

Buprenorphine plus naloxone, a new substitution treatment

Steve Chaplin MSc, MRPharmS and Alan Fraser BSc, MRCPsych

PRODUCT PROFILE

Proprietary name: Suboxone

Constituents: buprenorphine and naloxone

Indication: substitution treatment for opioid drug dependence

Dosage and method of administration: sublingual tablets dissolved under the tongue; initially one to two 2mg/0.5mg tabs at least six hours after last use of opioid, one or two additional tablets may be administered if necessary; dosage increased according to patient response; maximum single daily dose 24mg; dosage titrated according to clinical and psychological status of the patient in steps of 2-8mg; not recommended for use in children under 15 due to lack of data on safety

Contraindications: hypersensitivity to the active substance or to any of the excipients; severe respiratory insufficiency; severe hepatic insufficiency; acute alcoholism or delirium tremens

Precautions: caution advised in adolescents (age 15-18) due to lack of data; patients should be closely monitored during switching period from buprenorphine or methadone to Suboxone since withdrawal symptoms have been reported; diversion; precipitated withdrawal due to the partial agonist profile of buprenorphine; withdrawal symptoms may also be associated with suboptimal dosing; risk of serious adverse effects such as overdose or treatment drop-out is greater if a patient is underdosed and continues to self medicate; dependence, buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type; respiratory depression; hepatitis and hepatic events; athletes must be aware that this medicine may cause a positive reaction to 'antidoping' tests; as with other opioids, caution is requested in patients using buprenorphine and having head injury, increased intracranial pressure, hypotension, prostatic hypertrophy or urethral stenosis; patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine

Pregnancy and lactation: not recommended during pregnancy or breastfeeding

Interactions: alcoholic drinks or medications containing alcohol; when co-administered with benzodiazepines may result in death due to respiratory depression; reduced level of alertness can make driving and using machines hazardous with other CNS depressants, other opioid derivatives, sedative H₁-antagonists, barbiturates, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances; patients receiving Suboxone should be closely monitored if CYP3A4 inhibitors or inducers are co-administered

Side-effects: *very common:* insomnia; constipation, nausea; sweating; withdrawal, headache; *common:* infection; peripheral oedema, weight loss; anxiety, nervousness, depression, decreased libido, abnormal thinking; somnolence, dizziness, paraesthesia, hypertonia; lacrimation disorder, amblyopia; vasodilatation, hypertension, migraine; rhinitis, pharyngitis, cough; vomiting, dyspepsia, diarrhoea, anorexia, flatulence; abnormal liver function; rash, pruritus, urticaria; arthralgia, myalgia, leg cramps; albuminuria, urine abnormality; asthenia, fever, malaise, accidental injury, chills, chest pain, abdominal pain, back pain

Presentation/cost: sublingual tablet containing buprenorphine/naloxone, 2mg tab: 2mg/0.5mg, 28= £26.88; 8mg tab: 8mg/2mg, 28= £80.64



Suboxone, a combination of buprenorphine and the opiate antagonist naloxone, is a substitution treatment for opioid drug dependence intended to reduce potential abuse by intravenous injection. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Alan Fraser comments on its place in therapy.

In 2001, about half of GPs were seeing opiate users and, of these, half prescribed an opioid substitute.¹ GP prescribing of methadone in England has nearly doubled since then, reaching a total of 2.2 million prescriptions in 2006.^{2,3}

Prescribing of buprenorphine (Subutex) for opioid substitution has increased nearly 20-fold since 2000, with 611 000 prescriptions dispensed in 2006.³ These trends suggest an increase in treatment coverage for opioid substitution prescribing,⁴ much of which occurs in the community.

The National Treatment Agency for Substance Misuse estimates that the numbers of people in contact with treatment services in England was 192 248 in the year

to March 2007 compared with 179 628 in 2005/06⁵ and 160 450 in 2004/05.⁶

The National Institute for Health and Clinical Excellence (NICE) has published guidance on the use of buprenorphine and methadone as maintenance therapy in the management of opioid dependence.⁶

Methadone is the drug of choice if both drugs are equally suitable but treatment selection should be made on a case-by-case basis, taking into account the person's history of opioid dependence, their commitment to a long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person.

