%). It is unclear whether this is related to a lower dissolution time. The dose was adjusted in only one patient during the first 2 weeks and the dose was increased in 2% of the patients at any point during the study.

The FDA states that the safety of buprenorphine/naloxone film is supported by clinical trials using buprenorphine and buprenorphine/naloxone sublingual tablets and an open-label study in 194 patients with the novel film (unpublished data, see [68]). Safety data on buprenorphine are available from clinical studies in over 3000 opioid-dependent subjects [68]. Few differences in the adverse event profile were noted between buprenorphine/naloxone sublingual film and tablet and buprenorphine sublingual tablet. The most common adverse event (> 1%) associated with the novel film was oral hypesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

One possible advantage of the soluble film is that it has unit packing and can be tracked more readily by pharmacy [69].

9. Regulatory affairs

The novel buprenorphine/naloxone film was approved by the FDA in August 2010 but is not available in Europe or other countries to date but available in Australia.

10. Expert opinion and conclusion

Abundant literature is available on the clinical and cost-effectiveness of buprenorphine and buprenorphine/naloxone in the treatment of opioid dependence [34-36,71] (for a review see [37]). Both methadone and buprenorphine are well-established first-line medications in the treatment of opioid dependence [5,37]. Persisting safety concerns and the risk of diversion have already led to the introduction of a buprenorphine/naloxone combination (ratio 4:1) to prevent IV use. Both formulations are extensively used worldwide for the treatment of opioid dependence.

In its current forms, buprenorphine can only be administered sublingually, because of its poor bioavailability. The new buprenorphine film may represent a more convenient and preferred approach for patients as indicated by a recent study by Lintzeris et al. [70]. Unit-dose packaging improve the ability to track a dose of the medication. More importantly, it may reduce safety concerns and risk of diversion, which is particularly relevant as regards the risk of intoxication in children. In the United States, the number of children exposed to buprenorphine has grown exponentially over the last decade [57].

Very few data on the new formulation have been published to date and comments on the new formulation must be preliminary. Many of the available data come from official FDA information. The FDA recommends a target dose of buprenorphine/naloxone sublingual film of 16/4 mg buprenorphine/naloxone as a single daily dose (range 4/1 mg to 24/6 mg). While there is no doubt concerning the general clinical efficacy of buprenorphine and consequently of the new buprenorphine film in opioid dependence and maintenance therapy, the relevant benefits of the pharmacology of the new formulation have to be established and demonstrated. Generally, the major risks of the novel formulation – respiratory and CNS depression, hepatic reactions, allergic reactions, precipitation of opioid withdrawal, neonatal withdrawal, and so on – are the same as for the sublingual tablet. The new application form may be more convenient but the differences in pharmacokinetics between the sublingual form and the film seem to be small. Unpublished pharmacokinetic data in healthy subjects suggest that absorption is slightly higher with the buprenorphine/naloxone film than with the tablets. Although these differences are small, they might indicate that patients switched from tablets to film should be monitored for overdose and, vice versa, patients switched from film to tablet should be monitored for opioid withdrawal.

Results from an open-label study in 194 patients indicate that the adverse event spectrum of the novel film is similar to that of the sublingual tablet. Oral hypesthesia appears to be the most common adverse event. The new film has not been studied in special subgroups such as pregnant or nursing women.

Few other published data are available to date. A recent study by Strain *et al.* [69] in opioid-dependent volunteers maintained on morphine who underwent challenge sessions to confirm sensitivity to naloxone-induced opioid withdrawal showed that both buprenorphine and buprenorphine/naloxone soluble films suppress symptoms of opioid withdrawal. Strain *et al.* [72] concluded that both are safe and effective delivery methods for opioid induction.

The reduced risk of diversion and especially unintentional poisoning in children may be the most relevant advantage of the new film. Whether the assumed better taste of the new formulation may make it even more attractive for children and increase risk for accidental poisoning cannot be assessed in clinical studies but must be analyzed in surveillance studies.

Although buprenorphine is not a novel drug and has been extensively and successfully studied in opioid dependence, the buprenorphine/naloxone soluble film is a potentially interesting new formulation with some advantages over conventional formulations when it comes to absorption and especially safety. Some data indicate a clear patient preference for the film over the sublingual tablet. The mucoadhesion of the novel film may reduce risk of diversion [70]. The probable essential advantage, that is, a reduced risk for accidental intoxication especially in children, cannot be assessed in clinical studies. Post-marketing information from surveillance studies and other sources such as emergency room visits or the Drug Abuse Warning Network (DAWN) may help to fully understand the possible benefits of this new formulation. A risk evaluation and mitigation program is being implemented as part of the FDA requirements to ensure that the benefits of treatment with this medication outweigh the potential risks, particularly risk of accidental overdose, misuse, and abuse.

Acknowledgment

The figures have been put forward from Reckitt Benckiser, unpublished data, permission for publication granted.

