

Extended-Release Naltrexone Shows Rapid Onset

Pharmacokinetic data show that peak plasma concentration is reached on day 3 after injection.

BY TIMOTHY F. KIRN
Sacramento Bureau

SAN DIEGO — The new long-acting, injectable formulation of naltrexone takes effect rapidly and probably does not need to be combined with an oral dose to prevent alcohol-dependent patients from early hazardous drinking, according to a company presentation at the annual meeting of the American Society of Addiction Medicine.

Nor does it appear that treating a person with the new formulation decreases their motivation to attend self-help meetings such as those sponsored by Alcoholics Anonymous (AA), according to another presentation.

In a subgroup analysis of the 624 subjects in the randomized, placebo-controlled trial of injectable, extended-release naltrexone (Vivitrol) conducted for the formulation's approval, drinking was reduced significantly in just 2 days after the injection, said Dr. Domenic A. Ciraulo, professor of psychiatry at Boston University, in a poster presentation.

Two days after the first injection, the median number of drinks taken by those 209 subjects who received placebo was two. That compared with a median of one drink for the group of 210 subjects who received an injection dose of 190 mg, and a median of no drinks in the group of 205 subjects who received an injection dose of 380 mg, the dose that was approved.

Moreover, to be enrolled in the study, the subjects had to report a minimum of 2 days per week of "heavy" drinking in the month before they were screened, with heavy drinking being defined as a day in which male subjects had five or more drinks and female subjects had four or more drinks.

But in the first 3 days after the injection, while 35% of the subjects who received placebo reported a heavy drinking day, 32% of the subjects who received the lower dose and 20% of the subjects who received the higher dose reported a heavy drinking day.

The difference between the placebo and the high-dose percentages is statistically significant, Dr. Ciraulo said.

Of note, about 90% of the subjects enrolled in the study were not abstinent when they received their first injection, and only 43% stated that their goal was abstinence.

During the first month of treatment, the median number of heavy drinking days was 6.5 for the placebo group, 5.7 for the low-dose group, and 4.1 for the high-dose group. That compared with a baseline of a median of 19 heavy drinking days per month before treatment.

Pharmacokinetic data from healthy volunteers show that the peak plasma concentration of extended-release naltrexone is reached on day 3 after injection, at about 27-28 ng/mL, and then falls thereafter, reaching 1 ng/mL, the minimum concentration thought to be effective,

on day 30, Dr. Ciraulo said in the poster.

The analysis suggests that one does not need to give oral naltrexone to patients starting treatment in order to carry them over until the injectable, timed-release formulation takes over, and for most patients, the long-acting naltrexone treatment is going to have significant advantages over oral naltrexone, Dr. Ciraulo said in an interview.

"With depot agents, you never know about release," he said. "In my clinical practice, I would go to this [extended-release formulation] first."

Injectable, extended-release naltrexone was approved by the Food and Drug Administration in April. The approval is for one intramuscular, gluteal injection every 30 days.

In the 624 patient study, funded and conducted by Alkermes Inc., Cambridge, Mass., patients were treated for 6 months. The study found a 48% greater reduction in heavy drinking days with the high-dose regimen, compared with placebo.

The median number of days of heavy drinking, which had been about 19 days per month prior to treatment, dropped to 6 days per month in the placebo group and to about 3 days in the group on high-dose naltrexone.

Sixty-four percent of the study subjects remained compliant in the study and received all six doses of medication.

The other study presented at the meet-

ing looked at whether that success with the medication inspired complacency.

But if anything, it seemed to be associated with a "trickle-up effect," said Dr. David R. Gastfriend, a vice president of Alkermes.

In the month before treatment, 11% of the subjects attended a self-help group such as AA. During the trial, 10% of the placebo-treated patients attended such groups each month, as did 11% of those subjects who received the low-dose injections and 13% of those who received the high dose.

Moreover, among the patients who had some abstinence going into the study, reductions in drinking were even greater than for the study population overall,

Dr. Gastfriend said.

Eighty-two subjects had 4 days of abstinence leading into their first injection; 53 patients had 7 days of abstinence.

In the patients with 4 days of abstinence, the median number of days to their first drink following treatment initiation was 12 days in the placebo group (28 subjects), 24 days for the low-dose group (26 subjects), and 42 days for the high-dose group (28 subjects).

In the patients with 7 days of abstinence, the median was 84 days for the high-dose group (17 subjects).

The groups with 4 and 7 days of abstinence who received the high dose both also reduced their median days of heavy drinking per month to 0.2 days. ■

In the first month of treatment, the median number of heavy drinking days was 6.5 for the placebo group and 4.1 for the high-dose group.

For Older Women, Prenatal Alcohol Use Affects Children's Growth

BY BETSY BATES
Los Angeles Bureau

SANTA BARBARA, CALIF. — The children of older mothers who drank during pregnancy were shorter and had smaller head circumferences at the ages of 7 and 14 years than other children at those ages, it was reported at the annual meeting of the Research Society on Alcoholism.

Children of mothers who were 30 or older at delivery were affected above a threshold of moderate alcohol consumption, defined as about one alcoholic drink a day at the time of conception. Many women reduced their drinking during pregnancy, but the heaviest drinkers reduced their drinking less.

"Even if women reduce their drinking during pregnancy, their early drinking before they realize they are pregnant may have an impact on the infant," said Sandra W. Jacobson, Ph.D., professor of psychiatry and behavioral neurosciences at Wayne State University in Detroit, a senior author on the study.

"We see effects in infants whose mothers drink as little as one drink/day, on average."

Dr. Jacobson stressed that "average" drinks per day did not reflect the actual drinking patterns among women in the study. Just 1 woman of the 480 in the Detroit Longitudinal Prenatal Alcohol Exposure study actually drank every day.

Many of the others concentrated their drinking on 1 or 2 days a week, in some cases drinking three to four drinks at each session, she explained following the meeting.

Mean alcohol consumption at conception was about two drinks per day in the study of economically disadvantaged African American women and their children.

Mean alcohol intake dropped during pregnancy to a little more than two drinks per week.

Prenatal alcohol exposure was associated with lower birthweight and length in the entire sample of women, even after researchers controlled for smoking and other possible confounders, Dr. Jacobson said.

For mothers over 30 years of age at conception, the repercussions were long lasting.

With a cutoff point of 0.5 ounces of alcohol per day at conception, older mothers' children were 1.2 cm, 3.1 cm, and 3.7 cm

shorter at birth, 7.5 years, and 14 years, respectively, than children of mothers with minimal alcohol exposure, she reported.

Their mean head circumference was smaller by 4.6 mm, 7.3 mm, and 14.5 mm at birth, 7.5 years, and 14 years.

"Prenatal alcohol exposure was not related to weight or body mass index at 7.5 or 14 years, suggesting that the effects on height and head circumference were not attributable to poor maternal nutrition," the researchers reported in their poster presentation.

Smoking during pregnancy resulted in lower birthweight and reduced length and head circumference at birth, but had no discernible impact on children's growth over time.

In contrast, prenatal alcohol exposure's impact on size was evident at birth and became magnified as the study continued.

Although the study suggests that the children of older mothers are most vulnerable to prenatal alcohol exposure, all women who are considering pregnancy should be urged to stop drinking or to cut down as much as possible.

"At this time, no drinking is considered safe," said Dr. Jacobson.

The study was supported by grants from the National Institute on Alcohol Abuse and Alcoholism and the Joseph Young, Sr., Fund of Michigan.

Douglas Fuller, a research assistant in the Wayne State University department of psychiatry and behavioral neurosciences, contributed to the study. ■

