Submission No:16
AUTHORISED

Family and Human Services Committee
House of Representatives
Parliament of Australia

Sustained-Release Naltrexone

BACKGROUND

Significant Morbidity and Mortality is associated with the use of heroin and other illicit opioids **(See Appendix A).**

Treatment for heroin use: In Australia, a number of pharmacotherapies are available either as accepted treatments or are being evaluated as long-term therapies for heroin dependence. These include methadone, buprenorphine and naltrexone. Of these, the opioid substitution program of methadone maintenance treatment (MMT) is the earliest and continues to be the most widely used form of pharmacotherapy, with buprenorphine rapidly gaining a prominent treatment position. The clinical efficacy of both MMT and buprenorphine have been repeatedly demonstrated [1] **(Appendix B)**. Unlike methadone and buprenorphine, naltrexone is an opioid antagonist with detoxification (withdrawal) of the heroin dependent person a prerequisite for naltrexone maintenance [2].

Oral Naltrexone: The ability of naltrexone to effectively antagonise heroin use is unequivocal **(Appendix C)**. The generally cited therapeutic blood level required to treat heroin dependence is above 2ng/ml (25). Despite this pharmacological efficacy, non-compliance with oral naltrexone formulae has been a significant impediment to its adoption as a treatment. Non-compliance is often associated with a patient's withdrawal from treatment and return to heroin use. Even in patients who perform well on oral formulae, periodic relapse to heroin use is common [3]. Oral naltrexone is also approved for use in the treatment of alcohol dependence.

Sustained-release naltrexone: An alternative method of naltrexone maintenance delivery involves the injection or surgical insertion of a sustained release preparation of naltrexone. This approach removes the onus on patients to use daily oral naltrexone. The concept of sustained release preparations of naltrexone is not new. Beginning in the mid-1970s, a number of depot formulations of naltrexone were developed, although most had unacceptable tissue compatibility [4]. More recently developed formulations show greater promise **(Appendix D)**. Despite addressing issues of daily non-compliance associated with oral naltrexone formula, these sustained release formulations still rely on the patient returning for a second and subsequent treatments. Given the propensity of the population towards relapse it is likely that not all patients will return for subsequent monthly re-treatment. For example, with respect to heroin dependent persons, Comer *et al* using the injectable Depotrex® naltrexone formulation reported that in an 8-week trial, with re-treatment at 4 weeks, 32% of the high dose and 40% of the low dose participants failed to return for re-treatment [5]. Therefore, treatment with longer acting preparations that reduces the frequency of re-treatments is desirable.

Go Medical Industries naltrexone implant: Recently, a poly-DL-lactide implantable formulation of naltrexone has been developed which may provide longer-lasting blockade of opioid receptors. This implant is a diffusion-based delivery system, designed such that pockets of naltrexone are isolated by a polymer matrix to ensure a more gradual release of the naltrexone as fluid enters the core. The implant formulation incorporates naltrexone loaded poly [trans-3,6-dimethyl-1,4-dioxane-2,5-dione] (DL)lactide microspheres compressed into tablets and surrounded by a poly(DL)lactide coating. Each tablet (8mm diameter; 310mg total weight) contains approximately 108 mg of naltrexone. The poly(DL)lactide used in the manufacture of the Go Medical Inc. Australian naltrexone implant is commercially available from PURAC (Netherlands). It is manufactured and supplied in accordance with the US Food

and Drug Administration (FDA) technical specifications for use in humans. Ten tablets are formulated into a pellet and two pellets constitute an implant treatment for opioid dependence. Each implant is about the size of a "AAA" battery", has a total weight of approximately 4.4g and contains approximately 2.2g of naltrexone. The manufacturer's data showed that by December 2005, 1640 opioid or alcohol cases had received implants with 19 (1.2 %) later removed. These implants are currently manufactured under Therapeutic Goods Administration (TGA) Good Manufacturing Practice.

Mortality Associated with Naltrexone Treatment

Limited data from some research groups suggest elevated naltrexone mortality potentially due to: withdrawal related problems during induction, increased suicidal ideation and accidental overdose during maintenance, and particularly accidental overdose post-treatment **(Appendix E)**. This requires more rigorous investigation.

Management of the Pregnant Heroin (or Alcohol) User: Approximately 60% and 80% respectively of women with problem alcohol or heroin use are of reproductive age and may fall pregnant. Management of the pregnant user is aimed at both stabilising the mother and protecting the fetus. To date methadone, to a lesser extent buprenorphine, have been used. However, there are a number of problems associated with these drugs. Both are registered as ***"category C"*** for use during pregnancy because they have been **"shown to cause, or have been suspected as causing, harmful effects on the human fetus"** [6] **.**

Use of naltrexone during pregnancy: Naltrexone is registered as a ***"category B3"*** drug for use in human pregnancy and, by current definition, carries less risk than methadone or buprenorphine. However, B3 status means that clinical data are limited and, although there is ***"evidence of increased occurrence of fetal damage in animals, the significance of the data for humans is uncertain"*** [6]. An added twist pertinent to this medication is that the risk of becoming pregnant while being treated with naltrexone is increased because the drug increases fertility [7].

There are a number of scenarios in which naltrexone might inadvertently be used during human pregnancy, or part thereof. For daily oral naltrexone, administration can be readily stopped should a woman fall pregnant. By contrast, patients with sustained release implants who fall pregnant face difficult options. The implant can be removed or left in place. Both scenarios carry possible risk to the baby due, respectively, to general anaesthesia during surgical removal or to continued naltrexone exposure during pregnancy. Nevertheless, for both oral and sustained release formulations, continued management to ensure stabilisation would still be required and this may still involve naltrexone.

PRELIMINARY DATA

Blood profile of naltrexone release from the Australian implant: Published data from an "in treatment" study population indicating that this implant releases naltrexone within hours of insertion with blood free naltrexone levels remaining above 2 ng/ml for approximately 5.5 months in a standardised 70 kg person [8]. This translates to approximately 5 to 5.5 months coverage for female and 4.5 to 5 month coverage for male patients. This period of coverage is significantly greater than the period of coverage reported in published data for other sustained release preparations [9-11]. This data may be criticized as biased as it was derived from an opportunistic "in treatment" population with a possibility that those with higher blood naltrexone levels may have been retained in treatment.

NH&MRC (353545): Efficacy of the Australian implant in reducing opiate overdose:

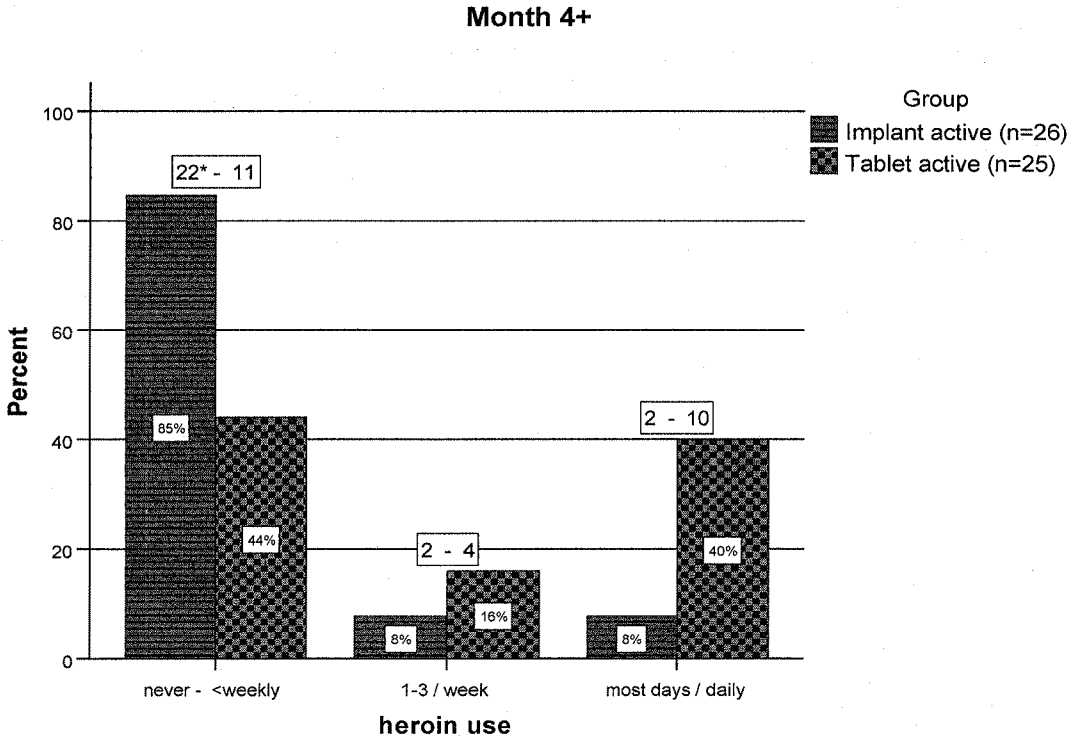
This potential bias is however not supported by other published work of a significant reduction in opiate overdose associated with naltrexone implant treatment in a sequential cohort of 361 first time implant treated patients. No opioid overdose were identified in the first

