REVIEWS

Buprenorphine as an Alternative for Treatment of Opioid Dependence

Somchai Sinchaisuk

Faculty of Pharmaceutical Science, Ubonratchathani University

Abstract

Besides its use as an opioid analgesic, buprenorphine is now becoming more favorable, as compared with methadone, to be used as an opioid maintenance agent in the treatment of opioid dependence. Several clinical studies have demonstrated that buprenorphine can be as effective as methadone in opioid maintenance treatment and has some advantages over methadone. With its partial agonist profile, buprenorphine has been proved to have high safety profile, low abuse potential, and low physical dependence. Considering that treatment of opioid dependence will require long-term commitment, all those properties of buprenorphine may determine whether a successful treatment can be achieved. This article will review pharmacology of buprenorphine, including cross-tolerance, physical dependence potential, its clinical efficacy and its safety profile as well as a review of how to use buprenorphine as a maintenance therapy for opioid dependence.

Key words : Buprenorphine, opioid dependence

Buprenorphine ทางเลือกใหม่สำหรับการรักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์

สมชาย สินชัยสุข

คณะเภสัชศาสตร์ มหาวิทยาลัยอุบลราชธานี

บทคัดย่อ

นอกเหนือจากการใช้เป็นยาแก้ปวดแล้ว ปัจจุบัน buprenorphine กำลังได้รับความนิยมมากขึ้นเรื่อยๆ เมื่อเทียบกับ methadone ในการใช้รักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์ (opioid dependence) การศึกษาทางคลินิกได้แสดงให้เห็นถึงประสิทธิภาพของ buprenorphine ที่เทียบเท่าได้กับการใช้ methadone รวมถึงข้อได้เปรียบบางประการ ด้วยคุณลักษณะที่เป็น partial agonist ของ buprenorphine ทำให้มีความปลอดภัยจากการใช้ยาสูง การใช้ยาในทางที่ผิดเป็นไปได้น้อย รวมถึงการติดยาก็น้อยด้วย เนื่องจากการรักษาผู้ป่วยติดยาเสพติดจะต้องใช้ระยะเวลานานในการรักษา คุณสมบัติเหล่านี้ของ buprenorphine อาจเป็นตัวกำหนดว่าการรักษาจะได้ผลหรือไม่ บทความนี้จะกล่าวถึงคุณลักษณะทางเภสัชวิทยาของ buprenorphine, การทนยาแบบ cross-tolerance, โอกาสการติดยา (physical dependence potential), ประสิทธิผลทางคลินิก (clinical efficacy) และความปลอดภัยจากการใช้ยา (safety profile) รวมไปถึงวิธีการใช้ buprenorphine ในการรักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์ (buprenorphine maintenance therapy for opioid dependence)

คำสำคัญ : Buprenorphine, opioid dependence

Over the past years, there have been only two types of medications for the treatment of opioid dependence. The first type is agonist substitution therapy (i.e. methadone). The second type is antagonist therapy (i.e. naltrexone), which unlike agonist therapy, naltrexone does not produce morphine-like agonist effects. Instead, it blocks agonistic effects. Both types have been effective in reducing illicit opioid use. However, both therapies have some pitfalls. Methadone, the standard substance in the substitution therapy of opioid dependence, still has high abuse potential and high level of physical dependence, whereas naltrexone has difficulty to retain patients in treatment due to its lack of desired positive agonistic effects.

With the discovery of multiple opioid receptors, newer opioid analgesics (mixed agonist/antagonists) have been developed to take advantage of the pharmacologic effects mediated by these receptors. This development effort has been aimed primarily at reducing the abuse potential and physical dependence property of these medications, while maintaining analgesic efficacy. Buprenorphine is one of those newer opioid analgesics. It has high affinity at both mu and kappa opioid receptors. It is a partial agonist at mu opioid receptor but acts as an antagonist at kappa opioid receptor. This unique pharmacologic profile has provided an opportunity to develop an alternative treatment for opioid dependence.

Pharmacology of Buprenorphine

Pharmacokinetics

For the treatment of opioid dependence, it is very important that injectable forms of administration be avoided. Otherwise, this can lead to the spread of infectious diseases such as HIV, hepatitis and other parenterally transferred infections. Since buprenorphine is less well absorbed when taken orally, and is quickly metabolized by the liver, known as the "first pass effect",[1,2] sublingual administration has been the primary route used in studies of clinical efficacy for treating opioid dependence. When taken sublingually, buprenorphine is well absorbed with 60-70% of the plasma concentration achieved by the parenteral route.[3] The drug is widely distributed throughout the body with a peak plasma concentration at approximately 90 minutes and a half life of 4 to 5 hours. Buprenorphine is highly bound to plasma proteins.[2] It is highly lipophilic and brain tissue levels far exceed serum level. Buprenorphine is metabolized in the liver by the CYP450 3A4 enzyme system.[4,5] It undergoes N-demethylation and conjugation.[2,6,7] Buprenorphine's metabolite, norbuprenorphine, has more potent respiratory depressive effects than the parent drug,[8,9] although the analgesic effect of norbuprenorphine is one-fiftieth that of buprenorphine following intravenous administration.[9] At present, there is no evidence that norbuprenorphine activity is responsible for effects observed in the treatment of opioid dependence.[9] Because of its high lipid solubility, buprenorphine is also expected to be active by intranasal route.[10]

Pharmacodynamics

Buprenorphine, generally described as a mixed agonist/antagonist opioid,[11] is a semi-synthetic opioid derivative of the thebaine.[12] It acts as a partial agonist at the mu opioid receptor, characterized by a reduced intrinsic activity compared to the pure agonist.[13-19] Buprenorphine also has the properties of a weak kappa opioid receptor antagonist (i.e. it does not show any intrinsic activity on this receptor but can block agonistic effects).[15,17-20] Clinically, the effects of buprenorphine are primarily expressed through the mu opioid receptor and are similar to those of full agonists like morphine and methadone.[16] Because it is a partial agonist, its effects plateau at higher doses, and it begins to behave more like an antagonist. This antagonistic activity in higher doses limits the maximal analgesic effect and respiratory depression.[21,22] This a so-called "ceiling effect" confers a high safety profile, a low level of physical dependence and only mild withdrawal

symptoms upon cessation after prolonged administration. These qaulities make it advantageous for the treatment of opioid dependence.[16,22,23] Moreover, slow dissociation from the opioid receptor of buprenorphine provides a long duration of action,[24,25] which allows dosing schedules to be varied from several times daily to several times weekly.

Although buprenorphine alone, taken in the form of a sublingual tablet, is efficacious and possesses other desirable therapeutic characteristics (i.e. high safety profile and low level of physical dependence), a combination containing buprenorphine and naloxone has been developed in order to decrease abuse and misuse. The addition of naloxone, whose its sublingual bioavailability is poor,[26,27] results in only buprenorphine effect when the combination tablet is taken by the therapeutic (i.e. sublingual) route.[28] However, if the combination is injected, the naloxone effect precipitates opioid withdrawal, thus detering intravenous abuse.[28,29] The issue of limiting buprenorphine's abuse liability with naloxone is complicated by the fact that naloxone does have some sublingual bioavailability. Thus, the buprenorphine : naloxone ratio must be chosen carefully in order to avoid naloxone effects when the combination is used as intended. It was determined that the optimum combination is a 4:1 ratio of buprenorphine to naloxone[30] and tablets containing 2/0.5 and 8/2 mg of buprenorphine/naloxone have been developed.