The technology

The effectiveness of buprenorphine as opioid maintenance treatment is attributed to its slowly reversible action at the mu opioid receptor which, over a prolonged period, might minimise the need of addicted patients for drugs.⁷ Compared with methadone, buprenorphine causes less respiratory depression (if taken alone), dysphoria and sedation. However, it may provoke withdrawal symptoms in opiate-dependent individuals if taken within six hours of the last dose of a short-acting opioid such as diamorphine, or within 24 hours of methadone.⁷

In comparative studies, methadone was associated with higher rates of retention in treatment programmes than buprenorphine, but the rates of serious adverse reactions were comparable.⁶

Although buprenorphine is a partial agonist at opioid receptors, its abuse potential may be comparable with that of methadone.⁸ The introduction of Suboxone, a

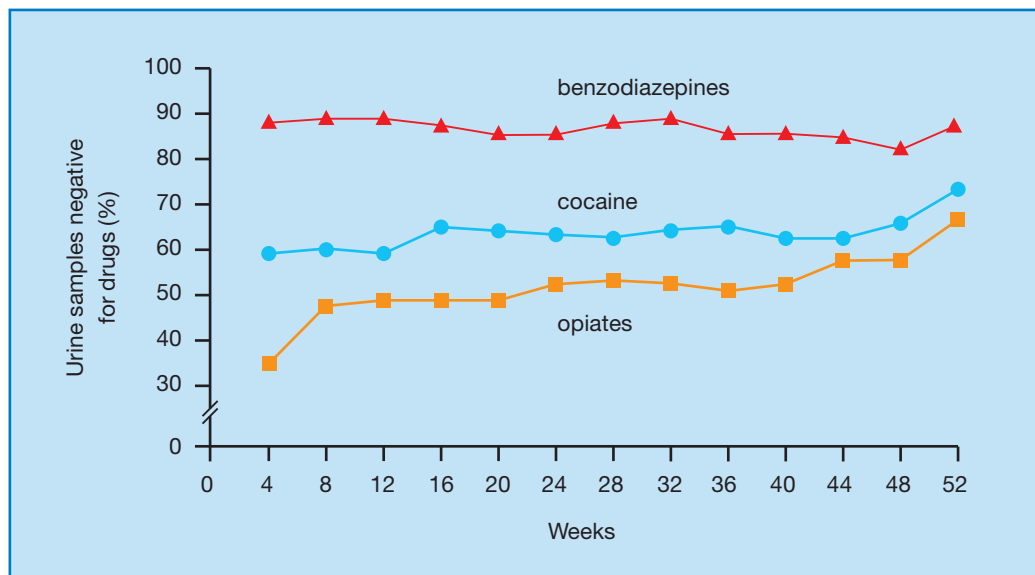


Figure 1. Proportions of urine samples negative for drugs of abuse during maintenance treatment with Suboxone in a community setting⁹

sublingual tablet combining buprenorphine and the opiate antagonist naloxone (which is not absorbed after oral administration), is intended to reduce its potential for abuse by intravenous injection.⁷

Suboxone is available in two strengths: 2mg buprenorphine plus 0.5mg naloxone, or 8mg plus 2mg. It is licensed as substitution

treatment for opioid drug dependence within a framework of medical, social and psychological treatment in adults and adolescents over 15 years of age who have agreed to be treated for addiction. Treatment should be supervised by a suitably experienced physician.