6 months, with a reduced number (n=7) in the 6 to 12 months post implant treatment, compared to 21 opioid overdoses involving 20 persons in the 6 months before treatment [12]. This period of prophylaxis against opioid overdose is consistent with the reported pharmacokinetic data [8].

Bio-Compatibility and Biodegradability: Recently an analysis of histological reactions proximal to implants has been published. Human in vitro assessment of tissue samples (biopsies) from 54 subjects (34 males) at various periods of time post-implant showed an early phase (up to 12 months post-implant) of inflammation, foreign body reaction, and fibrosis, which gradually settles over the next 12 months until tissue returned to normal by 25+ months [13]. We have also submitted a manuscript on biodegradation that found implants were no-longer detectable by ultrasound after 1085 days post insertion, with 20% biodegradation of original mass within 498 (mean) days.

NH&MRC (303106) A randomised double blind placebo controlled clinical trial of naltrexone implants for the treatment of heroin addiction:

The clinical efficacy of this implant compared to oral naltrexone is the subject of a current NH&MRC clinical study. Full recruitment of the 70 patients has taken place, and 51 participants have at least 4 months follow-up. In the active oral naltrexone arm, 40% were using heroin more than 3 times per week or were lost to follow-up. In the active implant arm 8% were using >3 times per week or lost to follow-up (a further 3 people had moved to illicit buprenorphine use and one was in jail and could not be interviewed) (see attached graph). At 4 months 2.4% of urine tests from the active implant group showed opioid use compared to 14.7% in the active oral group.



N.B. In NHMRC project grant application (513879), one case was listed as in prison: data has subsequently been collected on this person.

* Includes 3 cases using Subutex illicitly

REQUIRED INFORMATION

1. **Multi-centre trial of naltrexone implant compared with methadone or buprenorphine in the management of heroin dependent persons**
Although there is a preliminary basis for believing that this naltrexone implant treatment may offer significant benefits over oral (or other naltrexone depot) preparations, there are no data comparing its efficacy with buprenorphine or methadone. A proposal to investigate this is the subject of a current NH&MRC funding application.

2. **Comparing Long-term Mortality in Opioid Users Treated with Naltrexone Implant, Buprenorphine or Methadone Maintenance** Limited data from some research groups suggest elevated naltrexone mortality potentially due to: withdrawal related problems during induction, increased suicidal ideation and accidental overdose during maintenance, as well as accidental overdose post-treatment. These outcomes were not observed in our early studies of naltrexone implants. Nevertheless, an accurate and reliable estimate of mortality associated with naltrexone implants is urgently needed to help assess the safety of these products. This will require a sufficiently large cohort of patients who will be followed up for several years, from induction into post-treatment, and a comprehensive method to search and identify mortality outcomes among treated patients. This should be compared to person receiving methadone or buprenorphine maintenance. A proposal to investigate this is the subject of a current NH&MRC funding application. (This will involve a 5 Year Follow-up of approximately 1600 naltrexone implant; 1474 buprenorphine and 1965 methadone treated patients).

