Review: there is insufficient evidence for naltrexone maintenance treatment in opioid dependence


QUESTION: How effective is naltrexone maintenance treatment for preventing relapse in people addicted to opioids?

Design
Systematic review with meta-analysis.

Data sources
Studies were identified using Medline (1973–July 2000), EMBASE (1974–July 2000), the Cochrane Collaboration Trial register (issue 2; 2002), the Drug and Alcohol Specialised Registry (July 2000) and reference lists of included studies. Pharmaceutical companies and experts in the field were contacted for additional trials.

Study selection
Studies were selected using Cochrane Collaboration criteria. Randomised controlled trials or controlled clinical trials published in English, German or Italian between 1973 and February 2002 were eligible if they compared naltrexone maintenance treatment after opiate detoxification with placebo, pharmacological or behavioural interventions. The 11 studies included were heterogeneous. They included 707 inpatients and outpatients, mostly male. Oral naltrexone varied from daily to twice-weekly and doses ranged from 150 mg to 350 mg weekly. Treatment duration ranged from 10 days to 1 year.

Data extraction
Data were extracted on study design, participant characteristics, interventions, outcomes and main results. The main outcomes were successfully completed treatment (recovery); drug use during treatment; adverse effects; social behaviour; arrests, and craving level.

Main results
There was no significant difference between groups in treatment completion or use of opioids during treatment (table). Adding naltrexone to behavioural treatment completion 0.78 0.34 to 1.75. There was no significant difference between groups in treatment completion (table). Adding naltrexone to behavioural treatment completion 0.78 0.34 to 1.75.

Conclusions
There is no strong evidence that naltrexone maintenance following detoxification prevents relapse in people with opioid dependence. Naltrexone may have some benefits when combined with behavioural therapy.

Outcomes for opioid dependents receiving naltrexone maintenance vs placebo, other pharmacological treatment or behavioural therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
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<tbody>
<tr>
<td>Successful treatment completion</td>
<td>0.78</td>
<td>0.34 to 1.75</td>
</tr>
<tr>
<td>Use of opioids during treatment</td>
<td>0.85</td>
<td>0.45 to 1.62</td>
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COMMENTARY
The story of naltrexone for the treatment of opioid dependence is both puzzling and frustrating. Theoretically, and under certain experimental conditions, naltrexone appears to be an ideal medication for the treatment of opioid dependence. Yet controlled trials generally fail to find favourable effects. Kirschmayer et al’s meta-analysis suggests that there is insufficient evidence to support the use of naltrexone for opioid dependence.

A caveat is that trials for addiction medications are difficult to design and conduct. Blinding may be difficult to maintain because drug use lapses may unmask conditions. Trials with medications that have acute psychoactive effects can quickly reveal condition assignments (eg a comparison of methadone to naltrexone). A further complicating feature is the use of concurrent, non-pharmacological treatments, which may introduce variability in study outcomes, especially if cross-study comparisons are made. Clinical trials with naltrexone, like many studies of medications for the treatment of substance abuse disorders, need to be carefully designed and executed. Studies can appear to be methodologically sound, but closer scrutiny may reveal weaknesses that confound conclusions.

If naltrexone were a highly useful medication, then one would expect that it would be widely used regardless of study results. Why does naltrexone have a clinical reputation as a relatively valueless medication (with the caveat that some clinicians do anecdotally report high success rates)? In part, naltrexone’s reputation may suffer from comparisons to its successful sibling—methadone. Methadone is able to maintain patients in treatment and attenuate opioid use. In addition, methadone is relatively easy to use compared to naltrexone, especially at the start of treatment. Naltrexone requires opioid abstinence before it can be started, while methadone does not. Just as the sibling of a successful and popular child typically has unique strengths, however, naltrexone has important values that should not be overlooked.

An important factor in the use of naltrexone is a patient’s level of motivation. The source of motivation may be outside a person (eg a spouse, the criminal justice system) or within the person. The latter is more difficult for clinicians to assess. How often have we seen a patient who has repeated relapses in treatment and then seems to find an inner desire and motivation to achieve and maintain abstinence? One of the attractive features of medications such as methadone is that they are useful for people with lower levels of motivation. Naltrexone may have a role with people who have a high level of motivation, either externally or internally derived.

Addiction treatment should be based upon rigorously conducted research. Clinical experience suggests naltrexone can be useful in particular people, but further studies are needed to determine if there are parameters under which it is truly effective.

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