The recommended starting dose is one or two 2mg/0.5mg

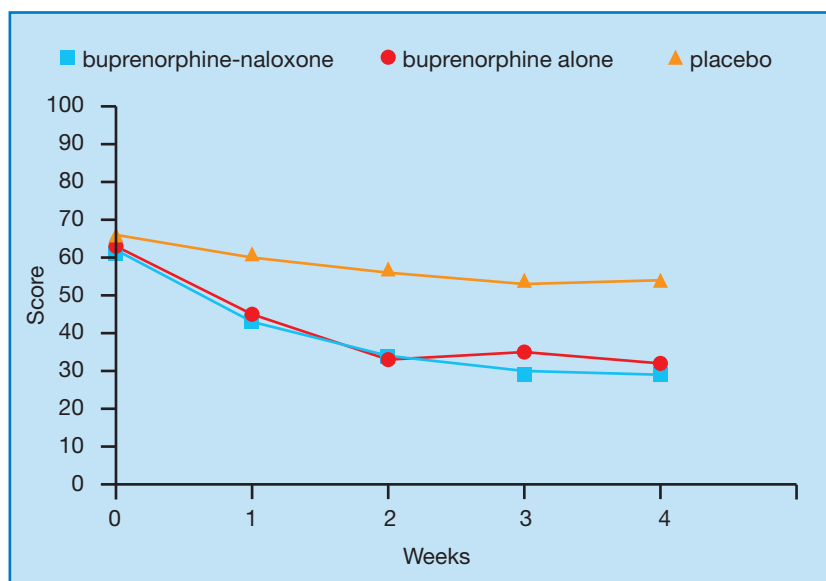


Figure 2. Opiate craving in opioid-dependent individuals taking Suboxone, buprenorphine or placebo, showing similar scores for the active treatments⁹

tablets, adjusted in increments of 2-8mg of buprenorphine to a maximum dose of 24mg/6mg daily. Doses may be taken on alternate days during stable maintenance treatment provided the maximum daily dose is not exceeded.

Suboxone is contraindicated in patients with severe respiratory or hepatic impairment, and in those with acute alcoholism or delirium tremens.

Clinical trials

Evidence for the efficacy and safety of Suboxone comes principally from one US trial involving 326 adults dependent on opiates who were seeking opiate substitution treatment.⁹ The trial took place in community settings, not specialist clinics. Participants were randomised to double-blind treatment with Suboxone (16mg/4mg daily), buprenorphine alone (16mg per day) or placebo for four weeks.

The primary end-points were the percentage of thrice weekly urine samples testing negative for opiates and self-reported opiate craving in participants treated with Suboxone or placebo (buprenorphine was included as an 'active control'). This was followed by a nonblinded 52-week phase to assess safety in a total of 461 individuals.

The double-blind phase was terminated prematurely when the active treatments were found to be superior to placebo. The proportions of opiate-negative urine samples were 17.8 per cent for Suboxone and 20.7 per cent with buprenorphine alone, both of which were significantly greater than placebo (5.8 per cent).

During nonblinded follow-up, 261 of 472 participants (55 per cent) completed at least six months' treatment and the pro-

Key points

- primary-care prescribing of substitution treatment for opioid-dependent people is increasing
- maintenance treatment with methadone or buprenorphine reduces illicit drug use but both are liable to abuse
- Suboxone is a sublingual tablet containing buprenorphine and naloxone that is designed to reduce the abuse potential of buprenorphine
- in community settings, Suboxone reduces illicit drug use and opioid craving, and is less likely to be abused than buprenorphine
- Suboxone is well tolerated

portion of urine samples negative for opioids or cocaine in participants taking Suboxone tended to increase after 44 weeks (see Figure 1).⁹

Both active treatments also reduced craving to a similar extent and significantly more than placebo (see Figure 2). Participant and physician ratings of well-being favoured both active treatments equally.

An unpublished, nonblinded US study has shown that approximately one-third of 582 opioid-dependent individuals continued a maintenance programme with Suboxone for one year.¹⁰ The proportions of urine samples negative for opioids were 70.4 per cent at three months, 76.3 per cent at six months and 81 per cent at one year.

Physician and participant global assessments recorded improvements, and scores for risk from drugs of addiction were significantly reduced.

Adverse effects

In the 52-week open-label study,⁹ 14 participants discontinued treat-

ment due to adverse reactions (most often detoxification or withdrawal symptoms).

A total of 81 serious adverse events were reported. The commonest (n=10) was raised hepatic enzymes, which was considered at least possibly treatment-related in seven cases; eight of these participants had confirmed hepatitis.

Headache and withdrawal syndrome were the adverse events most frequently reported with Suboxone. Other adverse events included pain, nausea, sweating, insomnia, abdominal pain and constipation.

Abuse of combined tablets

Abuse of buprenorphine/naloxone tablets has been reported. One survey of opioid users found that 81 per cent reported misuse of buprenorphine and 57 per cent reported misuse of the combined tablets;¹¹ of those misusing the combined tablets, one-third reported developing withdrawal symptoms.

A more recent survey of intravenous drug users found that buprenorphine was the drug most frequently injected by 73 per cent; 68 per cent had injected the combined tablet and, of these, 80 per cent reported a bad experience.¹²

Summary

Suboxone is a sublingual tablet of buprenorphine and naloxone designed to reduce the risk of intravenous misuse. In a community setting, it reduces the use of illicit drugs and craving compared with placebo and appears to be comparable with buprenorphine. It is well tolerated and less likely to be abused than buprenorphine alone.

