Neuroactive Steroids May Bolster Naltrexone

BY BRUCE JANCIN

ISTANBUL, TURKEY — Neuroactive steroids might have a future as adjunctive therapy for alcohol dependence in a subset of affected patients, a pharmacogenetic study suggests.

The therapeutic response to naltrexone is known to be best in alcoholic patients with the mu-opiate receptor gene OPRM1 polymorphism Asn40/Asp40. The mechanism for this selective benefit was previously unknown.

However, new data indicate that naltrexone substantially boosts levels of GABAergic neurosteroids in patients with Asn40/Asp40, but not in those who are Asp40/Asp40, A. Leslie Morrow, Ph.D., reported at the annual congress of the European College of Neuropsychopharmacology.

The clinical implication is that endogenous GABAergic neurosteroids contribute to naltrexone's efficacy. And this leads to a testable hypothesis: that administration of exogenous neurosteroids will boost the therapeutic response to naltrexone in patients lacking the OPRM1 Asn40/Asp40 polymorphism, said Dr. Morrow, professor of pharmacology at the University of North Carolina, Chapel Hill.

Naltrexone boosted activity of endogenous allopregnanolone in Asn40/Asp40 patients by a mean of 48%.

DR. MORROW

The study participants were 32 non–treatment-seeking alcoholics, who were aged between 21 and 35 years (average 22.2). Of the total, 9 were women, 26 (82.3%) were white, 4 (12.5%) Asian, and 2 (6.3%) Hispanic.

To be included, they had to have a score of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT), a self-reported drinking frequency of 3 or more drinks (2 for women) at least twice a week, no history of prior treatment for an alcohol use disorder and no current interest in treatment, no history of medical conditions that would contraindicate the study medication; and successfully complete a physical exam.

Female participants completed a pregnancy test before each alcohol administration session.

In this sample, the average number of drinks per drinking episode was 4.7 (range, 2-12), the average drinking frequency was twice a week, and the average AUDIT score was 12.8 (range, 8-21).

Dr. Morrow and her colleagues gave the participants naltrexone for 3 days at 50 mg/day, then administered alcohol or placebo by intravenous infusion. They measured serum neurosteroid levels at baseline and after subjects reached a target blood alcohol level of 0.06 g/dL in response to the infusion.

Naltrexone boosted activity of endogenous allopregnanolone and related neurosteroids by a mean of 48% in subjects who were Asn40/Asp40, but not in those who were homozygous for Asp40.

An audience member observed that the importance of neuroactive steroids in a variety of brain functions and behaviors has been known for decades. Why, he asked, is it taking so long to capitalize on the intriguing basic science findings and develop synthetic neurosteroids suitable for study in clinical trials?

"The real concern is that there might be hormonal effects on endocrine function other than brain function. That's been the real holdup. Some of the major drug companies are hesitant to use these neuroactive steroids because of effects they might have on the reproductive system or other systems," according to Dr. Morrow.

There is hope, however. Marinus Pharmaceuticals has a neurosteroid drug, ganaxolone, in phase III clinical trials for epilepsy. If ganaxolone eventually wins Food and Drug Administration approval, it will become easier to study it in clinical trials for other potential indications, she said.

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