Cross-tolerance

Tolerance, defined as a decreasing effect of a given drug following chronic administration of that drug, normally is a problem when opioids are used as analgesic agents. When they are used for the treatment of opioid dependence, however, it is an adventage. For example, tolerance to methadone maintenance therapy develops cross-tolerance to other opioid drugs such as heroin,[31] and this helps reduce illicit drug use since heroin abuser will no longer entertain the positive effects, which if not due to methadone cross-tolerance, would occur from the use of heroin. In the case of buprenorphine, due to its unique pharmacological profile, reducing illicit drug use may be through the development of cross-tolerance or through pharmacological antagonism.[32,33]

Buprenorphine-induced physical dependence

Although having low intrinsic activity at mu opioid receptor, buprenorphine does produce physical dependence as demonstrated by the ability of pure opioid receptor antagonists (i.e. naloxone and naltrexone) to precipitate an opioid withdrawal in patients maintained on buprenorphine.[34-37] The physical dependence, however, is considered to be low, as when compared to patients maintained on a full mu agonist such as methadone, higher doses of the opioid antagonist naloxone are necessary to precipitate withdrawal in patients maintained on buprenorphine. Clinically, spontaneous buprenorphine withdrawal symptoms can be observed after several days following abrupt cessation of buprenorphine treatment and is usually described as mild to moderate in intensity.[38-41] The symptoms include runny nose, watery eyes, hot flashes, lethargy, nausea, diarrhea, restlessness, and irritability.[16,41] Gradual reduction, rather than abrupt termination of buprenorphine would likely result in no opioid withdrawal symptoms.

Clinical efficacy of buprenorphine

A series of controlled clinical studies firmly established the clinical efficacy of buprenorphine. Some of the study were designed to compare buprenorphine to placebo, either to "active" or "inactive" placebo, and others compared buprenorphine to methadone. Retention in treatment and abstinence from illicit opiate use (commonly assessed by urine toxicology) were utilized as primary outcome measures of success, but other measures, such as request for dose changes, withdrawal symptoms and reduced heroin craving were also employed.

Buprenorphine versus placebo

In a double-blind trial designed to assess the early clinical effectiveness (1-2

weeks) of buprenorphine compared with placebo,[42] subjects were randomly assigned to received either 2 mg/day or 8 mg/day buprenorphine or placebo over a period of 14 days. Between day 6 and 13, the subjects were then given the option of receiving an altered dose. A randomization was then carried out to one of the other two treatment groups to which the subjects did not belong. The alternate dose then had to be taken up to and including day 14. The results showed that subjects treated with buprenorphine, irrespective of their dose, requested fewer dose changes, used less illicit opiates and reported higher ratings of medication adequacy than those treated with placebo.

Two other studies that compared the buprenorphine and placebo also showed higher maintenance rates and less illicit opiate use in subjects treated with buprenorphine.[43,44]

In another randomized, double-blind study designed to evaluate the safety and efficacy of 8 mg/day buprenorphine compared with 1 mg/day buprenorphine in maintenance treatment of opioid dependence[45], subjects were treated with buprenorphine over a period of 16 weeks. Since the administration of placebo to patients who are addicted to drugs is regarded as unethical, a dose of 1 mg/day buprenorphine was regarded as an "active" placebo. The results showed that subjects treated with 8 mg/day buprenorphine had higher maintenance rates and less illicit opiate use than those treated with 1 mg/day buprenorphine.

Similar results were observed in several other studies[46-48], in which subjects treated with 8 mg buprenorphine showed higher retention rates than those treated with 1 mg or 3 mg buprenorphine.

Buprenorphine versus methadone

In a double-blind study with a comparison of parallel groups[49], subjects were randomly assigned to receive 8 mg/day buprenorphine, 20 mg/day methadone, or 60 mg/day methadone. In term of maintenance rates and the percentage of opiate-negative urine, buprenorphine showed significant superiority compared to 20 mg/day methadone and an equivalence compared to 60 mg/day methadone. The results were similar to that of a further study[50], in which the subjects could changes their own dose until achieving an optimal dose response following an initial stabilization at buprenorphine 8 mg/day or methadone 50 mg/day. The mean maintenance dose was 8.9 mg/day buprenorphine and 54 mg/day methadone. Both drugs were effective on measures of treatment retention and opiate-free urine. These results were further confirmed by a study with similar flexible dosage protocol.[51] This variable dose study resulted in a mean stabilization buprenorphine dose of 10.5 mg/day and in a mean stabilization methadone dose of 69.8 mg/day. The percentage of opioid-free urine and heroin craving scores were similar in both groups, although retention rate was significantly better in the methadone group.

