TRIAL WATCH

Nalmefene reduces alcohol use in Phase III trial

Preliminary results from a Phase III clinical trial of nalmefene in individuals with alcohol addiction have shown that this opioid receptor antagonist reduces alcohol consumption. If this drug is approved, patients could take nalmefene as and when needed, and would not need to totally abstain from alcohol consumption.

"Because existing medications — such as the opioid receptor antagonist naltrexone — aim for total abstinence from alcohol and need to be taken every day, they are seldom prescribed and not acceptable to many patients," says Karl Mann, who is chair in addiction research and deputy director of the Central Institute of Mental Health, University of Heidelberg, Germany, and was an investigator on the trial. "Currently, only about 2 to 5% of patients with full-blown alcohol dependence get specific treatment."

In the trial, which was the last of three trials in the Phase III clinical programme of nalmefene, 718 individuals received 20 mg (orally) of nalmefene or placebo on an as-needed basis for 28 weeks. Patients who received nalmefene had a 50% decrease in the number of days of heavy drinking (defined as five or more drinks per day for men and four or more drinks per day for women). Furthermore, data from a 12-month safety study confirmed that this effect is maintained after 1 year of treatment, and leads to a 60% reduction in alcohol consumption.

Of note, the end points in the Phase III clinical trial programme included reductions in the number of days of heavy drinking and total alcohol consumption. Mann notes: "The use of such end points represents a paradigm shift for the regulatory agencies. The European Medicines Agency has accepted a reduction in drinking as an end point in treatment trials, expecting a subsequent improvement in the patient's overall situation, which then can result in abstinence. The US Food and Drug Administration (FDA) does not accept this approach yet."

Markus Heilig, clinical director of the US National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, USA, is concerned about the FDA's view on clinical trial end points. "The refusal of the FDA until now to accept a reduction in alcohol consumption as an end point is short-sighted. A reduction in drinking brings about many clinical benefits, such as a reduction in medical complications and better social functioning of the patient."

In the Phase III clinical programme of nalmefene, a medical compliance encouragement programme was included. Because ensuring patient compliance is a challenge, both Mann and Heilig think that it will be useful for patients to be enrolled in such a programme if the drug is marketed. This will help to ensure that patients reduce their alcohol consumption and so have the opportunity to change their lifestyle and behaviour.

Although the mechanism of action of nalmefene is not novel, compared to other opioid receptor antagonists it has a longer half-life and displays partial agonist activity at κ-opioid receptors; these differences could account for the beneficial effects of nalmefene over existing opioid receptor antagonists. Opioid receptor antagonists block the rewarding effects of alcohol, which are driven by positive reinforcement processes in the brain. However, as Heilig highlights: "In some groups of people — such as long-term addicted individuals or socially anxious addicted people — drinking behaviour is not driven by positive reinforcement, and so nalmefene will probably not work in these individuals." He concludes: "The challenge for alcohol addiction therapy is to find drugs with complementary mechanisms and to work out which patients to treat with which drugs at what stage in the addictive process."