Cardiovascular safety of obesity treatment naltrexone-bupropion uncertain

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The cardiovascular safety of the obesity treatment naltrexone-bupropion remains uncertain because of the unanticipated early termination of a trial to determine its safety, according to a study appearing in the March 8 issue of *JAMA*.

Drug treatments for obesity have yielded mixed results, with pharmacological agents achieving modest weight loss but without demonstrating a reduction in cardiovascular events. Two therapies, fenfluramine and sibutramine, were removed from the market after evidence of cardiovascular harm emerged. Accordingly, the medical community and regulatory authorities have expressed concern about the cardiovascular safety of new drugs to treat obesity. The combination of the drugs naltrexone and bupropion reduced weight during phase 3 clinical trials, but the U.S. Food and Drug Administration (FDA) deferred approval based on safety concerns related to small increases in blood pressure and heart rate in these trials.

Steven E. Nissen, M.D., of the Cleveland Clinic Center for Cardiovascular Research, Cleveland, and colleagues randomly assigned 8,910 overweight or obese patients at increased cardiovascular risk to receive placebo (n=4,454) or naltrexone and bupropion (n=4,456). An Internet-based weight management program was provided to all participants. The study was conducted at 266 U.S. centers. The researchers examined whether the combination of naltrexone and bupropion increases major adverse cardiovascular events (MACE, defined as cardiovascular death, nonfatal stroke, or nonfatal heart attack)

compared with placebo.

For the 25 percent interim analysis (after approximately 87 events), MACE occurred in 59 placebo-treated patients (1.3 percent) and 35 naltrexone-bupropion-treated patients (0.8 percent). After 50 percent of planned events, outcomes were less favorable for naltrexone-bupropion patients, with MACE occurring in 102 patients (2.3 percent) in the placebo group and 90 patients (2.0 percent) in the naltrexone-bupropion group. After public release of confidential interim data (after 25 percent of planned events) by the sponsor, the academic leadership of the study recommended termination of the trial and the sponsor agreed.

The authors write that given the unplanned early termination of the trial, which directly resulted from the inappropriate release of the highly favorable 25 percent interim data, these findings do not establish the prespecified margin of noninferiority (not worse than). "Accordingly, the cardiovascular safety of this treatment remains uncertain and will require evaluation in a new adequately powered outcome trial."

"The events leading to the termination of the study serve as a valuable reminder of the importance of maintaining confidentiality during ongoing trials. Premature release of interim data can result in inappropriate prejudgment about the benefits or risks of the studied therapy and make completion of the trial highly problematic. An FDA guidance for industry explicitly states that interim data from an ongoing clinical trial should remain confidential and warns that 'such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses.'"

"In the shadow of [this trial, LIGHT], the FDA should review its policy of permitting approval based on interim analyses of ongoing safety studies. At a minimum, when a company violates its commitment to confidentiality and the FDA requires a new trial, the agency should delay

approval at least until a viable replacement study is being conducted," write Joshua M. Sharfstein, M.D., of the Johns Hopkins Bloomberg School of Public Health, Baltimore, and Bruce M. Psaty, M.D., Ph.D., of the University of Washington, Seattle, in an accompanying editorial.

"The FDA should pursue additional safeguards to prevent breakdowns in sponsor-investigator relationships and avoid the dissolution of future trials. For example, the agency should consider having data monitoring committees report interim results directly to the FDA, not to the sponsor."

"The LIGHT study should serve as an important message to sponsors of clinical trials. ... Repeated breaches of confidentiality may leave the FDA no alternative other than to require that full safety studies be conducted prior to product approval. The demise of the LIGHT trial is a reminder that basing approval on interim safety data is a carefully drawn compromise, not an entitlement."

More information: *JAMA*, DOI: 10.1001/jama.2016.1558
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