Similar results could also be observed in several other studies. A 17-week, double-blind study[52] showed that 7-14 mg/day buprenorphine and high dose (60-100 mg/day) methadone were equally effective in term of maintenance rate and the percentage of opioid-free urine. Both high dose methadone and 7-14 mg/day buprenorphine were superior to low dose (20 mg/day) methadone. A recent published study compared the efficacy of buprenorphine and methadone in the treatment of opioid dependence. The results showed that 9.2 mg/day buprenorphine and 81.5 mg/day methadone were equally effective in term of retention in treatment at 12 weeks.

In contrast, better maintenance rates for methadone were demonstrated by other studies.[53,54] This could be due to the relatively low dose (2, 4 and 6 mg/day) of buprenorphine utilized in comparison with appropriate dose (65 mg/day) of methadone. Better maintenance rates for methadone were also observed in a study[55], in which an appropriate dose of 8 mg/day buprenorphine was compared to relatively high dose (80 mg/day) methadone.

Safety profile

Because buprenorphine is a partial agonist with relatively low intrinsic activity, it

should limit life-threatening respiratory depression, contributing to a safety profile that is better than that of methadone, a full mu opioid agonist currently used in the treatment of opioid dependence. For example, when buprenorphine was administered to non-dependent individuals, respiratory depression was increasingly related to buprenorphine dose over a range of 1-4 mg, but this dose effect began to level out at higher doses; administration of 32 mg buprenorphine produced no greater respiratory depression than that produced from 16 mg buprenorphine.[22] The safety of buprenorphine may be even greater in opioid-tolerant individuals, as snpported by studies showing that buprenorphine-dependent subjects can receive substantially higher doses than their usual maintenance doses without signs of toxicity. For example, administration of 16 mg buprenorphine in patients normally getting 8 mg buprenorphine daily produced no adverse effect.[56] The most compelling evidence for the excellent safety of buprenorphine may come from the fact that there is almost no lethal overdose cases associated with respiratory depression produced by buprenorphine alone[57], despite the extensive use of buprenorphine as an analgesic. Buprenorphine has been approved for the treatment of opioid dependence in France since 1996 (currently, it has also been approved in Australia in 2001 and in the US in 2002), a series of overdose deaths were reported. The vast majority of these cases resulted when buprenorphine and benzodiazepines were concomitantly abused via the parenteral route.[57-61] When compared to methadone, the death rate from buprenorphine overdose is still far less; the estimated risk of overdose death is at least 5 times higher for methadone than for buprenorphine.[62]

Some considerations before getting start on buprenorphine

Because buprenorphine is a partial mu opioid agonist and consequently has low intrinsic activity compared with full mu agonist, it can precipitate withdrawal in opioid-dependent animals and humans.[34-37,63-65] These studies suggested that heroin- or methadone-dependent patients may experience opioid withdrawal when they initially receive buprenorphine, thus potentially hindering induction onto clinically effective maintenance doses. Therefore, prior to administering the initial buprenorphine dose, consideration should be given to three important factors. These factors include

1. *The time since last opioid use.* The likelihood of buprenorphine-induced precipitated withdrawal increases as the time interval since last opioid use decreases. Because mild withdrawal has been observed at a time interval of 2 hours since last opioid use[66], the administration of the initial dose of buprenorphine in patients dependent on opioid should be delayed for at least 4 hours after the last ingestion of opioid.

