Injectable Naltrexone Shows Improved Efficacy

BY CARL SHERMAN
Contributing Writer

NEW YORK — An injectable depot formulation of naltrexone, now in phase III trials, may help overcome the adherence problems that have compromised the drug's efficacy in the treatment of alcohol dependence, Helen M. Pettinati, Ph.D., said at the annual conference of the Association for Research in Nervous and Mental Disease.

Naltrexone is one of three drugs that have received approval from the Food and Drug Administration for alcoholism. The compound, an opioid antagonist first used for opiate addiction, blocks reward pathways in the brain. It appears to reduce the excitement that some derive from alcohol ingestion, as well as alcohol craving.

Treatment with naltrexone appears less consistent with total abstinence than with reduction in excessive drinking.

In a study of 624 people, those receiving 380 mg of naltrexone monthly had 25% fewer days of heavy drinking per month than those receiving placebo.

Of 24 double-blind controlled trials, 77% found that there was significantly less harmful drinking with the drug, compared with placebo, but many found that there was no difference in drinking days or other measures of abstinence.

Clinically, compliance difficulties have limited the utility of naltrexone, according to Dr. Pettinati, who is professor of psychiatry at the University of Pennsylvania in Philadelphia.

In one study, rates of relapse to heavy drinking were significantly lower among 60 naltrexone patients than among 44 placebo patients who attended 80% of clinic visits (10% vs. 38%). But there was no difference in relapse rate between 50 patients who were nonadherent to placebo and 42 who failed to follow the naltrexone regimen: 40% vs. 42%, respectively.

Attention to adherence should be a routine, proactive part of naltrexone treatment, Dr. Pettinati said.

The actual use of the medication may be monitored with blister packs or diaries. "If there's a poor response to treatment, ask about adherence—it's one of the most common explanations," she pointed out at the meeting, which was cosponsored by the New York Academy of Medicine.

Reasons for nonadherence should be explored and strategies devised to overcome problems. "The most common reason patients give for not taking the medication is 'I forgot,' but usually it's because they feel they are getting better and want to go out drinking," she said.

The depot formulation of naltrexone should provide an alternative to tablets that will reduce adherence difficulties. The intramuscular preparation lasts for 30 days. In a 24-week study involving 624 people, those receiving 380 mg of naltrexone monthly had significantly (25%) fewer days of heavy drinking per month than did those receiving placebo. Participants on a lower dosage (190 mg) of the drug had 17% fewer drinking days, which was not significant.

"You see the effect right away—you don't have to wait 6 months," Dr. Pettinati said.

Contrary to some concerns, patients appeared to have no difficulty adhering to the regimen: Seventy-four percent took at least four of the six injections.

In another study of 315 alcohol dependent persons, those taking a somewhat lower dose (150 mg/mo) of depot naltrexone were significantly more likely to remain abstinent than was a placebo group during a 12-week study (18% vs. 10%).

Adherence was high: Three-fourths of patients in the naltrexone group received all scheduled injections, Dr. Pettinati said.

Other recent research suggests that variations in a μ-opiate receptor gene may account for differences in response to naltrexone.

In one study, those with one or two copies of the allele *Asp40* had significantly lower relapse rates and a longer time to heavy drinking, when treated with naltrexone, than did those who were homozygous for the *Asn40* allele, Dr. Pettinati said. ■