3. **Follow-up of neonates and infants exposed to naltrexone (Human follow-up & animal data).** This involves several approaches. First, collection of human data on existing births via hospital record linkage to identify all relevant infants exposed to either implantable or oral naltrexone and assemble general outcome (hospital morbidity data) should be undertaken. Individual assessment should also be conducted on infants / young children exposed to naltrexone to assess developmental milestones compared to normative values. Second, experimental data from animal models are urgently required as this would help to inform the testing regime of humans if specific deficits were identified. The latter proposal is the subject of a current NH&MRC grant application.

4. **Role of GoMedical implant in the management of alcohol & other drug problems.** Oral naltrexone is approved for use in the treatment of alcohol dependence and one sustained release product has been approved for use in the condition in the USA (Vivitrol).

5. **Role of other sustained preparations in the management of heroin (or alcohol) dependence (i.e. prison release).**

6. **Impact of naltrexone implant, buprenorphine or methadone maintenance on the course of HCV/HBV/HIV infection.** A recent publication [14] has shown the eradication of HVC in patients undergoing implant treatment. In contrast buprenorphine and methadone are thought to suppress immune response. Therefore, these agonist treatments may be sub-optimal in those with HCV, HVB or HIV and this requires further investigation.

Appendix A.

Mortality Associated with Heroin Use

World-wide, about 0.4% of the adult population abuses opioids, but this category of illicit drug use accounts for nearly 60% of treatment demand in Europe and Asia [15]. Opioid use is also associated with a high level of mortality, with a meta-analysis reporting 8.6 deaths per 1000 person-years [16]. A European multi-centre analysis reported standardised mortality ratios (SMRs) ranging from 6.3 to 53.7 compared to the general population [17] with a meta-analysis giving a combined SMR ratio of 13.2 compared to the general population [16]. As these deaths occur at a young age, the number of person years lost is extremely high, resulting in an enormous waste of human life and unfulfilled potential. According to an Australian review, the number of deaths due to opioid overdose increased from 70 in 1979 to 550 in 1995 [18]. Overall, the rate per million increased from 10.7 to 67.0 over the same time period (for the population aged 15-44 years). However, after reaching a peak in 1999 (112.5 / million), the number of deaths has declined with the "heroin drought" in Australia [19] with, for example, a 43% decline in the number of heroin deaths in New South Wales between 1995 and 2003 [20].

Appendix B.

Methadone: MMT has been the main pharmacotherapy for the management of heroin dependence and has been available in Australia since 1970, and in Western Australia since 1973. MMT results in significantly less heroin use than placebo or other psychological therapies in the short to medium term [1].

Methadone maintenance treatment is the best-established treatment for opioid dependence with the relevant National Consensus Development Panel (USA) reporting that those in MMT had a 30% lower mortality rate than opioid dependent persons not in treatment [21]. A significant body of evidence also suggests improvements across a broad range of health and social indicators associated with MMT, including reductions in illicit opioid and other drug use, unemployment, obstetric and foetal complications, transmission of blood-borne infection, and criminal activity [22, 23].

Negative aspects include its' potential to produce and/or maintain dependence on opioids, with patients experiencing withdrawal if doses are missed, as well as a continued option to return to or combine heroin use, with a number of patients continuing intermittent heroin use and having some contact with the narcotic network years after commencement of MMT [1]. Additionally, because of its full agonist action, there is no limit to the level of respiratory depression or sedation that methadone can induce, and methadone overdose (often in combination with heroin and other CNS depressant drugs) can therefore be fatal. Strategies aimed at preventing diversion to non-registered users or injection of methadone syrup (a cause of high mortality in those on MMT [2]), such as abolition of takeaway doses have detracted from the claim that methadone is "compatible with normal performance in work and at school" [24].