2. *The type of opioid dependence (i.e.long or short-acting opioid).* Patients dependent on shorter-acting opioid (heroin, morphine) may be less likely to experience buprenorphine-induced precipitated withdrawal than those dependent on long-acting opioid (methadone).[29,67,68] A longer time interval between methadone and subsequent buprenorphine dosing is recommended depending on the dose of methadone. For low dose of methadone, the initial dose of buprenorphine can begin at 24 hours after the last ingestion of methadone.[69,70] For higher doses of methadone, the initiation of buprenorphine can be delayed for more than 24 hours after the last ingestion of methadone.[71]

3. *The degree of opioid dependence.* The buprenorphine-induced precipitated withdrawal could occur if the degree of opioid dependence is high. For example, patients dependent on >40 mg daily of methadone should reduce their use to 40 mg daily or less of methadone before the first dose of buprenorphine is initiated.[72]

Buprenorphine maintenance therapy

Initial dose of buprenorphine

In most studies, the starting dose of buprenorphine administration on the first

day has been 2 mg of sublingual solution. However, 4 mg of buprenorphine can be administered without causing an opioid withdrawal in opioid-dependent patients. If there is concern for possible precipitation of an opioid withdrawal, the first daily dose can be split with the second half administered 3-4 hours after the first dose. Induction onto a dose as high as 16 mg of buprenorphine has been accomplished by administering 2, 4, 8, and 16 mg of buprenorphine on day 1-4, respectively.[73] However, the objective of induction should be to achieve a maintenance dose (i.e. 16 mg) as quick as possible (i.e. within 2-3 days).

Maintenance dose of buprenorphine

For most patients, an initial target dose should be 12-16 mg of daily buprenorphine. If illicit opioid use or withdrawal continues, then the dose should be increased. The minimum dose increase possible is increment of 2 mg.

Discontinuing buprenorphine

Abrupt discontinuation of buprenorphine produced a mild to moderate withdrawal.[38,40,41] Gradual dose reduction is recommended over rapid dose reduction or abrupt cessation since the former has been shown to provide less self-reported withdrawal, increased retention, and less illicit opioid use.

Less-than-daily use with buprenorphine

Because of buprenorphine's long duration of action,[22,74,75] less-than-daily dosing with buprenorphine has been suggested.[22,38,76-80] Less-than-daily dosing would likely improve buprenorphine's clinical acceptability to patients who are receiving their medication through a clinic by reducing the required number of clinic visits. Currently, it would be best to recommend a thrice-weekly schedule (e.g. Monday, Wednesday, and Friday), although additional studies of twice-weekly (e.g. Monday and Thursday) dosing may show this schedule is equally effective and also liked by patients. For patients on daily buprenorphine who are switching to thrice-weekly buprenorphine, doses ingested on medication days should be increased to compensate for the longer time period between doses. Because buprenorphine is a partial agonist, maximum agonist effects are below that expected for a full agonist, Thus, increases in the daily doses are safe and well tolerated by patients.

Summary

Clinical studies provide solid support for the use of buprenorphine in the treatment of opioid dependence and demonstrate an equality in the efficacy of buprenorphine and methadone. This suggests that these two medications can be used in opioid-dependent patients with equal success. However, buprenorphine seems to be a better choice, since, for example, it has better safety profile and more limited physical dependence.

Buprenorphine's partial mu opioid agonist profile is responsible for its high safety profile, decreased abused potential and a low level of physical dependence. Buprenorphine also has the ability to blunt the effects of concurrently administered opioid, either through cross-tolerance or pharmacological antagonism, reducing the risk of illicit drug use. Furthermore, buprenorphine's high receptor affinity and slow dissociation from its receptor help provide its long duration of action and make less-than-daily dosing possible, which may result in higher acceptability in some patients. However, despite its low abuse potential, buprenorphine can produce mu agonist effects, especially with the parenteral use. The likelihood of parenteral abuse can be reduced by using a sublingually administered combination medication containing buprenorphine and naloxone.

In conclusion, buprenorphine can be an effective, safer alternative for methadone in the treatment of opioid dependence.

References

1. McQuay HJ, Moore RA. Buprenorphine kinetics in humans. In: Cowan A, Lewis, JW. (Eds), *Buprenorphine: Combatting drug abuse with a unique opioid.* New York: Wiley-Liss Inc. 1995:137-147.

