Naltrexone for 3 or 12 months did not reduce drinking in alcohol dependence

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA, for the Veterans Affairs Naltrexone Cooperative Study 425 Group. **Naltrexone in the treatment of alcohol dependence.** N Engl J Med. 2001 Dec 13;345:1734-9.

QUESTION

In patients with alcohol dependence and a recent history of drinking to intoxication, is treatment with naltrexone for 3 or 12 months in addition to standardized psychosocial treatment more effective than placebo for reducing alcohol consumption?

DESIGN

Randomized {allocation concealed*}†, blinded (participants and health care providers),* controlled trial with 52-week follow-up.

SETTING

15 Veterans Affairs medical centers in the United States.

PATIENTS

627 outpatients (mean age 49 y, 98% men) who had a diagnosis of alcohol dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* criteria; who had not drunk for ≥ 5 days; and who had a recent history of drinking to intoxication (≥ 6 drinks for men and ≥ 4 drinks for women at least twice during a 1-week period in the 30 d before screening). Exclusion criteria included previous use of naltrexone and other substance abuse or dependence. Follow-up was 90% and 93% at 13 and 52 weeks, respectively.

INTERVENTION

209 patients each were allocated to naltrexone, 50 mg once daily, for 3 months (short-term group); naltrexone, 50 mg once daily, for 12 months (long-term group); or placebo. All patients received individual 12-step facilitation counseling for 13 months and were encouraged to attend Alcoholics Anonymous meetings. Visits were weekly for 16 weeks, every 2 weeks during weeks 17 to 36, and monthly during weeks 37 to 56.

MAIN OUTCOME MEASURES

Time to relapse (d from randomization to first d of heavy drinking) during the first 3 months, percentage of drinking days (PDD), and number of drinks per drinking day (NDPDD) for a 12-month period.

MAIN RESULTS

Analysis was by intention to treat. At 13 weeks, the combined short- and long-term naltrexone groups did not differ from the placebo group for time to relapse (Table). At 52 weeks, the short and long-term naltrexone groups did not differ from the placebo group for PDD or NDPDD (NDPDD evaluated for the 66% of patients who consumed alcohol during follow-up) (Table).

CONCLUSION

In patients with alcohol dependence and a recent history of drinking to intoxication, treatment with naltrexone for 3 or 12 months in addition to standardized psychosocial treatment was no more effective than placebo for reducing alcohol consumption.

Sources of funding: Department of Veterans Affairs Office of Research and Development and Dupont Pharmaceuticals.

For correspondence: Dr. J.H. Krystal, Veterans Affairs Connecticut Healthcare System, West Haven, CT, USA. E-mail john.krystal@yale.edu. ■

*See Glossary.

†Information provided by author.

Naltrexone for 3 months (short term) or 12 months (long term) vs placebo for alcohol dependence‡

Outcomes at 13 weeks	Comparison	Means	Difference between groups (95% CI)
Number of days to relapse	Short or long term vs placebo	72.3 vs 62.4	9.9 (–3.0 to 22.8)
Outcomes at 52 weeks			
Percentage of drinking days	Long term vs placebo	15.1 vs 18.0	–2.9 (–7.7 to 1.9)
	Short term vs placebo	19.4 vs 18.0	1.4 (–3.6 to 6.5)
Number of drinks per drinking day§	Long term vs placebo	9.6 vs 9.3	0.3 (–1.8 to 2.4)
	Short term vs placebo	10.5 vs 9.3	1.2 (–0.5 to 2.9)

‡CI defined in Glossary. None of the mean differences are statistically significant.

§Number of drinks per drinking day evaluated for the 66% of patients who consumed alcohol during follow-up.

COMMENTARY

2 meta-analyses have supported the effectiveness of naltrexone in reating alcohol dependence (1, 2). 2 further studies showing its efficacy have since been published (3, 4). The negative study by Krystal and colleagues and the 2 negative studies in the meta-analysis by Streeton and Whelan (1) are the only truly multicenter studies in which naltrexone or placebo was offered in addition to standard abstinence-oriented treatment programs.

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 (5) comment that CST differs from the 12-step facilitation therapy (used in this study) because a lapse to drinking is dedramatized in CST, with harm-free drinking being seen as an acceptable goal.

Standard end points 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 and 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 specialized research centers; it can also be seen as support for further trials of opiate antagonist treatment with alternative types of adjunctive psychotherapy.

Jonathan Chick, MA, MPhil, FRCPsych
Royal Edinburgh Hospital
Edinburgh, Scotland, UK

References

1. **Streeton C, Whelan G.** Alcohol Alcohol. 2001;36:544-52.
2. **Kranzler H, Van Kirk J.** Alcohol Clin Exp Res. 2001;25:1335-41.
3. **Morris PL, Hopwood M, Whelan G, Gardiner J, Drummond E.** Addiction. 2001;96:1565-73.
4. **Heinälä P, Alho H, Kiianmaa K, et al.** J Clin Psychopharmacol. 2001;21: 287-92.
5. **Fuller RK, Gordis E.** N Engl J Med. 2001;13:1770-1.

