Düşünen Adam The Journal of Psychiatry and Neurological Sciences 2012;25:93-100
DOI: 10.5350/DAJPN20122502001

Guest Editorial

Buprenorphine in The Treatment of Heroin Addiction

James Bell[1]

[1]BA(Hons), MBBS, MD, FRACP, FAChAM,
South London and Maudsley NHS Foundation Trust

Address reprint requests to: Dr. James Bell, 63-65 Denmark Hill, London SE5 8RS
E-mail address: James.bell@kcl.ac.uk
Phone: +44-203-228-1926, Fax: +44-203-229-1904

Introduction – Heroin Addiction

Heroin addiction is a significant health and social problem in most countries. A recent estimate is that there were between 15.2-21.1 million people abusing or dependent on opioids. The key determinant of the prevalence of heroin problems in a community appears to be availability. The highest levels of use (in terms of the proportion of the population aged 15-64 years) are found along the main drug trafficking routes out of Afghanistan (1), and more than half of the world's opioid-using population are thought to live in Asia.

Use of heroin is associated with a range of harms. The injecting of street drugs, and sharing of needles is a major route of transmission of blood-borne viruses (BBV), notably Hepatitis C and HIV. Age-adjusted mortality among heroin users is high, 1–3% per annum (2,3). Among younger heroin users, overdose is the most common cause of death, with suicide and violence also contributing to mortality (4). As addicts and former addicts age, deaths due to liver disease, AIDS, and a variety of medical conditions, become more common (5).

Heroin use is strongly associated with social disadvantage, psychological problems and deviant behaviour (6). International studies suggest that for opioid dependent persons in the criminal justice system, and those seeking treatment, addiction is a chronic, relapsing and remitting condition (7) with a high risk of relapse even after periods of abstinence.

Opioids have a range of physiological effects, but the critical issue which make opioids reinforcing is that, like most drugs of misuse, they act on a region of the brain dubbed the "reward pathway". Drugs which stimulate dopamine release in this pathway – such as alcohol and nicotine, as well as opioids - produce reduction in anxiety, and a sense of well-being and confidence. These reinforcing effects explain the appeal of recreational drugs. With repeated, especially continuous, exposure, higher doses are required to achieve the same subjective effects (tolerance), and with prolonged exposure, a withdrawal syndrome develops on stopping the drug. It is hypothesized that the chronic administration of opioids (and other drugs) produces enduring changes in brain neurotransmitter systems that leave the user vulnerable to relapse after abstinence has been achieved (8).

Opioid Substitution Treatment of Heroin Addiction

Use of drugs may initially be motivated by novelty seeking or pursuit of euphoria, but once dependence is established, drug use is primarily maintained by the need to avoid withdrawal. Drug free treatment is based on interrupting drug use long-enough for the acute withdrawal reaction to subside, and providing lasting support to remain abstinent. Opioid Substitution Treatment (OST) involves prescribing opioids (methadone, buprenorphine, and in some jurisdictions other agents) to patients who are opioid dependent. The importance of suppressing withdrawal symptoms has been confirmed in studies of methadone treatment.

A minority of patients with rapid methadone clearance, and therefore a wider range between peak and trough blood concentrations, experience daily withdrawal symptoms, and are at increased risk of persisting in use of heroin and other drugs (9,10). These observations confirm that the effectiveness of OST for most patients is based on maintaining blood concentrations within a reasonably narrow range, such that patients experience neither intoxication nor withdrawal.

Abolishing or minimizing withdrawal symptoms is necessary, but is not sufficient, for effective OST. Low dose treatment with methadone (30-60 mg/day) or buprenorphine (4-8 mg/day) can abolish withdrawal, but does not suppress heroin use. At higher methadone doses, people become more tolerant to opioids, and blocking the effects of heroin and suppressing continued heroin use.