2. Walter DS, Inturrisi CE. Absorption, distribution, metabolism and excretion of buprenorphine in animals and humans. In: Cowan A, Lewis JW. (Eds), *Buprenorphine: combatting drug abuse with a unique opioid.* New York: Wiley-Liss Inc. 1995:113-135.
3. Mendelson J, Upton RA, Everhart ET, et al. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997;37:31-37.
4. Iribarne C, Picart D, Dreano Y, et al. Involvement of P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. *Life Sci* 1997;60:1953-1964.
5. Kobayashi K, Yamamoto T, Chiba K, et al. Human buprenorphine N-dealkylation is catabolized by cytochrome P450 3A4. *Drug Metab Dispos* 1998;26:818-821.
6. Mistry M, Houston JB. Glucuronidation in vitro and in vivo. Comparison of intestinal and hepatic conjugation of morphine, naloxone, and buprenorphine. *Drug Metab Dispos* 1987;15:710-717.
7. Ohtani M, Kotaki H, Uchino K, et al. Pharmacokinetic analysis of enterohepatic circulation of buprenorphine and its active metabolite, norbuprenorphine, in rats. *Drug Metab Dispos* 1994;22:2-7.
8. Ohtani M, Kotaki H, Nisitateno K, et al. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. *J Pharmacol Exp Ther* 1997;281:428-433.
9. Ohtani M, Kotaki H, Sawada Y, et al. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther* 1995;272:505-510.
10. Lindhardt K, Ravn C, Gizurarson S, et al. Intranasal absorption of buprenorphine– in vivo bioavailability in sheep. *Int J Pharm* 2000;205:159-163.
11. Cowan A. Buprenorphine: new pharmacological aspects. *Int J Clin Pract* 2003;133:823-824.
12. Heel RC, Brogden RN, Speight TM, et al. Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1979;17:81-110.
13. Bickel WK, Stitzer ML, Bigelow GE, et al. Buprenorphine:dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther* 1988;247:47-53.
14. Cowan A, Lewis JW,McFarlane IR. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Br J Pharmacol* 1977;60:537-545.
15. Huang P, Kehner GB, Cowan A, et al. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: Norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther* 2001;297: 688-695.
16. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch Gen Psychiatry* 1978;35:501-516.
17. Leander JD. Buprenorphine is a potent kappa-opioid receptor antagonist in pigeon and mice. *Eur J Pharmacol* 1988; 151:457-461.
18. Lutfy K, Eitan S, Bryant CD, et al. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *J Neurosci* 2003;23:10331-10337.
19. Reisine T, Bell GI. Molecular biology of opioid receptors. *Trends Neurosci* 1993; 16:506-510.
20. Neguss SS, Picker MJ, Dykstra LA. Kappa antagonist properties of buprenorphine in non-tolerant and morphine-tolerant rats. *Psychopharmacology* 1989;98:141-143.
21. Raisch DW, Fye CL, Boardman KD, et al. Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother* 2002;36:312-321.
22. Walsh SL, Preston KL, Stitzer ML, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994;55(5):569-580.
23. Lewis JW. Buprenorphine. *Drug Alcohol Depend* 1985;14:363-372.
24. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *Br J Anaesth* 1985; 57:192-196.
25. Cowan A. Update on the general pharmacology of buprenorphine. In: Cowan A, Lewis JW. (Eds), *Buprenorphine: Combatting drug abuse with a unique opioid.* New York: Wiley-Liss Inc. 1995:31-47.
26. Harris DS, Jones RT, WelmS, et al. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend* 2000;61:85-94.
27. Preston KL, Bigelow GE, Liebson IA. Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend* 1990;25:27-34.
28. Stoller KB, Bigelow GE, Walsh SL, et al. Effects of buprenorphine/naloxone in opioid-dependent humans. *Psychopharmacology* 2001;154:230-242.
29. Fudala PJ, Yu E, Macfadden W, et al. Effects of buprenorphine and naloxone in morphine-stabilized opiate addicts. *Drug Alcohol Depend* 1998;50:1-8.