Buprenorphine: Buprenorphine hydrochloride (Subutex®; Suboxone®) a sublingually administered partial μ (mu) opiate receptor agonist and κ (kappa) opiate receptor antagonist was recently listed on the Australian Pharmaceutical Benefits Scheme (PBS) for both detoxification and maintenance of opioid dependence treatment.

Buprenorphine is a partial opioid agonist, which decreases the risk of opioid overdose compared to MMT. A French study [25] estimated a buprenorphine related death rate as being only one-third of that related to MMT. Many investigators attributed this reduced mortality to the 'ceiling' effect of respiratory depression of buprenorphine at high dose [26], although others

disagreed [27, 28]. An Australian assessment [29] using the National Coronial Information System to identify MMT, buprenorphine and naltrexone related deaths in heroin users estimated deaths per 1000 treatment episodes. Buprenorphine had the fewest deaths 0.02, compared with 2.7 for MMT and 10.1 for oral naltrexone [29].

One criticism of both MMT and buprenorphine is that they prolong the duration of opioid dependence, with many patients continuing co-heroin use [1], with poor outcomes, including return to heroin dependence following cessation [30].
Buprenorphine has for several years been used extensively in a number of countries. In France, doctors have been able to prescribe buprenorphine without specialist education or licensing since 1995. Consequently, buprenorphine is used to treat ten times more opiate addicted patients when compared to methadone, which has more restrictive prescribing protocols. It is estimated that half of France's 150,000 heroin addicts now receive buprenorphine, however, around 20% are suspected of intravenous diversion [31]. Evidence suggests diversion also occurs in Australia, though the exact rate is unclear [32]. One method of reducing its' abuse liability without affecting bioavailability has been to add naloxone hydrochloride to buprenorphine in a ratio of 1:4 in 2mg and 8mg tablets (Suboxone® (Reckitt Benckiser)) [33]. Sublingual administration of Suboxone does not affect absorption of buprenorphine through the mucous membrane because naloxone is poorly absorbed via this route. However, when injected, naloxone reaches the μ receptors more readily thereby precipitating withdrawal in a heroin dependent person. The reduced risk of abuse and overdose with Suboxone® raises the possibility of providing extended dosing to certain patients where compliance is more assured [34] and to facilitate compliance in otherwise non-compliant patients. Suboxone® was PBS listed in April 2006.

Appendix C.

Naltrexone's Antagonism of Heroin

The ability of naltrexone to effectively antagonise heroin use is unequivocal. Challenge studies have shown that serum naltrexone levels of 2.8ng/ml are effective in blocking 500mg of snorted pure pharmaceutical diamorphine [35]. Serum naltrexone levels ≤ 2ng/ml [36, 37] have been found to be effective in blocking the effects of 25mg intravenously administered heroin, and others have reported plasma levels of less than 1 ng/ml as being capable of antagonising the effects of 15mg morphine [38]. However, patients should be warned to the danger of overdose if they do attempt to override the blockade provided by naltrexone will large doses of opioids.

Appendix D.

Newer Formulations of Sustained-Release Naltrexone

Injectable formulations of naltrexone, such as those produced by Biotek, Inc. (Depotrex®) [9] Drug Abuse Sciences (Naltrel®) [39] and Alkermes, Inc. (Vivitrol®) [40] appear to produce both clinically relevant plasma concentrations of naltrexone (1-2ng/ml) for approximately 3–6 weeks, with clinically acceptable incident level of tissue reactivity. For example, an injectable, depot formulation of naltrexone (Depotrex®, 192 mg, 384 mg naltrexone base) antagonized the effects of intravenously-administered heroin (0-25 mg) for 3-5 weeks, depending on naltrexone dose. This study demonstrated that Depotrex® was safe, effective, and well tolerated in opioid abusers [9]. A subsequent "proof-of-concept" clinical trial of Depotrex® in treatment-seeking heroin abusers showed a robust, dose-related increase in treatment retention, supporting the use of depot naltrexone as a therapeutic strategy for opioid dependence [5]. Alkermes, Inc. (Vivitrol®) has now been approved for use in the USA for

management of alcohol dependence, and it is likely to be registered for the management of heroin dependence within the next few years.

