# Ensuring the safety of new medications and devices: are naltrexone implants safe?

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*Naltrexone implants have not been subject to the usual rigorous scrutiny required for new devices in Australia, but are widely used through the Special Access Scheme*

In this issue of the Journal, Lintzeris and colleagues report eight patients with naltrexone implants who developed serious medical complications considered to be related to the implant (*page 441*).[1] Intuitively, naltrexone is an attractive treatment for opioid dependence, as it is inexpensive, long-acting and generally well tolerated, and blocks the actions of heroin when taken orally. However, empirical support for naltrexone has been unimpressive,[2-4] with research showing that poor adherence to treatment limits its effectiveness. An Australian study found that, while patients who adhered to treatment did well, only 2% were still taking the drug 3 months after conventional inpatient detoxification.[5]

Naltrexone was registered by the Therapeutic Goods Administration (TGA) in 1998 as "an aid in the maintenance of previously opiate-dependent patients who have ceased the use of opioids".[6] However, the Pharmaceutical Benefits Advisory Committee twice rejected applications for the inclusion of naltrexone in the Pharmaceutical Benefits Scheme as a treatment for opioid dependence on the grounds of lack of evidence of efficacy. Controversy over efficacy was followed by growing doubts about naltrexone's safety. Intermittent naltrexone consumption lowers opioid tolerance, thereby increasing the risk of heroin overdose. An Australian study found the death rate for those leaving naltrexone treatment was eight times that recorded among participants leaving treatment with agonists such as methadone or buprenorphine.[7]

As the weakness of the case for oral naltrexone became clearer, a range of interventions were developed to overcome the inherent problems of treatment initiation and poor adherence. The publication in 1997 of an article entitled "I woke up . . . cured of heroin" in a popular Australian magazine[8] sparked intense community and political interest in the initiation of naltrexone treatment during general anaesthesia or heavy sedation, followed by oral administration. This was said to be a novel, dramatically effective treatment for heroin dependence. However, subsequent evaluation showed that these approaches increased the cost of oral naltrexone without increasing efficacy.[9] More recently, depot injections[10] and implants of naltrexone have become the focus of public and political hope.

In this historical context, it is concerning that the recent research on naltrexone implants in Australia has not followed usual scientific processes. In particular, naltrexone implants have not been subject to the usual rigorous scrutiny required for new drug products seeking registration in this country. Nevertheless, they are available through the TGA Special Access Scheme; there is no requirement for TGA approval for access to unapproved goods in Australia for Category A patients under this Scheme, and no apparent requirement for collection of efficacy or safety data. Supporters of the naltrexone implant have argued that heroin injectors meet the criteria for Category A patients under the Scheme as "persons who are seriously ill with a condition from which 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".[11]

Most Category A patients have malignant conditions or rare life-threatening diseases. The annual mortality of heroin injectors is in the order of 1%[12] — almost 15 times higher than expected for persons of the same age and sex with no history of heroin use, but hardly in the range generally considered appropriate for the Special Access Scheme. But the inclusion of naltrexone implants in the Scheme and their widespread use (reportedly by more than 1500 individuals) means the product has achieved a substantial market while not undergoing the rigorous evaluation usually applied to drugs before registration.

Some of the implants used in Australia are produced locally, while others are manufactured overseas. There are doubts about the quality of manufacture, as well as deficiencies in the safety and efficacy data. As far as we are aware, no major national drug regulatory authority has licensed naltrexone implants for management of opioid misuse. However, a depot injection of naltrexone has been approved by the Food and Drug Administration in the United States, but only for alcohol, not opioid, dependence.[10]

Although the effectiveness, safety and cost-effectiveness of methadone and buprenorphine treatments for heroin dependence are supported by substantial and compelling evidence, a greater range of pharmacological treatments suited to the broad range of individual patients is required. A recent randomised controlled study of depot naltrexone for the treatment of opioid dependence had encouraging results.[13] The strong theoretical rationale for the usefulness of naltrexone in treating heroin dependence justifies further rigorous investigations. However, the uncontrolled use of unregistered products of uncertain quality hampers the development of proper clinical trials.

Since the thalidomide disaster in the 1960s, all new medications introduced into Australia have been regarded as ineffective and unsafe until proven otherwise. Constant vigilance is required to ensure that only new medications and devices of proven effectiveness and safety are permitted widespread use. The disturbing suggestions of mortality and morbidity from unregistered naltrexone implants make a strong case for an independent review to determine whether this treatment is sufficiently safe for such widespread use. This review should also assess whether the TGA Special Access Scheme has been used to circumvent the requirement for rigorous assessment of the quality, safety and efficacy of naltrexone implants. This assessment is the cornerstone of a drug regulatory system designed to protect the public from ineffective and unsafe medicines. The TGA has the power under the *Therapeutic Goods Act 1989* (Cwlth) (s. 31A(2) and s. 41JD) to seek clarification of the Category A classification of patients, and should do so urgently regarding access to unapproved naltrexone products in Australia.

## Competing interests

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