30. Mendelson J, Jones RT. Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the 4:1 ratio for treatment?. *Drug Alcohol Depend* 2003;70 Suppl. 1:S29-S37.
31. Walker EA, Richardson TM, Young AM. Tolerance and cross-tolerance to morphine-like stimulus effects of mu opioids in rats. *Psychopharmacology* 1997;133:17-28.
32. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on muopioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003;28:2000-9.
33. Walker EA, Young AM. Differential tolerance to antinociceptive effects of mu opioids during repeated treatment with etonitazene, morphine, or buprenorphine in rats. *Psychopharmacology* 2001;154: 131-42.
34. Clark NC, Lintzeris N, Muhleisen PJ. Severe opiate withdrawal in a heroin user precipitated by a massive buprenorphine dose. *Med J Aust* 2002;176:166-67.
35. Eissenberg T, Greenwald MK, Johnson RE, et al. Buprenorphine's physical dependence potential:antagonist-precipitated withdrawal in humans. *J Pharmacol Exp Ther* 1996;276:449-59.
36. Kosten TR, Krystal JH, Charney DS, et al. Opiate antagonist challenges in buprenorphine-maintained patients. *Drug Alcohol Depend* 1990;25:73-8.
37. Walsh SL, June HL, Schuh K, et al. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology* 1995;119:268-6.
38. Fudala PJ, Jaffe JH, Dax EM, et al. Use of buprenorphine in the treatment of opioid addiction. II Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther* 1990;47:525-34.
39. Kuhlman JJ, Jr Levine B, Johnson RE, et al. Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, main- tenance and withdrawal from sublingual buprenorphine. *Addiction* 1998;93:549-59.
40. San L, Cami J, Fernandez T, et al. Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects. *Br J Addict* 1992; 87:55-62.
41. Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol Depend* 2003;70:S13-S27.
42. Johnson RE, Eissenberg T, Stitzer ML, et al. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend* 1995; 40:17-25.
43. Kakko J, Svanborg KD, Kreek MJ, et al. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomized, placebo-controlled trial. *Lancet* 2003; 361:662-8.
44. Krook AL, Brors O, Dahlberg J, et al. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction* 2001;97:533-42.
45. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475-86.
46. Ahmadi J. Methadone versus buprenorphine maintenance for the treatment of heroin-dependent outpatients. *J Subst Abuse Treat* 2003;24:217-20.
47. Ahmadi J, Babaee-Beigi M, Alishahi M, et al. Twelve-month maintenance treatment of opium-dependent patients. *J Subst Abuse Treat* 2004;26:61-4.
48. Ling W, Huber A, Rawson RA. New trends in opiate pharmacotherapy. *Drug and Alcohol review* 2001;20:79-94.
49. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *J Am Med Assoc* 1992;267:2750-5.
50. Strain EC, Stitzer ML, Liebson IA, et al. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry* 1994;151: 1025-30.
51. Petitjean S, Stohler R, Deglon JJ, et al. Double-blind randomized trial of buprenorphine and methadone in opiate dependence. *Drug Alcohol Depend* 2001; 62:97-104.
52. Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine and methadone for opioid dependence. *N Engl J Med* 2000;343: 1290-7.
53. Kosten TR, Schottenfeld RS, Ziedonis D, et al. Buprenorphine versus methadone maintenance for opioid dependence. *J of nerv Ment Dis* 1993;181:358-64.
54. Schottenfeld RS, Pakes JR, Oliveto A, et al. Buprenorphine vs methadone main- tenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 1997;54:713-20.
55. Ling W, Wesson DR, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone maintenance in opioid