Appendix E.

Mortality Associated with Naltrexone Treatment

The Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) reported that there were no deaths for those on oral naltrexone during treatment (44.4 person-years), but there were 3 deaths in 62.2 person-years of observation out of treatment, giving an overall mortality rate of 28/1000 person years [41]. This compares with no deaths in 141.3 person-years for MMT and 1 death in 100.4 person-years for buprenorphine [41].

As for implantable naltrexone, ultra-rapid opiate detoxification using some U.S.A. sustained release naltrexone products has been associated with serious and sometimes fatal complications, with 12 deaths linked with the procedure [42]. Three fatal overdoses related to the transition from implant to oral treatment were identified in a case study in the UK [43]. The overdose was subsequent to the implants being removed due to infection in two cases; in the third case, it was due to delay in re-treatment [43]. More recently, in Australia, using the National Coronial Information System, five deaths related to naltrexone implant have been identified for the period 2000-2004 [44].

In addition, some possible problems may be common to both sustained release and oral naltrexone treatment. It has been suggested that naltrexone can increase rates of depression and associated suicide, although research findings on this subject are mixed [45-47]. Naltrexone has been shown to suppress *subjective* effects of opioids more than *objective* physiological effects [37, 48]. This may increase the risk of opioid overdose, when an unusually high dose is taken to override the suppressed euphoric effect, while physiological effects (e.g., respiratory depression) remain potent [41]. The potential for naltrexone treatment to reduce tolerance, or increase sensitivity, to opioids has also been suggested as an explanation for the increase in opioid overdoses observed when patients cease naltrexone treatment [41]. Finally, because opioid overdoses are likely to occur once a person ceases treatment and thus very minimal (or no) blood naltrexone can be detected in autopsy, naltrexone related deaths can easily be overlooked when searching for coronial records that mention "naltrexone" [29].

Appendix E. Thus, although methadone results in many improvements compared to continued heroin use, it is unsatisfactory mainly because of the high rate of neonatal abstinence syndrome [49]. Other effects include depression of fetal activity, heart rate and respiration and an increase in intrauterine growth retardation and mortality compared to the drug-free population [50-52]. Compared to methadone, buprenorphine is associated with a reduced incidence and severity of neonatal abstinence syndrome but there is a higher rate of other drug abuse [53, 54].

References

1. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev.* DOI: 10.1002/14651858.CD002207.pub2 2005:CD002207.
2. Hando J, Hall W, Rutter S, Dolan K. *An information document on the current state of research on illicit drugs in Australia*Sydney: University of New South Wales; December 1998 1998.
3. Hulse GK, Basso MR. The association between naltrexone compliance and daily supervision. *Drug Alcohol Rev.* 2000;19:41-48.
4. Chiang CN, Hollister LE, Kishimoto A, Barnett G. Kinetics of a naltrexone sustained-release preparation. *Clin Pharmacol Ther.* 1984;36:704-708.
5. Comer S, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dackis C, O'Brien CP. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. *Arch Gen Psychiatry.* 2006;63:210-218.
6. Caswell A. *MIMS Bi-Monthly 4th ed.* Sydney, Australia: CMPMedica Australia; 2005.
7. Roozenburg B, van Dessel H, Evers J, Bots R. Successful induction of ovulation in normogonadotrophic clomiphene resistant anovulatory women by combined naltrexone and clomiphene citrate treatment. *Hum. Reprod. Update.* 1997;12:1720-1722.
8. Hulse GK, Arnold-Reed DE, O'Neil G, Chan CT, Hansson R, O'Neil P. Blood naltrexone and 6-β-naltrexol levels following naltrexone implant: comparing two naltrexone implants. *Addict Biol.* 2004;9:59-65.
9. Comer SD, Collins ED, Kleber HD, Nuwayser ES, Kerrigan JH, Fischman MW. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology (Berl).* 2002;159:351-360.
10. Galloway GP, Koch M, Gross J, Smith DE. Safety, tolerability and pharmacokinetics of a sustained-release formulation of naltrexone in alcoholics. *Drug Alcohol Depend.* 2001;63:S52.
11. Johnson BA, Ait-Daoud N, Aubin H-J, van den Brink W, Guzzetta R, Loewy J, Silverman B, Ehrich E. A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex (R)) in patients with alcohol dependence. *Alcohol Clin Exp Res.* 2004;28:1356-1361.
12. Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed DE. Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend.* 2005;79:351-357.
13. Hulse GK, Stalenberg V, McCallum D, Smit W, O'Neil G, Morris N, Tait RJ. Histological changes over time around the site of sustained release naltrexone-poly(DL-Lactide) implants in humans. *J Control Release.* 2005;108:43-55.
14. Jeffery GP, MacQuillan G, Chua F, Galhenage S, Bull J, Young E, Hulse G, O'Neil G. Hepatitus C virus eradication in intravenous drug users maintained with subcutaneous naltrexone implants. *Hepatology.* 2007;45:111-117.
15. United Nations Office of Drugs and Crime. *World Drug Report: Volume 1 Analysis.* Vienna: United Nations Publication; 2006.
16. Hulse GK, English DR, Milne E, Holman CDJ. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction.* 1999;94:221-229.
17. Bargagli AM, Hickman M, Davoli M, Perucci CA, Schifano P, Buster M, Brugal T, Vicente J. Drug-related mortality and its impact on adult mortality in eight European countries. *Eur J Public Health.* 2006;16:198-202.

