A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence

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CRD summary
This largely well-conducted review concluded that evidence on safety, efficacy, and effectiveness of naltrexone implants for treatment of opioid dependence was limited in quantity and quality, and had little clinical use in settings where effective treatments were already available; more research was needed. The authors' conclusions reflect the evidence presented and seem reliable.

Authors' objectives
To evaluate the effectiveness and safety of naltrexone implants for treating opioid dependence.

Searching
The search strategy built on one used in a previous review (see Other Publications of Related Interest). Studies published since that review (from 2009 to 2013) were sought from Evidence Based Medicine Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and PsycINFO databases. Current trials were searched in three trials registers. Search strategies were reported. Reference lists of systematic reviews were scanned for additional studies.

Study selection
Eligible for inclusion were randomised or non-randomised studies of naltrexone implants versus any comparator, treating any patient with opioid dependence; there was no restriction on length of follow-up. For randomised studies, the outcomes of interest were induction to treatment, retention in treatment, opioid use, non-opioid drug use, adverse surgical site-related events, or other adverse events and effects possibly related to treatment. Other outcomes from randomised and non-randomised studies were opioid overdose, non-opioid drug overdose, or mortality. Studies included in the previous review (Other Publications of Related Interest) were also assessed for eligibility.

In included studies, naltrexone implant doses ranged from 2.3mg to 2.2g (where reported). The included comparators were: placebo implant (with or without oral placebo); oral naltrexone with placebo implant; treatment as usual; methadone maintenance treatment; oral naltrexone; and buprenorphine maintenance treatment. Study participants were opioid and/or amphetamine dependent adults living in the community, those about to be discharged from abstinence-based inpatient treatment, or prisoners prior to imprisonment and those nearing the time of prison release.

Studies were selected by one reviewer, with discussion and agreement on final inclusion by all reviewers.

Assessment of study quality
Study quality was assessed using Cochrane criteria. Summary risk of bias judgements were made for each outcome. Quality of the evidence was assessed using GRADE criteria, and rated as high, moderate, low, or very low.

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
Data were extracted to calculation (where possible) risk ratios or mean differences, together with 95% confidence intervals. Study authors were contacted to clarify data or request additional data.

Two reviewers extracted the data. Discrepancies were resolved through discussion and referral to a third reviewer.

Methods of synthesis
For randomised studies, pooled risk ratios and standardised mean differences were calculated in meta-analyses using a fixed-effect (Mantel-Haenszel) model. Studies with zero events in the both arms were excluded from the meta-analyses. Statistical heterogeneity was assessed using X² and I².
Results of the review

Five randomised controlled trials (576 patients) and four non-randomised studies (8,358 patients) were included in the review. Risk of bias judgements were reported in the paper, with randomised studies showing mixed results, and non-randomised studies showing generally high risk of bias (where criteria were applicable).

Induction to treatment (five trials; moderate quality evidence): No statistically significant differences were found between naltrexone implants and placebo implants (two trials; $I^2=0\%$), oral naltrexone (two trials ($I^2=0\%$), methadone maintenance treatment (one trial), or treatment as usual (one trial).

Retention in treatment (two trials; low quality evidence): Naltrexone implants were significantly more effective than placebo implants (RR 3.20, 95% CI 2.17 to 4.72; two trials; $I^2=84\%$) and oral naltrexone (RR 3.38, 95% CI 2.08 to 5.49; one trial).

Opioid Use (five trials; low quality evidence): Naltrexone implants were significantly more effective in suppressing opioid use than placebo (RR 0.57, 95% CI 0.48 to 0.68; two trials) or oral naltrexone (RR 0.57, 95% CI 0.47 to 0.70; two trials). Further results at follow-up were reported in the paper.

Non-opioid drug use (four trials; low quality evidence): Non-opioid drug use was significantly more likely in patients with naltrexone implants than those taking oral naltrexone (RR 1.23, 95% CI 1.01 to 1.51; one trial). There were no statistically significant differences between naltrexone implants and other comparators.

Adverse events (moderate quality evidence): Patients with naltrexone implants were significantly more likely than those with placebo implants to report surgical site-related adverse events (RR 4.68, 95% CI 1.63 to 13.44; three trials; $I^2=0\%$). There were no statistically significant adverse events possibly related to treatment when naltrexone implants were compared with placebo implants (one trial) or oral naltrexone (two trials; $I^2=0\%$).

Further results (including those incorporating the non-randomised studies) for opioid/non-opioid drug overdose and mortality, were reported in the paper.

No evidence of publication bias was found.

Authors' conclusions

The evidence on safety, efficacy, and effectiveness of naltrexone implants was limited in quantity and quality, and the evidence had little clinical use in settings where effective treatments for opioid dependence (such as opioid substitution therapy) were available.

CRD commentary

The review question was supported by clear and replicable inclusion criteria. A number of relevant data sources were searched for published and unpublished studies, and publication bias was assessed. Some of the review processes incorporated attempts to minimise error and bias, although only one reviewer performed most of the screening process and detail was lacking on how the quality assessment was carried out.

Suitable quality assessment criteria were applied; the results were clearly presented and incorporated within the discussion of findings. The chosen methods of synthesis appropriately took account of risk of bias and variation in study characteristics.

This was largely a well-conducted review. The authors' conclusions reflect the evidence presented and seem reliable.

Implications of the review for practice and research

Practice: The authors stated that, pending further research, the use of naltrexone implants should be limited to clinical trials.

Research: The authors stated that better designed research was needed to establish the safety and efficacy of naltrexone implants. Future trials should manage participants expectations about treatment allocation, and ensure adequate sample
size in anticipation of likely dropout rates.

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