The Royal Australasian College of Physicians

The Use of Sustained Release Formulations of Naltrexone in Opioid Dependence

Position Statement

April 2013

The RACP's Australasian Chapter of Addiction Medicine is responsible for this position statement

1 Acknowledgements

The Royal Australasian College of Physicians (RACP) gratefully acknowledges the efforts of the Working Group of the Australasian Chapter of Addiction Medicine who produced this document:
Dr Leon Nixon M.B. Ch.B. Ph.D. FAChAM
Addiction Medicine Specialist, Department of Health, Northern Territory
Health House, 87 Mitchell Street
Darwin NT 0810

Prof Paul Haber FRACP FAChAM
Medical Director, Drug Health Services | Sydney South West Area Health Service
Discipline of Addiction Medicine | Faculty of Medicine
Royal Prince Alfred Hospital
Missenden Road
Camperdown NSW 2050

Dr. Alex Wodak AM,
Emeritus Consultant, Alcohol and Drug Service, St Vincent's Hospital
Visiting Fellow, Kirby Institute, UNSW
President, Australian Drug Law Reform Foundation
Darlinghurst NSW 2010

A/Prof Nicholas Lintzeris MBBS, PhD, FAChAM
Director, Drug and Alcohol Services, SESLHD
Chief Addiction Medicine Specialist, Mental Health Drug & Alcohol Office, NSW Ministry of Health
The Langton Centre, 591 South Dowling Street, Surry Hills, NSW, Australia, 2010

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Author:	Australasian Chapter of Addiction Medicine, The Royal Australasian College of Physicians
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2 Purpose

The Royal Australasian College of Physicians (RACP) does not support the routine use of sustained release naltrexone formulations (implants or depot injections) while the product is not registered with the Therapeutic Goods Administration (TGA).

The current RACP position statement is not intended as a literature review and has the following objectives:

1. To present the views of the RACP of sustained release naltrexone formulations that are not registered with the TGA.

2. To highlight circumstances where treatment with unapproved sustained release naltrexone formulations could be considered acceptable, and

3. To present the conditions that should be met to protect consumers and health care professionals when using sustained release naltrexone formulations.

3 Executive Summary

The Royal Australasian College of Physicians (RACP) does not support the routine use of sustained release naltrexone formulations (implants or depot injections) while the product is not registered with the TGA.

The controversy in this area of medical practice is acknowledged. However, the rate of both good and adverse outcomes and the outcome relative to other treatment options remains unclear. Until naltrexone implants are proven safe and efficacious, through formal clinical trials against the gold standard, proven therapies such as methadone and buprenorphine should continue to be the preferred medication to treat opioid dependency.

The only circumstances where treatment with an unapproved sustained release naltrexone formulation could be considered to be acceptable is in the context of formal clinical trials approved by a human research ethics committee (meeting the National Health and Medical Research Council (NHMRC) guidelines) to determine the efficacy, safety and cost effectiveness of long-acting naltrexone formulations in Australia. In such cases, the following criteria should be met and are explained in detail below:

1. *Informed consent* should be obtained in writing from the patient without coercion from other parties

2. *Specialist patient assessment* should be performed before commencing treatment with unlicensed long-acting naltrexone products

3. *Good clinical follow-up and care* is needed to address complications and adverse events

4. *Continued independent research* to establish the safety, efficacy and cost effectiveness of long-acting naltrexone products

5. *Ongoing monitoring of the appropriateness, safety and effectiveness of treatment with unlicensed products.*

4 Background

Abstinence can be a valid goal of treatment for people with alcohol and drug problems. For some, this can be safely achieved through involvement in appropriate ambulatory or residential rehabilitation treatment. For most people dependent on heroin or other opioids, approved opioid replacement treatment (ORT) programs remain the “gold standard” (1).

Naltrexone is an opioid antagonist that works by binding to opioid receptors in the brain without activating them, therefore blocking the effects of opioids (for example heroin and morphine). Naltrexone blocks both the analgesic and euphoric effects of opioids on the receptor sites. Naltrexone does not cause dependence.