In addition to adequate dose, extensive research indicates that the other critical component of effective OST is duration of treatment. The duration of treatment is a linear, non-threshold predictor of outcome, with better outcomes from longer treatment (11). For this reason, retention in treatment is accepted as a proxy marker of effectiveness. After leaving OST, relapse is usual (12). The disabling, long-term, relapsing course of heroin addiction means that treatment is better conceptualised as management of a chronic disease, rather than an acute problem in need of cure (13). By the time they present for treatment, most dependent drug users are socially marginalised, lacking access to the rewards arising from employment, personal relationships and family participation, and the objectives of long-term management are reduced risk of death and disease, suppression of drug misuse, improvement in mental health and outlook, and restoration of impaired social role. These objectives are only likely to be achieved if patients stop or markedly reduce their use of street heroin and other drugs.

Buprenorphine Pharmacology

At low doses, buprenorphine acts as a potent mu opioid receptor agonist. Administered to non-tolerant subjects, 1 mg subcutaneous (s.c.) buprenorphine produced similar subjective effects (euphoria and sedation) as 30 mg s.c. morphine, or 30 mg s.c. methadone. Physiologically, it produced reductions in respiratory rate, heart rate, blood pressure and pupil size. Administered to opioid-dependent subjects, it produces prolonged suppression of withdrawal symptoms. On discontinuing regular administration of buprenorphine 8 mg sublingual, a mild-moderate withdrawal syndrome peaking on days 3-5 was observed (14). Higher doses of buprenorphine result in a more prolonged duration of action, delaying the onset of withdrawal.

Buprenorphine has high first-pass metabolism, making it unsuitable for oral administration. Sublingual bioavailability of buprenorphine tablets is approximately 30-35%. Administered sublingually, it is slowly absorbed, reaching peak effects 2-4 hours after administration. It has a long half-life. It is mainly excreted in bile, and reports suggest that the dose does not need to be adjusted in patients with impaired renal function (15).

Unlike full opioid agonists, buprenorphine has high affinity for the mu receptor, and remains bound to receptors for some time, rendering the receptor unavailable for further activation. Due to its high affinity for the mu receptor, buprenorphine has a flattened dose-response curve. Above a very low dose, increasing doses do not produce increasing opioid effects. Higher doses produce more prolonged opioid actions, but the respiratory depressant effects remain similar to those experienced on low doses (16).

The high receptor affinity and resultant "ceiling effect" has three consequences. Firstly, it means that respiratory depression is limited, and overdose on buprenorphine alone is very unlikely to produce fatal respiratory depression, suggesting buprenorphine should be safer in overdose than full opioid agonists such as heroin and methadone. This expectation has been confirmed in surveillance studies of overdose deaths in France and Australia (17,18).

The second consequence is that administered to tolerant individuals with high circulating levels of an agonist present, buprenorphine can act as an opioid antagonist, precipitating withdrawal. This means that during initiation of treatment, if buprenorphine is given

within 6 hours of last use of heroin, or within 24 hours after administration of low dose methadone, it can precipitate withdrawal. Even without frank precipitated withdrawal, minor withdrawal symptoms are common early in treatment (19).

Third implication of high receptor affinity is blunting of the effects of opioids such as heroin. Positron emission tomography scanning demonstrated that buprenorphine in increasing doses produces blockade of carfentanil binding; 4 mg produced 41% inhibition, 16 mg produced 80% inhibition, and 32 mg produced 84% inhibition (20).

In summary, buprenorphine has opiate-agonist actions, prolonged suppression of withdrawal in dependent subjects, and in a dose-dependent fashion attenuates the effects of administered opioids. These pharmacological actions are the basis for the use of buprenorphine as maintenance treatment.

Efficacy and Safety

A meta-analysis of published trials reported that buprenorphine was statistically significantly superior to placebo in retaining patients in treatment, and in doses >8mg was effective in suppressing heroin use. Importantly, low doses of buprenorphine (2-4 mg/day) were not effective in suppressing heroin use. Comparisons with methadone have been reported as showing that methadone was more effective than buprenorphine in retaining patients in treatment (21).