18. Hall W, Darke S. Trends in opiate overdose deaths in Australia 1979-1995. *Drug Alcohol Depend.* 1998;52:71-77.
19. Longo MC, Henry-Edwards SM, Humeniuk RE, Christine P, Ali RI. Impact of the heroin 'drought' on patterns of drug use and drug-related harms. *Drug Alcohol Rev.* 2004;23:143-150.
20. Degenhardt LJLJ, Conroy EE, Gilmour SS, Hall WDWD. The effect of a reduction in heroin supply on fatal and non-fatal drug overdoses in New South Wales, Australia. *Med J Aust.* 2005;182:20-23.
21. National Consensus Development Panel. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA.* 1998;280:1936-1943.
22. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. *JAMA.* 1998;280:1936-1943.
23. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. *Mount Sinai J Med.* 2000;67:347-364.
24. Dole V, Nyswander ME, Kreek MJ. Narcotic blockade. *Arch Intern Med.* 1966;118:304-309.
25. Auriacombe M, Franques P, Tignol J. Deaths Attributable to Methadone vs Buprenorphine in France. [Letter]. *JAMA* 2001;285:45.
26. Lintzeris N, Clark N, Winstock A, Dunlop A, Muhleisen P, Gowing L, Ali R, Ritter A, Bell J, Quigley A, Mattick R, Monheit B, White J. National Clinical Guidelines and Procedures for the Use of Buprenorphine in the Treatment of Opioid Dependence. Accessed 11-01-2007.
27. Kintz P. Deaths involving buprenorphine: a compendium of French cases. *Forensic Science International.* 2001;121:65-69.
28. Schifano FF, Corkery JJ, Gilvarry EE, Deluca PP, Oyefeso AA, Ghodse AHAH. Buprenorphine mortality, seizures and prescription data in the UK, 1980-2002. *Hum Psychopharmacol.* 2005;20:343-348.
29. Gibson A, Degenhardt L. *Mortality Related to Naltrexone in the Treatment of Opioid Dependence: A Comparative Analysis.* Technical Report No. 229. Sydney: National Drug and Alcohol Research Centre; 2005.
30. Kornor H, Waal H. From opiod maintenance to abstinence: a literature review. *Drug Alcohol Rev.* 2005;24:267-274.
31. Auriacombe M, Fatseas M, Dubernet J, Daulouede J, Tignol J. French field experience with buprenorphine. *Am J Addict.* 2004;13:S17-28.
32. Feeney GFX, Fairweather P. Groin tissue necrosis requiring skin graft following parenteral abuse of buprenorphine tablets. *Drug Alcohol Rev.* 2003;22:359-361.
33. Benckiser R. Treating Opioid Dependence. 2004; www.suboxone.com.
34. Federal Drug Authority Center for Drug Evaluation and Research. Subutex and Suboxone. 8 October 2002; www.fda.gov//cder/drug/infopage/subtex_suboxone/subtex-qa.htm.
35. Brewer C. Serum naltrexone and 6-beta-naltrexol levels from naltrexone implants can block very large amounts of heroin: a report of two cases. *Addict Biol.* 2002;7:321-323.
36. Navaratnam V, Jamaludin A, Raman N, Mohamed M, Mansor SM. Determination of naltrexone dosage for narcotic agonist blockade in detoxified Asian addicts. *Drug Alcohol Depend.* 1994;34:231-236.
37. Verebey K, Volavka J, Mule SJ, Resnick RB. Naltrexone: disposition, metabolism, and effects after acute and chronic dosing. *Clin Pharmacol Ther.* 1976;20:315-328.