Naltrexone is quickly absorbed after oral administration and will dose-dependently block the pharmacological effects of heroin for up to 72 hours. The drug is, however, subject to first pass metabolism and bioavailability varies from 5 to 40%.

Naltrexone should be seen as a medication which may help selected patients to remain abstinent, rather than a medication which reduces patients’ desire to use heroin. Limited compliance with oral naltrexone has led to the development of both one month and six month depot formulations. These depot products are now approved in Russia and in the USA by the United States of America Food and Drug Administration for treating opioid dependence (2) but not yet approved by the TGA in Australia.

4.1 Clinical research on the use of long-acting naltrexone formulations

A 2008 Cochrane review concluded that ‘there is insufficient evidence from randomised controlled trials to evaluate the effectiveness of sustained-release naltrexone” (3). Two published randomised controlled clinical trials (RCT) on naltrexone implants were considered in the review by the NHMRC (4). The NHMRC concluded in relation to efficacy that ‘caution should be exercised in interpreting the results of these studies as the sample sizes were small, duration of treatment and follow up was inadequate, the comparators inappropriate and many studies reported on the same base cohort’. The review also noted ‘Further research on adverse events is required before a statement about safety can be confidently made.’ The NHMRC concluded overall that ‘naltrexone implants are an experimental product and as such should only be used in the context of a well conducted RCT with sufficient sample size, appropriate duration of treatment and follow up, regular robust monitoring, provision of a comprehensive psychosocial treatment program and with comparison to current best practice. Until these trials have occurred and the relevant data are available and validated, the efficacy of the treatment, alone or in comparison to conventional first line treatment, cannot be determined.

A number of other important publications have appeared since the NHMRC review (5-7). For example, Kelty and Hulse (5) have reported on the mortality in cohorts of patients treated with oral and implant naltrexone. Some concerns with the methodology of this study have been raised including the comparison used; it was suggested that comparison with currently accepted modes of treatment such as opioid substitution treatment would be more appropriate.

There are some published reports of deaths attributable to naltrexone implants (8-10) and other reports claiming significantly reduced mortality (11). Further research is needed to establish the risk of mortality during and after treatment with naltrexone implants and other treatment approaches (including methadone and buprenorphine), and in comparison with these other treatments to better understand the following factors:

a. Risk factors for relapse - in order to strengthen relapse prevention strategies

b. Rates of development of other alcohol and drug problems. Is sustained release naltrexone protective or do patients transfer active addiction to another substance?
c. Effect of motivation, social support and supplementary treatments (individual, family or group therapy) on patient outcomes i.e. abstinence or relapse

d. Therapeutic blood levels of naltrexone and the duration for which the implant or depot preparation maintains therapeutic naltrexone levels

e. Optimal dosing and minimal effective dose

f. Safety over longer duration of treatment and post treatment

g. Efficacy of naltrexone implants in relation to injectable depot preparations and best practice treatments

4.2 Opiate Replacement Therapy (ORT)

Opiate Replacement Therapy (ORT) involves replacing a short-acting agonist opiate, such as heroin, with a longer acting but less euphoric agonist opiate such as methadone, or with the partial agonist, buprenorphine. A buprenorphine/naloxone combination (buprenorphine-with-naloxone sublingual tablets) formula as listed on the Pharmaceutical Prescribing Scheme (PBS) in 2011 is becoming more popular on the basis that naloxone, which is a short acting antagonist, limits the abuse potential of buprenorphine alone products (naloxone is used to discourage injection of buprenorphine. Naloxone is poorly absorbed sublingually and orally but if injected can reduce the agonist effects of buprenorphine and may precipitate unpleasant withdrawal symptoms in people who are opioid dependent).

Such therapies have been used for more than 40 years in Australia in the treatment of opioid dependence. They have been recognised as the 'best-practice' in reducing harm and supporting sustainable change. The use of longer-acting, orally or sublingually well-absorbed opioids over shorter acting and injectable opioids achieves substantial health, social and economic gains because of their superiority in maintaining therapeutic plasma levels.