The public health benefit of OST lies in reducing the risks associated with heroin addiction – in particular, reducing overdose deaths and reducing acquisitive crime associated with dependence on street heroin. The beneficial results of clinical trials of buprenorphine have been supported by observations from the widespread implementation of buprenorphine treatment in France in the 1990s. In 1994, there were only 52 people in treatment with methadone, and an estimated 160.000 people injecting illicit opioids in France. Five years later, there had been an expansion in methadone treatment to 7000 people, and 60.000 people were being prescribed buprenorphine. Opioid overdose deaths in France fell from 505 in 1994 to 92 in 1999 (22).

A similar, if less dramatic observation was made in Sweden following liberalisation of access to OST (23). The number of patients in treatment increased more than threefold from 2000 to 2006, with the greatest increase for buprenorphine, introduced in year 2000. There was a significant 20-30% reduction in opiate-related mortality and inpatient care between 2000-2002 and 2004-2006, but not of other drug-related mortality and inpatient care. A small but significant increase in buprenorphine- and methadone-related mortality occurred. The authors concluded that liberalization of Sweden's drug policy, and expanded access to OST, contributed to a decrease in overall opiate-related mortality and inpatient care. Although the overall mortality rate declined due to a fall in heroin overdoses, there was a small but significant increase in buprenorphine- and methadone-related mortality – the trade-off involved in introducing OST.

Safety

Although lower, risk of overdose can occur, especially in non-tolerant individuals who combine buprenorphine with benzodiazepines and or alcohol. Consistently, studies have found that the greatest risk of overdose associated with OST results from diversion to people not in treatment. In France, overdose deaths in which buprenorphine was detected almost always involved concomitant use of benzodiazepines and/or alcohol (24).

The most common side effects of chronic buprenorphine treatment are (1) symptoms associated with opioid toxicity - particularly nausea, vomiting, and constipation (2) symptoms associated with withdrawal, particularly headache, generalized pain, and asthenia. A number of cases of raised transaminases, jaundice, and/or liver have been reported, but it remains unclear whether episodes of liver inflammation relate to adverse drug reactions or to viral hepatitis.

Diversion

Like other opioids, buprenorphine, particularly when administered by injection, is a reinforcing drug,

and there have been many reports of periods and places where heroin was scarce, and buprenorphine was the major illicit opioid used by injecting drug users (25).

In France, despite the impressive reductions in opioid-related mortality described above, the expansion of buprenorphine treatment was not without problems. Prescribing was unregulated and there was very little supervision of dosing. As a result, diversion and intravenous misuse of buprenorphine has been widespread (26,27). Pharmacists reported selling injecting kits along with dispensing buprenorphine on 30% of dispensing occasions. Most seriously, massive diversion of buprenorphine from France has contributed to an extensive black market in some other European countries, where injected buprenorphine has become the primary drug of abuse. For example, it has been reported that the availability of diverted buprenorphine from France led to an 80% increase in the number of injecting opioid dependent people in Georgia between 2003 and 2006 (28).

Measures to Minimize Diversion and Misuse

Diversion is the weakness of OST. The extent of diversion rises in parallel with the extent to which the number of doses prescribed to be taken unsupervised rises. The French experience of buprenorphine diversion emphasizes the critical importance of minimizing diversion of prescribed buprenorphine. All practitioners need to be aware of the risks of diversion, and take steps to minimize it.

The traditional method used in methadone treatment was to ensure that all doses were taken under direct observation (29). This is an effective way to monitor compliance and minimize diversion.

Measures to reduce the potential for injection of diverted medication have also been employed. Issuing methadone doses as dilute solutions makes injecting difficult, due to the high volume which needs to be injected (30). The other approach to minimizing intravenous misuse has been to issue combination medications of an opioid agonist with naloxone, a pure antagonist which is not absorbed orally. The rationale is that taken orally or sublingually, the agonist is fully bioavailable, but the naloxone is not. However, if the medication is crushed and injected, the presence of naloxone attenuates the opioid effect, and in dependent subjects precipitates withdrawal. This is the rationale behind Suboxone®, a combination of buprenorphine and naloxone in a 4:1 ratio, designed to deter intravenous use.