By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Although the efficacy of buprenorphine as an opiate analgesic is well established, its usefulness in the treatment of opiate dependence is less so. During the 1980's in Glasgow, it was widely abused by opiate addicts who crushed and injected buprenorphine tablets in the form of Temgesic. Perhaps as a result of this, its reintroduction as a detoxification and maintenance treatment for opiate dependence has been slow to take off, especially in Scotland.

Theoretically, buprenorphine has advantages over methadone, especially with regard to safety, but the weight of evidence from clinical trials suggests, at best, a similar overall degree of efficacy rather than any clear superiority. Further studies will hopefully identify the patient characteristics that can predict when buprenorphine is indicated in preference to methadone.

Suboxone

The recent introduction of Suboxone (combining buprenorphine with the opiate antagonist naloxone) is an attempt to further enhance the supposed superiority of buprenorphine, especially with regard to the problems of diversion and intravenous misuse, but the evidence so far available (and outlined above), is disappointing. In particular, a recent study of untreated intravenous drug abusers showed that almost as many had injected the combined

tablet as had injected buprenorphine alone.¹²

This suggests that it is unlikely that Suboxone could become suitable for unsupervised dispensing, something that would be a major advance in locations where diversion is a problem and large numbers of opiate abusers are being treated.

What is required, and is currently awaited, is a UK-based randomised, controlled trial comparing the efficacy of the buprenorphine/naloxone combination with methadone, taking into account the different dose ranges in which the latter drug is used.

By Dr Fraser, a consultant psychiatrist at the Southern General Hospital, Glasgow

References

1. National Treatment Agency for Substance Misuse. *GP prescribing of opioids to opiate-dependent patients*. Secondary analyses of data collected during a national survey of general practitioners in England and Wales in mid-2001. Research Briefing 28. April 2007 (www.nta.nhs.uk/publications/documents/nta_modelsofcare_update_2006_moc3.pdf; accessed 17.05.07).
2. Department of Health. Prescription Cost Analysis: England 2001 (www.dh.gov.uk/en/Publicationsandstatistics/Statistics/StatisticalWorkAreas/Statisticalhealthcare/DH_4015540; accessed 17.5.07).
3. Department of Health. Prescription Cost Analysis England 2006 (www.ic.nhs.uk/webfiles/publications/pca_2006/PCA_2006.pdf; accessed 17.5.07).
4. National Treatment Agency for Substance Misuse. The NTA's 2006

National Prescribing Audit. *An assessment of prescribing practices for opioid substitution treatment in England, 2004-05*. April 2007 (www.nta.nhs.uk/publications/documents/nta_npa1_prescribing_audit.pdf; accessed 17.05.07).

5. National Treatment Agency for Substance Misuse. National Drug Treatment Monitoring System (NDTMS), www.ndtms.net/NDTMSHome.aspx; accessed 17.05.07.

6. National Institute for Health and Clinical Excellence. *Methadone and buprenorphine for the management of opioid dependence*. NICE Technology Appraisal Guidance 114. January 2007.

7. Schering-Plough Ltd. Suboxone tablets 2mg and 8mg. Summary of Product Characteristics. December 2006.

8. Comer SD, Sullivan MA, Walker EA. Comparison of intravenous buprenorphine and methadone self-administration by recently detoxified heroin-dependent individuals. *J Pharmacol Exp Ther* 2005;315:1320-30.

9. Fudala PJ, Bridge TP, Herbert S, *et al*. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med* 2003;349:949-58.

10. European Medicines Agency. Suboxone EPAR. Supportive studies. NIDA #1018 (www.emea.europa.eu/humandocs/PDFs/EPAR/suboxone/069706en6.pdf; accessed 17.05.07).

11. Robinson GM, Dukes PD, Robinson BJ, *et al*. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend* 1993;33:81-6.

12. Alho H, Sinclair D, Vuori E, *et al*. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. *Drug Alcohol Depend* 2007; 88:75-8.



Forum

If you have any issues you would like to air with your colleagues or comments on articles published in *Prescriber*, the Editor would be pleased to receive them and, if appropriate, publish them on our Forum page. Please send your comments to:

The Editor, *Prescriber*, The Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, or e-mail to prescriber@wiley.co.uk