dependence. *Arch Gen Psychiatry* 1996; 53:401-7.
56. Strain EC, Walsh SL, Preston KL, et al. The effects of buprenorphine in buprenorphine-maintained volunteers. *Psycho pharmacology* 1997;129:329-38.
57. Kintz P. Buprenorphine-related deaths. In: Kintz P, Marquet P (Eds), Buprenorphine therapy of opiate addiction. Humana Press, Totowa, NJ 2002:109-17.
58. Reynaud M, Tracqui A, Petit G, et al. Six deaths linked to misuse of buprenorphine-benzodizepines combinations. *Am J Psychiatry* 1998;155:448-9.
59. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol* 1998;22:430-4.
60. Tracqui A, Tournoud C, Flesch F, et al. Buprenorphine poisoning in drug abusers on substitution therapy; 29 non-fatal and 20 fatal cases. *La Presse Medicale* 1998; 27:557-61.
61. Kintz P. Deaths involving buprenorphine: a compendium of French cases. *Forensic Sci Int* 2001;121:65-9.
62. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in Franc [letter]. *JAMA* 2001;285(1);45.
63. Cowan A, Doxey JC, Harry EJR. The animal pharmacology of buprenorphine, an oripavine analgesic gent. *Br J Pharmacol* 1977;60:547-54.
64. Dm JE, Herz . In vivo receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonist and antagonistic actions. *Br J Pharmacol* 1981;74:627-33.
65. Fukase H, Fukuzaki K, Koja T, et al. Effects of morphine, naloxone, buprenorphine, butorphanol, haloperidol and imipramine on morphine withdrawal signs in cynomolgus monkeys. *Psychopharmacology* 1994;116: 396-400.
66. Strain EC, Preston KL, Liebson IA, et al. Buprenorphine effects in methadone-maintained volunteers:effects at 2 hr after methadone. *J Pharmacol Exp Ther* 1995; 272:628-38.
67. Schuh KJ, Walsh SL, Bigelow GE, et al. Buprenorphine, morphine, and naloxone effects during ascending morphine maintenance in humans. *J Pharmacol Exp Ther* 1996;278:836-46.
68. Mendelson J, Jones RT, Fernandez I, et al. Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther* 1996;60:105-14.
69. Law FD, Bailey JE, Allen DS, et al. The feasibility of abrupt methadone-buprenorphine transfer in British opiate addicts in an outpatient setting. *Addict Biol* 1997;2:191-200.
70. Harris DS, Jones RT, Welm S, et al. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. *Drug Alcohol Depend* 2000;61:85-94.
71. Bouchez J, Beauverie P, Touzeau D. Substitution with buprenorphine in methadone- and morphine sulfate-dependent patients. *Eur Addict Res* 1998;4:8-12.
72. Levin FR, Fischman MW, Connerney I, et al. A protocol to switch high-dose, methadone-maintained subjects to bupre- norphine. *Am J Addict* 1997;6:105-16.
73. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction* 1998;93:475-86.
74. Roughan JU, Flecknell PA. Buprenorphine: A reappraisal of its antinociceptive effects and therapeutic use in alleviating postoperative pain in animals. *Lab Anim* 2002;36:322-43.
75. Walsh SL, Preston KL, Bigelow GE, et al. Acute administration of buprenorphine in humans: partial agonist and blockade effects. *J Pharmacol Exp Ther* 1995; 274:361-72.
76. Amass L, Bickel WK, Crean JP, et al. Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. *Psychopharmacology* 1998;136:217-25.
77. Amass L, Bickel WK, Higgins ST, et al. Alternate-day dosing during buprenorphine treatment of opioid dependence. *Life Sci* 1994;54:1215-8.
78. Eissenberg TR, Johnson RE, Bigelow GE, et al. Controlled opioid withdrawal evaluation during 72 hr dose omission in buprenorphine-maintained patients. *Drug Alcohol Depend* 1997;45:81-91.
79. Johnson RE, Eissenberg T, Stitzer ML, et al. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug Alcohol Depend* 1995;40:27-35.
80. Petry NM, Bickel WK, Badger GJ. Examining the limits of buprenorphine interdosing interval: daily, every-third-day and every-fifth-day dosing regimens. *Addiction* 2001;96:823-34.