There is conflicting evidence of the effectiveness of adding naloxone to buprenorphine to make the drug less susceptible to intravenous misuse. Reports of changes in injecting practices following replacement of buprenorphine with buprenorphine-naloxone have come from Malaysia (no change in injecting) (31), and from Finland (a reduction in black market value of the combination product compared to Subutex) (32). The most systematic data comes from Australia, based on interviews with large samples of injecting drug users (IDU) both in and out of treatment (33). Among OST clients, the reported rate of injection (per 1000 doses dispensed) was highest with buprenorphine. Buprenorphine-naloxone was lower, at a similar rate as methadone injection. Among injecting drug users not in treatment, adjusting for background availability, the level of buprenorphine-naloxone injection was markedly less than for buprenorphine, and was similar to the level of injecting of methadone. There were higher levels of injection of pharmaceutical opioids (morphine and oxycodone in particular) than of any of the opioids used in OST.

In summary, it appears that the addition of naloxone reduces, but does not abolish, diversion. Clinicians need to employ patient selection for prescribing of doses without observation, and monitor patients regularly, rather than rely solely on the formulation of the medication to minimize risk.

Critical Issues in Treatment

Buprenorphine Dose

The foundation of OST is suppression of street heroin use. The commonest problem in treatment is patients settling on low doses sufficient to abolish withdrawal, enabling them to persist in heroin use.

Even when prescribed an apparently adequate dose, some patients in unsupervised treatment omit doses, divert doses, allowing them to continue heroin use. Persisting injecting during treatment is not effective as risk reduction (34).

Unlike methadone treatment, in which progressive dose increases need to be undertaken slowly, buprenorphine induction can be undertaken rapidly. The key issue is avoiding precipitated withdrawal. An initial dose of 4 mg causes less precipitated withdrawal than higher doses, and thereafter dose can be increased rapidly, reaching 12-16 mg/day by the third day. Patients need to be warned that the first 24 hours on buprenorphine may be difficult, but that initial symptoms settle fairly rapidly. In patients who cease heroin use, it may be possible to reduce the maintenance dose if patients experience side-effects, but patients should be monitored for relapse to opioid use as doses are reduced.

Structure

"Structure" refers to both cognitive and behavioural elements of treatment. In all areas of mental health, clinical interactions are most useful if focused on specific performance goals related to the patients circumstances (35). Effective treatment need clear direction and rationale, and the cognitive elements of buprenorphine treatment are defined and agreed objectives, a sense of the direction and purpose of treatment. Treatment needs to be based on adequate assessment, identifying patient's circumstances and aspirations, and reaching agreed goals of treatment. Progress in treatment should be monitored, and urine toxicology is an important component of monitoring.

Behavioural structure includes regular appointments, and where indicated, attendance for supervised administration. Rather than being merely a regulatory requirement, or a punitive step, supervised administration has important therapeutic elements. Daily interaction with health professionals, in a non-judgmental, non-punitive environment in which there are clear rules and expectations of behaviour, enforced consistently, offers safety and containment to previously marginalised and chaotic individuals. The randomised trials establishing the effectiveness of methadone, buprenorphine and diamorphine treatment have all involved supervised administration. Reports from France have shown that less clinical monitoring was associated with more heroin use and more injecting or prescribed buprenorphine (36), and that less supervision of administration was associated worse retention and more heroin use (37).

Pregnancy

Heroin use during pregnancy has an adverse effect on pregnancy outcomes, with increased risk of placental abruption, prematurity, low birth weight, and foetal death; treatment with methadone has been demonstrated to reduce these adverse outcomes, to the extent that treatment suppresses use of heroin (38). It is hypothesized that the cycle of intoxication and withdrawal experienced during active addiction, along with the lifestyle of many addicted women, contributes to this risk. In particular, opioid withdrawal during the third trimester of pregnancy is associated with foetal distress and foetal death.

