Relapse prevention in formerly opioid-dependent drug users

Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

Naltrexone is an opiate antagonist that is licensed for use orally as adjunctive therapy in the treatment of detoxified formerly opioid-dependent individuals (after around 10 days of being opiate free). It is taken in a dose of 50 mg per day and blocks the pleasurable and euphoric effects of heroin and other opiates. It works to help former opioid-dependent individuals to stay off drugs through the knowledge that these drugs will produce no positive effects. It does not increase motivation to stay abstinent and thus if people choose not to take the dose daily it will not work.

It is not widely used in England and Wales and the current cost to the NHS in England is around £500,000 per annum and there is no evidence of an increasing trend in use. Moreover, not all of these prescriptions will be for use in the prevention of relapse in formerly opioid-dependent individuals, as it is also used in alcohol misuse and other conditions.

Objectives

The objectives of the report were:

- to undertake a systematic review of the clinical effectiveness of oral naltrexone for helping to prevent formerly opioid-dependent people from returning to illicit drug use
- to review systematically enhanced treatment packages designed to improve compliance with oral naltrexone treatment
- to review published economic evaluations and undertake a *de novo* cost–utility analysis of oral naltrexone
- to see whether the evidence allows particular subgroups of opioid users or particular settings or care packages to be identified in which oral naltrexone is likely to be more effective or cost-effective.

Methods

The study systematically reviewed the literature about (1) the effectiveness of naltrexone and (2) measures to increase compliance with naltrexone, since naltrexone is only effective if taken, using established methods. Bibliographic databases were searched from database inception to September 2005. The focus of this review was to investigate the clinical and cost-effectiveness of naltrexone for relapse prevention in detoxified formerly opioid-dependent individuals compared with any strategy that does not use naltrexone, including treatment with placebo, other pharmacological treatments, psychosocial interventions or no treatment.

A decision-analytic model using Monte Carlo simulation was developed that compared naltrexone as an adjunctive therapy to no naltrexone. It assumed compliance rates that were not enhanced by contingent management rewards (because this is current UK practice). It took an NHS/Personal Social Services perspective and was modelled to 12 months. Given the time-horizon no discounting was applied. Utility values could not be identified from the literature and so were obtained by research specially commissioned from the Value of Health Panel.

Results

Quality

Out of 1013 identified citations, 26 studies met the inclusion criteria: nine were randomised controlled trials (RCTs) of interventions to increase compliance with naltrexone (with a total number of 841 participants) and 17 were studies considering the effectiveness of naltrexone. Of the latter 17, one was a systematic review, 13 were RCTs (with a total of 940 participants) and three were controlled but non-randomised studies. The methodological quality of the RCTs was poor to moderate at best.

Effectiveness

Naltrexone

The results suggest that naltrexone as maintenance therapy for relapse prevention in opioid addicts may be better than placebo in terms of retention in treatment, but this was ▶

not statistically significant: in a meta-analysis of seven included RCTs the relative risk (RR) of loss of retention in treatment in the naltrexone arm was 0.94 [95% confidence interval (CI) 0.84 to 1.06]. The pooled hazard ratio (HR) reported in five of the RCTs for retention in treatment data followed up to 35 weeks was calculated as 0.90 (95% CI 0.69 to 1.17) in favour of naltrexone and also did not reach statistical significance.

With respect to the risk of drug abuse in naltrexone versus placebo, with or without psychological support given in both arms, the pooled RR from six RCTs was 0.72 (95% CI 0.58 to 0.90), which was a statistically significant difference in favour of naltrexone. The pooled HR from three RCTs for opioid relapse-free rates was significantly different from placebo in favour of naltrexone 0.53 (95% CI 0.34 to 0.82). However, this effect can be seen to fall off over time and may be of limited clinical significance.

The RR of reimprisonment while on naltrexone therapy showed results in favour of naltrexone in the combined two studies of parolees or people on probation (RR 0.5, 95% CI 0.27 to 0.91), but the number of participants was small.

One study reported results using the Risk Assessment Battery, which is a self-report instrument questionnaire measuring HIV risk. There were 52 participants in this study. The difference in improvement score for risky sexual behaviour in the naltrexone group compared with the placebo group was not statistically significant.

The adverse events data reported in the included studies showed no significant difference between the naltrexone and placebo arms.

Interventions to increase compliance with naltrexone treatment

Nine RCTs of interventions designed to increase retention with naltrexone (three RCTs for contingency management programmes, four RCTs for psychosocial therapy and two RCTs for additional pharmaceutical agents) were identified and analysed. The quality of these studies was poor to moderate at best, with calculation errors in one study and one study only reporting data-driven analyses, rather than randomised comparisons. All three different modalities of enhanced care showed some evidence of effectiveness in improving retention on naltrexone.

All of the contingency management programmes used incentive vouchers that could be exchanged for goods or services to reward participants when they complied with treatment. The mean duration of treatment retention was 7.4 weeks for the contingency management intervention compared with 2.3–5.6 weeks for the naltrexone treatment alone.

The mean length of time for which patients stayed on naltrexone was 84–103 days with additional psychosocial therapy compared with 43–64 days for the control group.

In trials with added pharmacological agents the RRs of stopping treatment were 1.63 at 6 months and 1.31 at 12 months (in favour of naltrexone plus fluoxetine). It reached statistical significance at 6 months, but not at 12 months. There were only 13 participants in the RCT of the pharmaceutical agent sertaline and there are insufficient data to draw any conclusions.

Different studies used different outcome measures with different follow-up periods. It is debatable whether it is appropriate to combine such clinically heterogeneous interventions. This has been done for the sake of completeness, but the results should be interpreted with caution. A meta-analysis was conducted of the RR of stopping treatment at week 12 (the minimum follow-up period) using six of the nine studies. The pooled RR of stopping treatment was 0.81 (95% CI 0.71 to 0.94). The results indicated that overall the intervention groups had 19% fewer patients who stopped treatment compared with the control group. However, owing to the small number of studies and the relatively poor quality of the studies, it is difficult to estimate the real effectiveness of these interventions.

Economic evaluation

Existing economic evaluations

No existing economic evaluations were identified.

De novo cost–utility analysis

The point estimate for the cost-effectiveness of naltrexone was £42,500 per quality-adjusted life-year (QALY). Sensitivity analysis was carried out and the incremental cost-effectiveness ratio varied between £34,600 and £42,500 per QALY gained. Because of the uncertainty in the estimates, the cost-effectiveness acceptability curves never went above 55% for any willingness-to-pay threshold.

▶

Conclusions

Following successful withdrawal from opioids, naltrexone may be administered on a chronic basis to block any future effects of opioids. Naltrexone appears to have some limited benefit in helping formerly opioid-dependent individuals to remain abstinent, although the quality of the evidence is relatively poor and heterogeneous. The limited quality and extent of the studies found in this review precluded an analysis of subgroups particularly likely to benefit from naltrexone prescribing.

Oral naltrexone is used infrequently in current UK practice, and this review suggests that this is appropriate as there is little evidence to support its wider implementation.

Recommendation for future research

There is an important deficit in information about the quality of life of people who use illicit opioids and this would perhaps be a worthwhile area of research in informing policy questions about the cost-effectiveness of different programmes and interventions.

Publication

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