The Royal Australasian College of Physicians

The Royal Australasian College of Physicians (RACP) Position Statement on Naltrexone Treatment

Developed by Chapter of Addiction Medicine, RACP

The Royal Australasian College of Physicians (RACP) recognises that long-acting naltrexone products may ultimately prove to be a safe and effective treatment approach for opioid dependence. Accordingly, it is appropriate to support the development of registered products that safely and effectively deliver this treatment. However, until suitable product(s) have undergone normal regulatory assessment procedures and are licensed with the Therapeutics Goods Administration (TGA), unregistered products should not be used on a routine basis and a range of safeguards are required to protect patients, their families, and health professionals.

Safeguards are required in the introduction of experimental treatment in all areas of medicine. Safeguards are particularly pertinent in the treatment of opioid dependent populations, who are often marginalised, desperate and vulnerable. This population is also often subjected to extreme pressure to undertake treatment from their family or authorities.

Recommendations

The RACP believes that the following appropriate safeguards should be followed when considering the use of unlicensed naltrexone implants.

1) *Unlicensed treatments should generally be reserved for clinical trials. If ever considered as a 'second-line' option for patients with terminal conditions not responding to conventional treatments, applications should be made and promptly considered by independent experts.* Treatment with unlicensed long-acting naltrexone products should only be considered as a second-line treatment approach in patients who are not responding to conventional treatment, and who continue to actively use unsanctioned opioids in a high-risk manner such that "death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment". Heroin dependence also does not meet the criteria identified by Category A of the Special Access Scheme in Australia given the range and accessibility of effective evidence-based treatment options available to those seeking help. For example, patients already engaged in opioid substitution treatment who are no longer using opioids in a high-risk manner should not be eligible for this treatment approach. However, such patients have apparently been treated with naltrexone implants.

2) *Adequate informed consent and specialist patient assessment of potential patients.* Potential patients should be informed (verbally and in writing):

I. of the range, usual outcomes and adverse events of conventional treatment approaches for opioid dependence in Australia;

II. of the extent to which the implant meets Australian regulatory manufacturing standards;

III. that naltrexone implants are not licensed in Australia for treatment of heroin dependence or in other countries with comparable regulatory systems;

IV. that evidence for the safety and effectiveness of naltrexone implants has not yet been established;

a. of the range of potential adverse events and other consequences (e.g. impaired opioid analgesia) associated with long-acting naltrexone products, and how these will be addressed in the event that they occur (e.g. possible need for surgical excision);

b. of the financial implications including the costs of treatment with unlicensed products in comparison with conventional treatment approaches.

c. of the medico-legal implications of treatment with unlicensed products, including possible lack of indemnity for patients seeking compensation.

3) Continuing independent research is required to establish the safety, efficacy and cost effectiveness of this treatment approach, conducted in accordance with National Medical Research Council (NHMRC) constituted Human Research Ethics Committees and the TGA CTN/CTX processes.

4) *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 substance use, treatment history, medical, psychiatric and cognitive conditions, social circumstances, willingness and capacity to engage in continuing psychosocial treatment, and the perspectives of other relevant health professionals engaged in the patient's care.

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 to ensure that unlicensed treatments are delivered safely and only to appropriate patients. The current SAS system of the TGA provides no mechanism for professional or regulatory bodies to monitor the use of unlicensed products. This deficiency enables unlicensed treatment approaches to be provided widely to vulnerable patient populations without appropriate regulatory review. An independent review system (e.g. a national registry, jurisdictional committee) is required to

ensure that patients have been selected appropriately, and treatment delivered safely and effectively.

6) The extensive use of naltrexone implants in Australia over the last decade warrants an independent enquiry to review:

   a. the utilisation of implants which failed in part or in full to meet Good Manufacturing Practise (GMP);

   b. the utilisation of implants not approved by the Therapeutic Goods Administration;

   c. whether heroin dependence is an appropriate condition as defined by Category A of the Special Access Scheme;

   d. whether other conditions also treated with naltrexone implants are appropriate for Category A of the Special Access Scheme;

   e. the appropriateness of mechanisms covering compounding;

   f. the number of deaths and severe adverse events associated with either Rapid Opioid Detoxification or naltrexone implants or both;

   g. monitoring of applications for Category A of the Special Access Scheme.

Summary

No long-acting naltrexone product (implant or depot injection) is licensed currently for use in Australia. The RACP recognises that sustained release naltrexone products may ultimately prove to be a safe and effective additional treatment approach for opioid (and alcohol) dependence. However, until one or more suitable products have undergone normal regulatory assessment and are licensed with the TGA, unregistered products should not be used on a routine basis. Until then a range of safeguards are required to protect patients, their families and health professionals.

Background:

Illicit opiate use, affecting approximately 0.5% of the Australian population, is associated with a range of harms to individuals, their families and communities including poor physical and mental health, infections with blood borne viruses (HIV, HCV, HBV), crime, lost productivity, impaired social relationships and markedly elevated mortality rates.