The problem of OST during pregnancy is neonatal abstinence syndrome. The decision to maintain a woman on buprenorphine during pregnancy is a balance between the risks of heroin use, and the risk of NAS. If withdrawal is to be attempted, it should be in second trimester. However, relapse after withdrawal is common.

For these reasons, traditional advice to opioid-dependent women has been to remain on methadone throughout pregnancy. Recent randomised trial evidence indicates that neonatal outcomes following buprenorphine in pregnancy are very similar to those observed with methadone, and some evidence that neonatal abstinence following a buprenorphine-maintained pregnancy may be of less severity (39).

During active addiction to heroin, women's fertility is diminished, and on entry to buprenorphine their fertility is likely to improve, increasing the risk of unplanned pregnancy. Women should be warned of this risk and given advice regarding contraception.

All babies born to drug-dependent mothers should receive routine postnatal monitoring, plus specific assessment with the Finnegan or modified Finnegan scale, commencing 2 hours after birth and subsequently every 4 hours.

Pain Management

Given that buprenorphine produces blockade of opioid receptors, and diminishes the effect of additional opioids, there has been concern that patients on buprenorphine may have problems receiving analgesia, for example following elective surgery. However, the blockade produced by buprenorphine is not complete, and clinical experience in patients undergoing elective surgery is that adequate analgesia can be maintained by administering drugs such as morphine, sometimes in slightly increased dose. The clinical recommendation is that patients undergoing elective surgery continue their usual dose of sublingual buprenorphine, and have additional opioid analgesia titrated against response (40).

Role of Counselling

Dole and Nyswander (41) reported that in their original methadone program, while counselling was offered to their patients, very few availed themselves of it. Similarly, Ball and Ross (42) reported that most of the work of methadone clinic staff can more properly be described as casework rather than counselling. Consistent with these observations, a recent Cochrane review analysed results of trials of psychosocial interventions in conjunction with OST, and found no significant benefit of psychosocial services in terms of retention, non-prescribed opioid use, psychiatric symptoms, compliance or depression (43). This finding does not negate the possibility that some individuals can benefit from psychological interventions – but in randomised trials, no benefit was shown overall.

While there is little evidence for formal counselling, there is substantial evidence that the quality of interaction between patient and clinician is an important ingredient of treatment. Practitioners treating drug dependent patients require not just skills and knowledge, but also need a positive attitude towards treatment and recovery. Four decades ago, Dole and Nyswander, pioneers of methadone treatment, recognised the critical importance of changing the addict identity, a change encapsulated in Marie Nyswander's phrase "From Drug Addict to Patient". Their theme was that, freed from the cycle of addiction and treated with respect and dignity, heroin users can develop a different image of themselves, and behave with self-respect and dignity. They emphasized that negative assumptions about drug users need to be balanced by a belief in their capacity to change, and a sense of the practitioner's role in fostering that change (41).

An Orientation to Maintenance

Studies on methadone treatment in the US have identified two broad approaches to treatment, characterised as "an orientation to maintenance" and an "orientation to abstinence". The former approach generally involved high dose, indefinite treatment, and a degree of tolerance of persisting drug misuse. The alternate approach tended to use lower doses, and sometimes time-limited treatment. It also featured "limit-setting" - rewards for abstinence, and punishments for persisting drug use (such as dose reductions or removal from treatment). Paradoxically, efforts to promote abstinence appear to diminish the effectiveness of treatment (42,44,45).

The majority of patients aspire to an opioid-free life without methadone (46), and an orientation to maintenance does not mean that people should be discouraged from seeking to withdraw from treatment if they are doing well, and have sufficient "recovery capital" (social role, relationships, positive outlook and stable mental and physical health) to sustain long-term abstinence. People who achieve good social reintegration, particularly employment, are more likely to be able to leave treatment without relapse (12).

Summary – The Role of Medical Practitioners

Former heroin users entering treatment are often under many pressures – from the courts, from friends, from current drug users, from their families, and from

their own entrenched assumptions and patterns of behaviour. Treatment of heroin addiction is challenging, involving working with stigmatised and sometimes behaviourally challenging patients with fluctuating motivation and a history of conflict with authority figures.

