Clinical Policy Bulletin: Naltrexone Implants

**Number:** 0878

**Policy**

Aetna considers naltrexone implants experimental and investigational for treatment of alcohol addiction, amphetamine use, narcotic addiction, and all other indications because of insufficient evidence in the peer-reviewed published medical literature of their safety and effectiveness.

**Background**

Naltrexone is a drug used in the management of alcohol and opioid dependence. When taken, naltrexone attaches to the opiate receptors in the brain and blocks them, preventing the euphoric effect from the opiate.

Naltrexone is available in oral, ‘depot’ (slow-release) injection or implant preparations, however only the oral and depot forms of naltrexone have been approved for use by the Food and Drug Administration (FDA). The potential benefits of a naltrexone implant include less frequent dosage and reduced rates of withdrawal and relapse between doses.

An assessment by the Australian National Health and Medical Research Council (NHMC, 2011) concluded that naltrexone implants are unproven for treatment of opioid dependence. The review concluded that evidence is currently at an early stage and as such, naltrexone implants remain an experimental product and should only be used within a research setting. Until the relevant data are available and validated, the efficacy of the treatment, alone or in comparison to best practice, cannot be determined (NHMC, 2011). NHMRC’s position on naltrexone implants is that further research on adverse effects is required before a statement on safety can be confidently made.

Specifically regarding the use of the naltrexone implant for alcoholism, a systematic evidence review concluded that larger longitudinal studies of the naltrexone implants are needed (Lobmaier et al, 2011).
World Journal of Biological Psychiatry Guidelines on the Treatment of Substance Use and Related Disorders (2011) state: “Naltrexone implants cannot yet be recommended for clinical use because although there are promising efficacy data for them, safety concerns remain and require further evaluation”.

However, since then, some randomized controlled clinical trials of naltrexone implants have been published examining the effectiveness of the naltrexone implants for narcotic addictions. Limitations include the fact that these studies were not U.S. based, they examined short-term impact, and compared the implants to oral naltrexone rather than the depot injection (Vivitrol) that has been approved by the FDA.

Kelty and Hulse (2012) 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 (Hickman et al, 2012).

There are some published reports of deaths attributable to naltrexone implants (Gibson et al, 2007a; Gibson et al, 2007b; Olivier, 2005) and other reports claiming significantly reduced mortality (Ngo et al., 2008). Further research is needed to establish the risk of mortality during and after treatment with naltrexone implants and other treatment approaches.

Kelly et al (2013) examined self-reported abstinence from amphetamines following treatment with a sustained release naltrexone preparation in patients with self and clinically identified problems with amphetamine use and the relationship between naltrexone blood levels and abstinence from amphetamines. A total of 44 patients with problematic amphetamine use, who were treated with a naltrexone implant, completed an interview evaluating self-reported reduction in amphetamine use following treatment. Additional data were collected from the patients' clinical treatment files. Of the 44 subjects, 29 (65.9 %) interviewed reported that following treatment they ceased using and maintained abstinence from amphetamines for at least 1 month. Of these patients, 14 (48.3 %) were reportedly still abstinent at 6 months. Rates of abstinence were found to be 2.27 times higher (95 % confidence interval (CI): 1.38 to 3.74) in patients when blood naltrexone levels were above 2 ng/ml, with rates as high as 100 % and 90.9 % for greater than or equal to 5 and greater than or equal to 2 ng/ml, respectively, compared with 42.9 % for 1 to 2 ng/ml and 38.9 % low less than 1 ng/ml. The authors concluded that although this study has several limitations, the findings provided preliminary data in support of the use of implant naltrexone for the treatment of problematic amphetamine use and suggested that naltrexone levels above 2 ng/ml should be targeted for use in patients. Moreover, they stated that further research is needed.

Larney et al (2014) systematically reviewed the literature to evaluate the safety and effectiveness of naltrexone implants for treating opioid dependence. Studies were eligible if they compared naltrexone implants with another intervention or placebo. Examined outcomes were induction to treatment, retention in treatment, opioid and non-opioid use, adverse events, non-fatal overdose and mortality. Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach. Data from randomized
studies were combined using meta-analysis. Data from non-randomized studies were presented narratively. A total of 5 randomized trials (n = 576) and 4 non-randomized studies (n = 8,358) were eligible for review. The quality of the evidence ranged from moderate to very low. Naltrexone implants were superior to placebo implants [risk ratio (RR): 0.57; 95 % confidence interval (CI): 0.48 to 0.68; k = 2] and oral naltrexone (RR: 0.57; 95 % CI: 0.47 to 0.70; k = 2) in suppressing opioid use. No difference in opioid use was observed between naltrexone implants and methadone maintenance (standardized mean difference: -0.33; 95 % CI: -0.93 to 0.26; k = 1); however, this finding was based on low-quality evidence from 1 study. The authors stated that the evidence on safety and effectiveness of naltrexone implants is limited in quantity and quality, and the evidence has little clinical utility in settings where effective treatments for opioid dependence are used. They concluded that better designed research is needed to establish the safety and effectiveness of naltrexone implants; until such time, their use should be limited to clinical trials.

CPT Codes / HCPCS Codes / ICD-9 Codes

**Naltrexone Implants:**

No specific code

**ICD-9 codes not covered for indications listed in the CPB (not all inclusive):**

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<th>Code</th>
<th>Description</th>
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The above policy is based on the following references:
