

the careful analysis of clinical findings in patients suspected of having meningitis.

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## REFERENCES

1. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* 1993;328:21-8.
2. Pfister HW, Feiden W, Einhaupl KM. Spectrum of complications during bacterial meningitis in adults: results of a prospective clinical study. *Arch Neurol* 1993;50:575-81.
3. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998;129:862-9.
4. Greenlee JE, Carroll KC. Cerebrospinal fluid in CNS infections. In: Scheld WM, Whitley RJ, Durack DT, eds. *Infections of the central nervous system*. 2nd ed. Philadelphia: Lippincott-Raven, 1997:899-922.
5. Horwitz SJ, Boxerbaum B, O'Bell J. Cerebral herniation in bacterial meningitis in childhood. *Arch Neurol* 1980;7:524-8.
6. Rennick G, Shann F, de Campo J. Cerebral herniation during bacterial meningitis in children. *BMJ* 1993;306:953-5.
7. Minns RA, Engleman HM, Stirling H. Cerebrospinal fluid pressure in pyogenic meningitis. *Arch Dis Child* 1989;64:814-20.
8. Baker ND, Kharazi H, Laurent L, et al. The efficacy of routine head computed tomography (CT scan) prior to lumbar puncture in the emergency department. *J Emerg Med* 1994;12:597-601.
9. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med* 2001;345:1727-33.
10. Mellor DH. The place of computed tomography and lumbar puncture in suspected bacterial meningitis. *Arch Dis Child* 1992;67:1417-9.

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## NALTREXONE TREATMENT FOR ALCOHOL DEPENDENCE

TREATMENT for alcohol dependence has been limited almost entirely to various types of counseling. An exception has been the use of the medication disulfiram, which acts indirectly by making a person feel ill if he or she drinks alcohol. The efficacy of disulfiram is limited, however, because compliance is often poor, and it is not widely used.

Counseling patients with alcoholism leads to rates of remission similar to those achieved with treatment of other chronic medical conditions, such as asthma.<sup>1</sup> Nonetheless, the large number of people dependent on alcohol in the United States (over 8.1 million<sup>2</sup>) and the substantial costs of alcoholism to society — an estimated \$185 billion and 100,000 deaths each year — make it imperative that treatment be improved. Thus, it is not surprising that reports in 1992<sup>3,4</sup> that the opiate antagonist naltrexone reduced the relapse rate in people dependent on alcohol generated substantial interest. The reports suggested that treatment could be improved through the use of medication in conjunction with counseling.

Since the initial report by Volpicelli et al.<sup>3</sup> and the confirmation by O'Malley et al.,<sup>4</sup> there have been additional randomized, placebo-controlled clinical trials of the effectiveness of naltrexone in treating alcoholism.<sup>5-11</sup> Six<sup>5-10</sup> found that naltrexone was effective in preventing relapse in compliant patients. The clinical

end points varied. Four studies<sup>3,6-8</sup> defined relapse as having five or more drinks on one occasion, having five or more drinking occasions in one week, or arriving at a clinic visit intoxicated (blood alcohol concentration above 100 mg per deciliter). Two studies<sup>4,5</sup> used the time to the first day of heavy drinking as a measure of the time to relapse; one of these<sup>4</sup> also used the time to any drinking. One study<sup>9</sup> found a greater reduction in the amount of alcohol consumed and in the levels of  $\gamma$ -glutamyltransferase in patients who were compliant with the naltrexone regimen, whereas another<sup>10</sup> found significantly fewer heavy drinking days and fewer drinks on the days patients drank.

A double-blind, placebo-controlled trial of another opioid antagonist, nalmefene, found that it also prevented relapse of heavy drinking.<sup>12</sup> A controlled study of naltrexone, nefazodone, and placebo in 183 patients found no benefit from naltrexone; naltrexone was associated with more adverse events than placebo and more attrition from the study than nefazodone and placebo.<sup>11</sup> Finally, a recent meta-analysis found that naltrexone was moderately effective in reducing alcohol consumption in alcoholics.<sup>13</sup>

In this issue of the *Journal*, Krystal and his colleagues from the Veterans Affairs Naltrexone Cooperative Study 425 Group report the results of a multicenter, double-blind, placebo-controlled evaluation of naltrexone as an adjunct to standardized counseling for alcohol dependence.<sup>14</sup> In 627 veterans (almost all men), they found no benefit from naltrexone, as measured by the time to relapse, the percentage of days on which drinking occurred, or the number of drinks per drinking day. Although the study by Krystal et al. is larger than the previous studies, additional factors may explain the discordant findings.

The typical patient in the study by Krystal et al. was about 10 years older than the patients in the previous studies (except for one study, in which the objective was to study naltrexone in older patients<sup>7</sup>). The typical patient had also been drinking for a longer period of time. Alcoholics who have families and are employed have a better prognosis than those who live alone or are unemployed. Only one third of the veterans in the study by Krystal et al. were married or living with a partner; these are smaller percentages than in most of the previous studies. Employment data are not given, but one third of the veterans were receiving disability pensions, a fact that may have affected their motivation to stop drinking. As Krystal et al. acknowledge, their results may not be generalizable to people who are not veterans, to women, or to patients whose dependence on alcohol is of shorter duration.

One of the early studies of naltrexone also involved patients treated at a Veterans Affairs hospital.<sup>1</sup> The study was conducted at a single site, and for three months patients returned to the hospital daily for six to eight hours of rehabilitation activities. In the study by Krystal et al.,<sup>14</sup> which involved multiple sites, patients received outpatient counseling for one hour per week for 16 weeks and then at a decreasing frequency

for the remainder of a year. It is possible that in order to benefit from naltrexone, patients with more severe alcohol dependence require more intensive counseling.

The studies involving naltrexone also vary in the types of counseling used in conjunction with the medication. Four of the studies that showed a benefit<sup>4-6,8</sup> used coping-skills therapy or relapse-prevention training. These types of counseling are commonly used in the treatment of alcoholism. In both, patients are taught to identify situations or mood states that place them at high risk for a relapse and are helped to develop coping skills to reduce the probability of a relapse. Although a negative study<sup>11</sup> also used a relapse-prevention approach, the preponderance of the evidence suggests that this approach should be used in combination with naltrexone. Coping-skills therapy is different from the 12-step facilitation counseling used in the study by Krystal et al., which encourages involvement in Alcoholics Anonymous.

As the value of any medication is being established, randomized clinical trials are not always consistent in their findings. Our institute is currently supporting a multicenter, placebo-controlled clinical trial of naltrexone and acamprosate, another medication for the treatment of alcoholism, alone or in combination in a younger group of patients (30 percent of whom were women) than those in the study by Krystal et al. The efficacy of acamprosate appears to be similar to that of naltrexone. It is not an opiate antagonist, although the precise mechanism of its action is not known. Acamprosate affects the activity of *N*-methyl-D-aspartate receptors, which are components of the glutamate system; the effects of alcohol are mediated to some extent by this system. At least 12 of 14 controlled clinical trials conducted in Europe support its effectiveness.<sup>15</sup> Diarrhea may be a side effect of acamprosate but is usually not severe enough to require cessation of treatment. Acamprosate is approved for use in most European countries, several Latin American countries, and Australia. In the United States, acamprosate is under review by the Food and Drug Administration.

If additional studies find that naltrexone works, it will be important to identify which patients are likely to benefit and which are not. If no benefit is found, such results, coupled with the results of the study by Krystal et al., would weigh against the use of naltrexone as an adjunctive treatment for alcoholism. Until we have more information, we recommend that physicians continue to prescribe naltrexone for patients they think might benefit. Such patients appear to be those who have been drinking heavily for 20 years or less and have stable social support and living situations.

Advances in our understanding of the neurobiology of alcohol dependence provide the foundation for developing new medications to treat the disorder. In addition to the opioid system, preclinical studies have shown that alcohol affects neurotransmitters in the brain, including dopamine, serotonin, glutamate,  $\gamma$ -aminobutyric acid, and norepinephrine. Second-

messenger systems, such as the  $\epsilon$  isoform of protein kinase C and the hypothalamic-pituitary-adrenal axis, are involved in problem drinking. The hypothalamic-pituitary-adrenal axis also has a pivotal role in stress. A number of compounds affecting these systems have shown efficacy in reducing alcohol consumption in studies in animals. They include an *N*-methyl-D-aspartate agonist, a compound that is both a serotonin 1A-receptor agonist and a serotonin 2-receptor antagonist, and a corticotropin-releasing-factor antagonist. At the clinical level, a recent trial indicated that ondansetron, a selective serotonin 3-receptor antagonist,<sup>16</sup> shows promise for the treatment of people who become dependent on alcohol before the age of 25 years. Because so many new approaches seem promising, we are optimistic that more effective medications will be found.

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## REFERENCES

1. McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000;284:1689-95.
2. Grant BF, Harford TC, Dawson DA, Chou P, Dufour M, Pickering R. Prevalence of DSM-IV alcohol abuse and dependence: United States, 1992. *Alcohol Health Res World* 1994;18:243-8.
3. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 1992;49:876-80.
4. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. *Arch Gen Psychiatry* 1992;49:881-7.
5. Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK. Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. *Am J Psychiatry* 1999;156:1758-64.
6. Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2001;21:287-92.
7. Oslin D, Liberto JG, O'Brien J, Krois S, Norbeck J. Naltrexone as an adjunctive treatment for older patients with alcohol dependence. *Am J Geriatr Psychiatry* 1997;5:324-32.
8. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence: role of subject compliance. *Arch Gen Psychiatry* 1997;54:737-42.
9. Chick J, Anton R, Chęcinski K, et al. A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol Alcohol* 2000;35:587-93.
10. Monti PM, Rohsenow DJ, Swift RM, et al. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. *Alcohol Clin Exp Res* 2001;25:1634-47.
11. Kranzler HR, Modesto-Lowe V, Van Kirk J. Naltrexone vs. nefazodone for treatment of alcohol dependence: a placebo-controlled trial. *Neuropsychopharmacology* 2000;22:493-503.
12. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 1999;56:719-24.
13. Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcohol Clin Exp Res* 2001;25:1335-41.
14. Krystal JH, Cramer JA, Krol WF, Kirk GE, Rosenheck RA. Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 2001;345:1734-9.
15. Mason B, Ownby RL. Acamprosate for the treatment of alcohol dependence: a review of double-blind, placebo-controlled trials. *CNS Spectrums* 2000;5:58-69.
16. Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. *JAMA* 2000;284:963-71.

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