Although a range of effective treatment approaches is available for opiate dependence, a broader range of options is much needed. Opioid substitution treatment (OST) with methadone or buprenorphine has been demonstrated to be safe and effective(1, 2). Over 40,000 Australians are currently in OST(3). OST is more successful in attracting, retaining and benefiting heroin dependent persons than all other treatments for heroin dependence. However not all opioid dependent people are attracted to, or benefit from OST. Detoxification can achieve worthwhile short-term outcomes, such as interrupting intensive drug use and relief of withdrawal symptoms. But detoxification alone rarely results in long-term benefits. Residential

rehabilitation treatment, while sometimes effective, is expensive, attracts few, retains even fewer and is supported by meagre evidence. Post-withdrawal psychosocial (counselling) interventions have modest benefits on their own(4, 5). Many patients cycle in and out of substitution treatment (6) and between the above treatments(7). Some heroin dependent persons benefit from self-help organisations, telephone help lines or internet programmes. There is a strong case for broadening the range of existing treatment approaches.

Naltrexone, an opioid antagonist that blocks the effects of additional opioids, has been available since the 1960s and has been used in the treatment of opioid dependence for over 20 years. In Australia the TGA registered oral naltrexone hydrochloride tablets (50mg, Revia®) in 1998 and approved their use for *"adjuvant therapy in maintenance of former opioid dependent patients"(8).* However, Australian and international research has demonstrated poor compliance with oral naltrexone (9, 10) with only a small minority of patients (typically less than 10%) remaining in treatment for 6 months or more. Oral naltrexone is only recommended in Australia for a small minority of carefully selected, highly motivated patients with intensive monitoring and supervision(11). The Pharmaceutical Benefits Advisory Committee twice considered applications to add oral naltrexone for the treatment of heroin dependence to the Pharmaceutical Benefits Scheme but did not recommend this because of a lack of supporting evidence. In addition, oral naltrexone treatment of heroin dependent patients is accompanied by high mortality rates resulting from patients losing opioid tolerance while taking naltrexone and then experiencing an overdose on relapse to heroin.

Poor compliance with naltrexone led to a number of attempts to develop long-acting depot injection or implant naltrexone preparations to obviate the need for daily dosing. Similar approaches have been used successfully in other areas of medicine where medication compliance is also problematic (e.g. Implanon™ for contraception, Risperdal Consta™ in schizophrenia). A once-a-month depot intramuscular injectable naltrexone suspension (Vivitrol®) has been licensed in the USA for the management of alcohol dependence; however this product is not licensed (for any indication) in Australia. The US Food and Drug Administration approved Vivitrol® for the treatment of opioid dependence on 12 October 2010. FDA assessment of efficacy relied on data from a single unpublished Russian study with very limited follow up. Safety was assessed using data from this Russian study and a US study of alcohol dependent patients (some of whom were also opioid dependent). Several naltrexone implant products have been developed by international and Australian companies. To date, no naltrexone implant product has been licensed for general use by the TGA in Australia, or by equivalent American or European regulatory bodies.

Some evidence regarding the safety and efficacy of long-acting naltrexone products in the treatment of opioid dependence has been published. However, the Cochrane review concluded in 2010 that 'there is insufficient evidence from randomised controlled trials to evaluate the effectiveness of sustained-release naltrexone' (12). In Australia the NHMRC is undertaking a review. Several small randomised controlled trials have been completed (13-15)or are in progress. As is conventional with new medicines or devices, unless and until there is evidence to the contrary, naltrexone implants should be assumed to be ineffective, unsafe and cost-ineffective. On the

current limited evidence available, long-acting naltrexone treatment may be better than treatment with placebo or oral naltrexone, and may reduce (but not prevent) relapse to unsanctioned opioid use. To date, all trials have only compared naltrexone implants to oral naltrexone or placebo. None have used current best practise as a control. There have also been concerns raised regarding severe adverse events with naltrexone implants (13, 16, 17).

Manufacture of naltrexone implants in Australia began soon after 2000. In recent years naltrexone implants have also been imported from China. For about five years, the Australian made naltrexone implants did not meet Good Manufacturing Practise (GMP) of the TGA. The manufacturer states that Research GMP was achieved in 2005 and full GMP in 2009. This suggests that a large number of of naltrexone implants have been inserted while the devices did not meet GMP in part or full. As clinicians claim to have implanted these devices into thousands of patients, it seems that use extended to many patients not involved in clinical trials while only Research GMP had been achieved.

Apart from the question of manufacturing standards, the TGA has not approved the use of naltrexone implants in Australia. As naltrexone implants or depot injection products are not licensed for human use in Australia, current access to naltrexone implants is through formal clinical trials and/or the TGA Special Access Scheme. Clinicians inserting naltrexone implants have argued that heroin dependence fits criteria of Category A of the Special Access Scheme (*"persons who are seriously ill with a condition from which …. premature death is reasonably likely to occur in the absence of early treatment"*). As the mortality of heroin dependence is about 1.5% per annum, it is difficult to see how this condition can be considered to be one where 'premature death is reasonably likely to occur in the absence of early treatment.' Clinicians may now also be using Category A of the Special Access Scheme to insert naltrexone implants for a range of other conditions (alcohol dependence, amphetamine dependence, nicotine dependence and gambling). Some may be inserting these unapproved implants under compounding arrangements without applying for Category A of the Special Access Scheme.

Some deaths and severe adverse events have been reported occurring soon after Rapid Opioid Detoxification (ROD) or insertion of naltrexone implants.

These concerns covering manufacturing standards, use of unapproved products, apparent inappropriate use of Category A of the Special Access Scheme, extending the indications to other conditions, and the occurrence of severe adverse events (including deaths) warrant an independent enquiry.

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