While the use of medication is straightforward, ensuring delivery of effective care is more challenging. Doctors need skill, patients, and clinical supervision – essentially, the opportunity to discuss issues with their colleagues, to maintain a therapeutic relationship with OST patients.

REFERENCES

1. United Nations Office on Drugs and Crime. World Drug Report. New York, USA: United Nation, 2007.
2. Davoli M, Bargagli AM, Perucci CA, Schifano P, Belleudi V, Hickman M, Salamina G, Diecidue R, Vigna-Taglianti F, Faggiano F, VEdeTTE Study Group. Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study. Addiction 2007; 102:1954-1959.
3. Hulse G, English D, Milne E, Holman C. The quantification of mortality resulting from the regular use of illicit opiates. Addiction 1999; 94:221-229.
4. Darke S, Ross J. Suicide among heroin users: rates, risk factors and methods. Addiction 2002; 97: 1383-1394.
5. Maxwell JC, Pullum TW, Tannert K. Deaths of clients in methadone treatment in Texas: 1994-2002. Drug Alcohol Depend 2005; 78:73-81.
6. McLellan AT, Arndt IO, Metzger DS, Woody GE, O'Brien CP. The effects of psychosocial services in substance abuse treatment. JAMA 1993; 269:1953-1959.
7. Hser Y, Hoffman V, Grella C, Anglin MD. A 33-year follow-up of narcotic addicts. Arch Gen Psychiatry 2001; 58:503-508.
8. Volkow ND, Li TK. Drugs and alcohol: treating and preventing abuse, addiction and their medical consequences. Pharmacol Ther 2005; 108:3-17.
9. Holmstrand J, Anggard E, Gunne LM. Methadone maintenance: Plasma levels and therapeutic outcome. Clin Pharmacol Ther 1978; 23:175-180.
10. Dyer KR, Foster DJ, White JM, Somogyi AA, Menelaou A, Bochner F. Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: comparison of those who do and do not experience withdrawal and concentration-effect relationships. Clin Pharmacol Ther 1999; 65:685-694.
11. Zhang Z, Friedmann PD, Gerstein DR. Does retention matter? Treatment duration and improvement in drug use. Addiction 2003; 98:673-684.
12. Milby JB. Methadone maintenance to abstinence: how many make it? J Nerv Ment Dis 1988; 176:409-422.
13. McLellan AT, McKay JR, Forman R, Cacciola J, Kemp J. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. Addiction 2005; 100: 447-458.
14. Fudala PJ, Jaffe JH, Dax E, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioural effects of daily and alternate-day administration and abrupt withdrawal. Clin Pharmacol Ther 1990; 47; 525-534.
15. Hand CW, Sear JW, Uppington J, Ball MJ, McQuay HJ, Moore RA. Buprenorphine disposition in patients with renal impairment: Single and continuous dosing, with special reference to metabolites. Br J Anaesth 1990; 64;276-282.
16. Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug Alcohol Depend 2003; 70:13-27.
17. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. JAMA 2001; 285:45.
18. Bell J, Butler B, Lawrance A, Batey R, Salmelainen P. Comparing overdose mortality associated with methadone and buprenorphine treatment. Drug Alcohol Depend 2009; 104:73-77.
19. Petitjean S, Stohler R, Deglon JJ, Livoti S, Waldvogel D, Uehlinger C, Ladewig D. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. Drug Alcohol Depend 2001; 62:97-104.
20. Greenwald MK, Johanson C, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR, Zubieta J. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. Neuropsychopharmacol 2003; 28:2000-2009.
21. Mattick, RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. The Cochrane Library, 2008.
22. Bell J, Dru A, Fischer B, Levit S, Sarfraz MA. Substitution therapy for heroin addiction. Subst Use Misuse 2002; 37:1145-1174.
23. Romelsjo A, Engdahl B, Stenbacka M, Fugelstad A, Davstad I, Leifman A, Thiblin I. Were the changes to Sweden's maintenance treatment policy 2000-06 related to changes in opiate-related mortality and morbidity? Addiction 2010; 105:1625-1632.

24. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int 2001; 121:65-69

25. Sze-Ming Chua, Tih-Shih Lee. Abuse of prescription buprenorphine, regulatory controls and the role of the primary physician. Ann Acad Med Singapore 2006; 35:492-495.

26. Vidal Trecan G, Varescon I, Nabet N, Boissonnas A. Intravenous use of prescribed sublingual buprenorphine tablets by drug users receiving maintenance therapy in France. Drug Alcohol Depend 2003; 69:175-181.

27. Bouchez J, Vignau J. The French experience – the pharmacist, general practitioner and patient perspective. Eur Addict Res 1998; 4(Suppl.1); 19-23.

28. Cleaver H. Georgian drug misusers switch to Western heroin substitute. BMJ 2007; 334:821.

29. Jaffe J, O'Keeffe C. From morphine clinics to buprenorphine; regulating opioid agonist treatment of addiction in the United States. Drug Alcohol Depend 2003; 70:3-11.

30. Bell J. The global diversion of pharmaceutical drugs. Opiate treatment and the diversion of pharmaceutical opiates: a clinician's perspective. Addiction 2010; 105:1531-1537.

31. Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. Am J Drug Alcohol Abuse 2009; 35:68-72.

32. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend 2007; 88:75-78.

33. Larance B, Degenhardt L, Mattick R, O'Brien S, Lintzeris N, Bell J, Winstock A, Ali R. The diversion and injection of the pharmaceutical opioids used in opioid substitution treatment: Findings from the Australian post-marketing surveillance studies of buprenorphine-naloxone, 2006-2008. Technical report , National Drug and Alcohol Research Centre, Sydney, 2009.

34. Van Ameijden EJC, van den Hoek AAR, Couthino RA. Injecting risk behaviour among injecting drug users in Amsterdam, 1986-1992, and its relationship to AIDS prevention programs. Am J Public Health 1994; 84:275-281.

35. Moos RH. Addictive Disorders in Context: Principles and Puzzles of Effective Treatment and Recovery. Psychol Addict Behav 2003; 17:3-12.

36. Barau K, Thirion X, Micallef J, Chuniaud-Louche C, Bellemin B, San Marco J. Comparison of methadone and high dosage buprenorphine users in French care centres. Addiction 2001; 96:1433-1441.

37. Auriacombe M, Fatséas M, Dubernet J, Daulouède JP, Tignol J. French field experience with buprenorphine. Am J Addict 2004; 13(Suppl.1):17-28.

38. Hulse, G, Milne E, English D, Holman C. The relationship between maternal use of heroin and methadone and infant birth weight. Addiction 1997; 92:1571-1579.

39. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G. Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure. N Engl J Med 2010; 363:2320-2331.

40. Kornfeld H, Manfredi L. Effectiveness of Full Agonist Opioids in Patients Stabilized on Buprenorphine Undergoing Major Surgery: A Case Series. Am J Ther 2010; 17: 523-528.

41. Dole VP, Nyswander M. Rehabilitation of patients on methadone programs. Proceedings of the 5th National Conference on Methadone Treatment, 1973.

42. Ball JC, Ross A. The effectiveness of methadone maintenance treatment: patients, programs, services and outcome. New York: Springer-Verlag, 1991.

43. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev 2011; 10: CD004147.

44. Brands B, Blake J and Marsh, D. Impact of Methadone Program Philosophy Changes on Early Treatment Outcomes. J Addict Dis 2003; 22:3:19-38.

45. Gjersing L, Waal H, Caplehorn JR, Gossop M, Clausen T. Staff attitudes and the associations with treatment organisation, clinical practices and outcomes in opioid maintenance treatment. BMC Health Serv Res 2010; 10:194.

46. De Maeyer J, Vanderplasschen W, Camfield L, Vanheule S, Sabbe B, Broekaert E. A good quality of life under the influence of methadone: A qualitative study among opiate-dependent individuals. Int J Nurs Stud 2011; 48:1244-1257.