38. Chiang CN, Hollister LE, Gillespie HK, Foltz RL. Clinical evaluation of a naltrexone sustained-release preparation. *Drug Alcohol Depend.* 1985;16:1-8.
39. Kranzler HR, Wesson DR, Billot L, Drug Abuse Sciences Naltrexone Depot Study Group. Naltrexone depot for treatment of alcohol dependence: A multicenter, randomized, placebo-controlled clinical trial. *Alcohol Clin Exp Res.* 2004;28:1051-1059.
40. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW, Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA.* 2005;293:1617-1625.
41. Digiusto E, Shakeshaft A, Ritter A, O'Brien S, Mattick RP, The NEPOD Research Group. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). *Addiction.* 2004;99:450-460.
42. Hamilton RJ, Olmedo RE, Shah S, Hung OL, Howland MA, Perrone J, Nelson LS, Lewin NL, Hoffman RS. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med.* 2002;9:63-68.
43. Oliver P, Horspool M, Keen J. Fatal opiate overdose following regimen changes in naltrexone treatment (letter). *Addiction.* 2005;100:560-561.
44. Gibson A, Degenhardt L, Hall W. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust.* 2007;186:152-153.
45. Miotto K, McCann M, Basch J, Rawson R, Ling W. Naltrexone and dysphoria: fact or myth?[see comment]. *Am J Addict.* 2002;11:151-160.
46. Ngo H, Tait R, Arnold-Reed D, Hulse GK. Mental Health Outcomes Following Naltrexone Implant Treatment for Heroin Dependence. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2006;accepted 5 Dec 2006.
47. Ritter AJ. Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose. *Aust N Z J Psychiatry.* 2002;36:224-228.
48. Schuh KJ, Walsh SL, Stitzer ML. Onset, magnitude and duration of opioid blockade produced by buprenorphine and naltrexone in humans. *Psychopharmacology.* 1999;145:162-174.
49. Ebner N, Rohrmeister K, Winklbaur B, Baewert A, Jagsch R, Peternell A, Thau K, Fischer G. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. *Drug Alcohol Depend.* 2007;87:131-138.
50. Jansson LM. Methadone Maintenance and Lactation: A Review of the Literature and Current Management Guidelines. *J. Hum. Lact.* 2004;20:62-71.
51. Ramirez-Cacho W, Flores S, Schrader R, McKay J, Rayburn W. Effect of chronic maternal methadone therapy on intrapartum fetal heart rate patterns. *J Soc Gynecol Investig.* 2006;13:108-115.
52. Wouldes TA, Roberts AB, Pryor JE, Bagnall C, Gunn TR. The effect of methadone treatment on the quantity and quality of human fetal movement. *Neurotoxicology & Teratology.* 2004;26:23-34.
53. Fischer G, Ortner R, Rohrmeister K, Jagsch R, Baewert A, Langer M, Aschauer H. Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction.* 2006;101:275-281.
54. Nocon JJ. Buprenorphine in pregnancy: The advantages (letter). *Addiction.* 2006;101:608.