By providing a consistent dose of long acting opioids, ORT removes the need for injecting drug use, reduces cravings and the risk of overdose, and prevents withdrawal symptoms. ORT is available for a fraction of the cost of illicit opioids. Opiate replacement therapies have been shown to reduce drug use, improve health, improve social functioning, reduce blood-borne virus transmission and reduce criminal activity (1). Over the long term, the stability provided by remaining on ORT allows patients the opportunity to make sustainable changes to their health, lifestyle and family relationships. Furthermore, expanding current methadone and buprenorphine treatment programs would make them more affordable to drug users, who generally have low incomes. This action would also make the black market for opioids less lucrative.

The pharmacotherapies for the management of opioid dependence that are available in Australia include both methadone and buprenorphine.

Methadone taken orally on a daily basis is currently the most common pharmacotherapy used in Australia and is recognised nationally and internationally as an effective method for treating opioid dependence. Methadone reduces the use of heroin through cross tolerance which results in a reduction of heroin withdrawal symptoms, less desire to use heroin, and reduced euphoric effect when heroin is used.

Buprenorphine, a longer acting opioid, offers potential advantages over methadone in terms of the relative ease of withdrawal, the need for less frequent administration, ease of transition into other treatments and flexibility of treatment. Buprenorphine is a partial opioid agonist with high receptor affinity but low intrinsic activity. It has actions similar to the full agonist drugs but with less efficacy such that increases in dose have progressively less increase in effect. In opioid tolerant people the receptor blockade state is reached below the threshold for loss of consciousness and suppression of respiration which is usually associated with opioid overdose. Nevertheless, fatal respiratory depression may occur when buprenorphine is used in conjunction with other central nervous system depressants.

The World Health Organisation, UNODC (United Nations Office on Drugs and Crime) and UNAIDS (United Nations Program on AIDs/HIV) have endorsed treatment with methadone and buprenorphine (12). The World Health Organisation has included methadone and buprenorphine in its Essential Medicines List. Naltrexone has not been endorsed by any United Nations organisations nor is it included on the Essential Medicines List (13).

5 Recommendations

The RACP does not support the routine use of sustained release naltrexone formulations (implants or depot injections) while the product is not registered with the TGA.

More research on effectiveness and safety is needed in support of sustained release naltrexone treatment for opioid dependency. Further research comparing sustained release preparations with the gold standard and, preferably, opioid agonist medications will help characterise the role of opioid antagonist-mediated treatment of opioid dependency.

The only circumstances where treatment with an unapproved sustained release naltrexone formulation could be considered acceptable is in the context of formal clinical trials approved by a human research ethics committee (meeting NHMRC guidelines) to determine the efficacy, safety and cost effectiveness of long-acting naltrexone formulations in Australia.

In these situations, a range of safeguards must be implemented to protect patients, their families, and health professionals. These include:

5.1 Informed consent should be obtained in writing from the patient without coercion from other parties (such as relatives, social agencies or health care professionals). Potential patients should be informed (verbally and in writing):

a. of the range, usual outcomes and adverse events of conventional treatment approaches for opioid dependence in Australia
b. that naltrexone products are not licensed for opioid treatment in Australia or in practically any other countries with comparable regulatory systems
c. that evidence for the safety and effectiveness of naltrexone implants is still emerging, but has not yet been established
d. of the range of potential adverse events and other consequences (for example: impaired opioid analgesia) associated with long-acting naltrexone products, and how these will be addressed in the event that they occur
e. of the costs of implant treatment and ancillary care and the likely costs of future treatment. All of these costs should be explained clearly to patients and compared with the costs of alternative treatment approaches.

5.2 Specialist patient assessment Potential patients should have a comprehensive assessment by a suitably qualified specialist in addiction medicine before commencing treatment with unlicensed long-acting naltrexone products. Assessment should include the patient's psychoactive drug use, treatment history, medical, psychiatric and cognitive conditions, social circumstances, willingness and capacity to engage in ongoing psychosocial treatment, and the perspectives of other relevant health professionals engaged in the patient's care. The assessment should confirm the presence of opioid dependence and the unsuitability or unavailability of opioid maintenance treatment, or the patient's informed decision to prefer antagonist rather than opioid maintenance or residential rehabilitation treatment.