Declaration of interest

The author has received no payment in preparation of this manuscript. M Soyka has worked as a consultant or received travel or research grants from Sanofi, Essex, Eli Lilly, Reckitt Benckiser and Lundbeck.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. United Nations Office on Drugs and Crime. 2006 world drug report. UNODC; Vienna: 2006
2. Mathers BM, Degenhardt L, Phillips B, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet 2008;372:1733-45
3. European Monitoring Centre for Drugs and Drug Addiction. Mortality related to drug use in Europe: public health implications. EMDCCA; Lisbon: 2011
4. Kessler RC, Avenevoli S, Costello EJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV DIsorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry 2011;69(4):372-80
5. Kleber HD, Weiss RD, Anton RF Jr, et al. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry 2007;164:5-123
6. World Health Organization. The world health report 2004. World Health Organization; Geneva: 2004
7. Dacher M, Nugent FS. Opiates and plasticity. Neuropharmacology 2011;61:1099-6
8. Koob GF. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol Sci 1992;13:177-84
9. Koob GF, Simon EJ. The neurobiology of addiction: where We have been and Where We are going. J Drug Issues 2009;39:115-32
10. Gianoulakis C. Endogenous opioids and addiction to alcohol and other drugs of abuse. Curr Top Med Chem 2004; 4:39-50
11. Le Merrer J, Becker JA, Befort K, Kieffer BL. Reward processing by opioid system in the Brain. Physiol Rev 2009;89:1379-412
12. Wee S, Koob GF. The role of the dynorphin –K opoiod system in the reinforcing effects of drugs of abuse. Psychopharmacology (Berlin) 2010;210:121-35
13. Christie MJ. Cellular neuroadaptations to chronic opioids: tolerance, withdrawal and addiction. Br J Pharmacol 2008;154:384-96
14. Schwarzer C. 30 years of dynorphine – new insights on their function in neuropsychiatric sideases. Pharmacol Ther 2009;123(3):353-70
15. Koob GF, Le Moal M. Neurobiology of addiction. Academic Press; Amsterdam: 2006
16. Luscher C, Ungless MA. The mechanistic classification of addictive drugs. PLoS Med 2006;3:e437

• **Landmark Paper on the molecular basis of addiction.**

17. Trigo JM, Martin-Garcia E, Berrendero F, et al. The endogenous opioid system: a common substrate in drug addiction. Drug Alcohol Depend 2010;108:183-94
18. Rada P, Barson JR, Leibowitz SF, Hoebel BG. Opioids in the hypothalamus control dopamine and acetylcholine levels in the nucleus accumbens. Brain Res 2010;1312:1-9
19. Schreckenberger M, Klega A, Grunder G, et al. Opioid receptor PET reveals the psychobiologic correlates of reward processing. J Nucl Med 2008;49:1257-61
20. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacology 2003;28:2000-9
21. Greenwald M, Johanson CE, Bueller J, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. Biol Psychiatry 2007;61:101-10
22. Ghitza UE, Preston KL, Epstein DH, et al. Brain mu-opioid receptor binding predicts treatment outcome in cocaine-abusing outpatients. Biol Psychiatry 2010;68:697-703
23. Berglund M, Thelander S, Jonsson E. Treating alcohol and drug abuse: an evidence based review. Wiley-VCH; Weinheim: 2003
24. Bargagli AM, Hickman M, Davoli M, et al. Drug-related mortality and its impact on adult mortality in eight European countries. Eur J Public Health 2006;16:198-202
25. Bjornaas MA, Bekken AS, Ojlert A, et al. A 20-year prospective study of mortality and causes of death among hospitalized opioid addicts in Oslo. BMC Psychiatry 2008;8:8
26. Hser YI, Anglin D, Powers K. A 24-year follow-up of California narcotics addicts. Arch Gen Psychiatry 1993;50:577-84
27. Termorshuizen F, Krol A, Prins M, van Ameijden EJ. Long-term outcome of chronic drug use: the Amsterdam Cohort Study among Drug Users. Am J Epidemiol 2005;161:271-9
28. Degenhardt L, Bucello C, Mathers B, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 2011;106:32-51

• **Important review.**

29. Hulse GK, English DR, Milne E, Holman CD. The quantification of mortality resulting from the regular use of illicit opiates. Addiction 1999;94:221-9
30. Amato L, Davoli M, Perucci CA, et al. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. J Subst Abuse Treat 2005;28:321-9
31. Bukten A, Skurtveit S, Gossop M, et al. Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. Addiction 2012;107:393-9
32. Maremmani I, Gerra G. Buprenorphine-based regimens and methadone for the medical management of opioid dependence: selecting the appropriate drug for treatment. Am J Addict 2010;19:557-68
33. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2009;CD002209
34. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-171; iii-iv

•• **Important review on opioid maintenance therapy.**

35. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2008;CD002207

36. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. Int J Neuropsychopharmacol 2008;11:641-53

37. Soyka M, Kranzler HR, van den Brink W, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: opioid dependence. World J Biol Psychiatry 2011;12:160-87

38. Wittchen HU, Apelt SM, Soyka M, et al. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centers and primary care facilities in Germany: a naturalistic study in 2694 patients. Drug Alcohol Depend 2008;95:245-57

39. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ 2009;338:b2225

40. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial. Lancet 2003;361:662-8

41. Schottenfeld RS, Pakes JR, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. Arch Gen Psychiatry 1997;54:713-20

42. Kamien JB, Branstetter SA, Amass L. Buprenorphine-naloxone versus methadone maintenance therapy: a randomised double-blind trial with opioid-dependent patients. Heroin Addict Relat Clin Probl 2008;10:5-18

43. New South Wales (NSW) Department of Health. Opioid treatment program: clinical guidelines for methadone and buprenorphine treatment. NSW Government; Sydney: 2006

44. World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. World Health Organization; Geneva: 2009

45. National Institute for Health and Clinical Excellence. Drug misuse. Opioid detoxification. NICE Clinical Guideline 52. National Institute for Health and Clinical Excellence; London: 2007

46. Barnett PG, Rodgers JH, Bloch DA. A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence. Addiction 2001;96:683-90

47. Ling W, Jacobs P, Hillhouse M, et al. From research to the real world: buprenorphine in the decade of the Clinical Trials Network. J Subst Abuse Treat 2010;38(Suppl 1):S53-60

48. Mattick RP, Ali R, White JM, et al. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction 2003;98:441-52

49. Montoya ID, Gorelick DA, Preston KL, et al. Randomized trial of buprenorphine for treatment of concurrent opiate and cocaine dependence. Clin Pharmacol Ther 2004;75:34-48

50. Aitken CK, Higgs PG, Hellard ME. Buprenorphine injection in Melbourne, Australia–an update. Drug Alcohol Rev 2008;27:197-9

51. Nordmann S, Frauger E, Pauly V, et al. Misuse of buprenorphine maintenance treatment since introduction of its generic forms: OPPIDUM survey. Pharmacoepidemiol Drug Saf 2012;21:184-90

52. 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;4:28-41

53. Cicero TJ, Surratt HL, Inciardi J. Use and misuse of buprenorphine in the management of opioid addiction. J Opioid Manag 2007;3:302-8

54. Larance B, Degenhardt L, Lintzeris N, et al. Post-marketing surveillance of buprenorphine-naloxone in Australia: diversion, injection and adherence with supervised dosing. Drug Alcohol Depend 2011;118:265-73

55. Amass L, Pukeleviciene V, Subata E, et al. A prospective, randomized, multicenter acceptability and safety study of direct buprenorphine/naloxone induction in heroin-dependent individuals. Addiction 2012;107:142-51

56. Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2010;59:705-9

57. Boyer EW, McCance-Katz EF, Marcus S. Methadone and buprenorphine toxicity in children. Am J Addict 2010;19:89-95

58. Hayes BD, Klein-Schwartz W, Doyon S. Toxicity of buprenorphine overdoses in children. Pediatrics 2008;121:e782-6

59. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. Int J Drug Policy 2008;19:450-8

60. Orman JS, Keating GM. Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence. Drugs 2009;69:577-607

• **Comprehensive review.**

61. Mammen K, Bell J. The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence. Expert Opin Pharmacother 2009;10:2537-44

62. Compton P, Ling W, Moody D, Chiang N. Pharmacokinetics, bioavailability and opioid effects of liquid versus tablet buprenorphine. Drug Alcohol Depend 2006;82:25-31

63. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth 2006;96:627-32

64. Pirnay S, Borron SW, Giudicelli CP, et al. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. Addiction 2004;99:978-88

65. Stoller KB, Bigelow GE, Walsh SL, Strain EC. Effects of buprenorphine/naloxone in opioid-dependent humans. Psychopharmacology (Berl) 2001;154:230-42

66. Doolittle B, Becker W. A case series of buprenorphine/naloxone treatment in a primary care practice. Subst Abus 2011;32:262-5

67. Hanon S, Seewald RM, Yang F, et al. Ventricular arrhythmias in patients treated with methadone for opioid dependence. J Interv Card Electrophysiol 2010;28:19-22

68. U.S. Food and Drug Administration. Prescribing information for Suboxone. 2012.Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf [Cited 1 March 2011]

69. Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. Clin Pharmacol Ther 2011;89:443-9

•• **Important experimental study.**

70. Lintzeris N, Leung S, Dunlop AJ, et al. Cross-over RCT comparing Buprenorphine-naloxone Film to Tablets. Poster given an the CPDD conference; 2012

71. Davids E, Gastpar M. Buprenorphine in the treatment of opioid dependence. Eur Neuropsychopharmacol 2004;14:209-16

72. Meyer MR, Maurer HH. Absorption, distribution, metabolism and excretion pharmacogenomics of drugs of abuse. Pharmacogenomics 2011;12:215-33

Affiliation

Michael Soyka[1,2] MD
[1]University of Munich,
Psychiatric Hospital, Nussbaumstr. 7
Munich Munich, Germany
Tel: +0049 89 51605387;
E-mail:
Michael.Soyka@privatklinik-meiringen.ch
[2]Private Hospital Meiringen,
Willigen, CH 3860 Meiringen,
Switzerland