Naltrexone for 3 or 12 months in addition to psychosocial counselling did not reduce drinking in alcohol dependence


QUESTION: In patients with chronic severe alcohol dependence and a recent history of drinking to intoxication, does naltrexone in addition to standardised psychosocial treatment reduce alcohol consumption?

Design
Randomised (allocation concealed†,‡, blinded (participants, clinicians, data collectors, and outcome assessors)¶, controlled trial with 52 weeks of follow up.

Setting
15 Veterans Affairs medical centres in the US.

Patients
627 outpatients (mean age 49 y, 98% men) who had a diagnosis of alcohol dependence according to DSM-IV criteria, who had not drunk for ≥5 days, but who had a recent history of drinking to intoxication (heavy drinking at least twice during a 1 week period in the 30 days before screening, where heavy drinking was defined as ≥6 drinks for men and ≥4 drinks for women). Exclusion criteria included previous use of naltrexone, other substance abuse or dependence, and psychiatric diagnoses requiring medication. Follow up was 90% and 93% at 13 and 52 weeks, respectively.

Intervention
209 patients each were allocated to naltrexone (50 mg/d) for 3 months (short term group), naltrexone (50 mg/d) for 12 months (long term group), or placebo. All patients received individual 12 step facilitation counselling for 13 months and were encouraged to attend Alcoholics Anonymous meetings.

Main outcome measures
Time to relapse (days from randomisation to first day of heavy drinking) during the first 3 months, and percentage of drinking days (PDD) and number of drinks per drinking day (NDPDD) over a 12 month period.

Main results
Analysis was by intention to treat. At 13 weeks, the combined short and long term naltrexone group did not differ from the placebo group for time to relapse (table). At 52 weeks, neither the short nor the long term naltrexone group differed from the placebo group for PDD or NDPDD (NDPDD was evaluated for the 66% of patients who drank during follow up) (table).

Conclusion
In patients with chronic severe alcohol dependence and a recent history of drinking to intoxication, naltrexone for 3 or 12 months in addition to standardised psychosocial treatment was not effective.

‡See glossary.
¶Information provided by author.

COMMENTARY
2 meta-analyses‡‡ have supported the effectiveness of naltrexone in treating alcohol dependence. Further studies showing its efficacy have since been published.¶¶ This negative study by Krystal et al, and the 2 negative studies in the meta-analysis by Streten and Whelan,¶¶ are the only truly multicentre studies in which naltrexone or placebo was offered as an addition to standard abstinence oriented treatment programmes.

Although no large trial of naltrexone has used coping skills therapy (CST), naltrexone has shown efficacy when adjunctive CST has been used in small studies. Fuller and Gordis§ comment that CST differs from the 12 step facilitation therapy used in this study because a lapse to drinking is not dramatised in CST, with harm free drinking being seen as an acceptable goal.

Standard endpoints for treatment trials of patients with alcoholism including PDD and NDPDD were used in this study. However, some investigators consider that naltrexone has an effect in reducing the number of days of heavy drinking (>5 drinks). Under this assumption, NDPDD blurs the distinction between those who sometimes drink a little and sometimes drink a lot, from those who drink equally frequently but who usually consume moderate amounts. The negative result of this study can be seen as an example of how results of treatment trials weaken when extrapolated outside specialised research centres; or as support for further trials of opiate antagonist treatment with alternative types of adjunctive psychotherapy.

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Naltrexone for 3 months (short term) or 12 months (long term) v placebo for alcohol dependence:

<table>
<thead>
<tr>
<th>Outcomes at 13 weeks</th>
<th>Comparison</th>
<th>Means</th>
<th>Difference between groups (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days to relapse</td>
<td>Short or long term v placebo</td>
<td>72.3 ± 62.4</td>
<td>9.9 (−3.0 to 22.8)</td>
</tr>
<tr>
<td>Percentage of drinking days</td>
<td>Long term v placebo</td>
<td>15.1 ± 18.0</td>
<td>−2.9 (−7.7 to 1.9)</td>
</tr>
<tr>
<td>Short term v placebo</td>
<td>19.4 ± 18.0</td>
<td>1.4 (−3.6 to 6.5)</td>
<td></td>
</tr>
<tr>
<td>Number of drinks per drinking day (NDPDD)§</td>
<td>Long term v placebo</td>
<td>9.6 ± 9.3</td>
<td>0.3 (−1.8 to 2.4)</td>
</tr>
<tr>
<td>Short term v placebo</td>
<td>10.5 ± 9.3</td>
<td>1.2 (−0.5 to 2.9)</td>
<td></td>
</tr>
</tbody>
</table>

‡CI defined in glossary. None of the mean differences is statistically significant.
§NDPDD was evaluated for the 66% of patients who consumed alcohol during follow up.