5.3 Good clinical follow-up and care is needed to address complications and adverse events to ensure satisfactory progress is being made and to identify the recurrence or development of other substance use problems.

5.4 Continuing research *to establish the safety, efficacy and cost effectiveness of this treatment approach.* Such research should be independently conducted in accordance with NHMRC constituted Human Research Ethics Committees and the TGA regulatory processes. The research should be of sufficient quality to generate new clinical evidence and should involve adequate numbers of subjects, appropriate controls, and sufficient follow-up periods.

5.5 The establishment of robust mechanisms for monitoring the appropriateness, safety and effectiveness of treatment with unlicensed products, including a process of case review by relevant professional and regulatory groups. There are inadequate safeguards currently in place to ensure that unlicensed treatments are delivered safely, and to appropriate patients groups. The current special access scheme (SAS) system of the TGA provides no mechanism for professional bodies or regulatory groups to monitor the use of unlicensed products enabling unlicensed treatment approaches to be widely delivered to vulnerable populations without appropriate regulatory review. The SAS was not intended to provide a pathway for routine use of non-approved medications. A national register is required to ensure that patients have been appropriately selected, and treatment safely and effectively delivered. The establishment of a register will require funding and should be administered by an appropriate body independent of treatment agencies after an open tendering process.

In summary, The RACP does not support the routine use of sustained release naltrexone formulations (implants or depot injections) while the product is not registered with the TGA. Furthermore, randomised controlled clinical trials to determine the effectiveness and safety are needed in support of sustained release naltrexone treatment for opioid dependency.

References

1. *Stotts, A; Dodrill, CL and Koste, TR. Opioid dependence treatment: options in pharmacotherapy. Expert Opinion on Pharmacotherapy (2009), 10: 1727-1740 (doi:10.1517/14656560903037168)*

2. *FDA approves injectable drug to treat opioid-dependence patients, U.S. Food and Drug Administration press announcement http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm (accessed Feb 15, 2012).*

3. *Lobmaier P, Kornor H, Kunoe N, Bjørndal A. Cochrane: Sustained-Release Naltrexone for Opioid Dependence. http://onlinelibrarywileycom/o/cochrane/clsysrev/articles/CD006140/framehtml 2008.*

4. *NHMRC Naltrexone implant treatment for opioid Dependence Literature Review: Naltrexone implant treatment for opioid dependence - Literature Review (2011) (PDF, 330KB); accessed Feb 15, 2012*

5. *Kelty E and Hulse G: Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opioid use. Addiction (2012) 107:1817-24.*

6. *Krupitsky, E: Injectable extended-release naltrexone for the prevention of relapse to opioid dependence following opioid detoxification. Neuropsychiatry (2012) 2, 355–362*

7. *Hickman, M., Degenhardt, L., Farrell, M. and Hall, W. Commentary on Kelty & Hulse (2012): Is the comparison of mortality between patients prescribed implanted or oral naltrexone an unbiased and unconfounded comparison? Addiction, (2012), 107: 1825–1826. doi: 10.1111/j.1360-0443.2012.03966.x*

8. *Gibson AE, Degenhardt LJ, Hall WD. Opioid Overdose deaths can occur in patients with naltrexone implants. Medical J. Australia 2007; 186: 152-153*

9. *Gibson AE and Degenhardt LJ, Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. Drug Alcohol Rev, (2007): 26 405-10*

10. *Olivier, P; Fatal opiate overdose following regimen changes in naltrexone treatment, letter to the Editor. Addiction, (2005): 100, 560–563 doi:10.1111/j.1360-0443.2005.01020.*

11. *Ngo HT, Tait RJ, Hulse GK. Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation., Arch Gen Psychiatry (2008); 65*

12. *Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention: position paper / World Health Organization, United Nations Office on Drugs and Crime, UNAIDS (United Nations Program on AIDs/HIV) (http://www.unodc.org/documents/hiv-aids/PositionPapersub.maint.therapy.pdf)*

13. *Herget G: Methadone and buprenorphine added to the WHO list of essential medicines. HIV AIDS Policy Law Rev. 2005 10: 23-4 (http://www.ncbi.nlm.nih.gov/pubmed/16544403*