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RESPONSE TO LETTER

Potential Cardiovascular Risks Associated with Naltrexone-Bupropion Treatment in Overweight Patients [Response to Letter]

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Dear editor

We appreciate the interest of Wu et al[1] in our recent publication on safety and effectiveness of naltrexone-bupropion in Korean adults with obesity.[2] While we appreciate the thoughtful observations of Wu et al, we believe that some aspects of their commentary could benefit from a broader consideration of the evidence base regarding naltrexone-bupropion's safety and efficacy profile.

Wu et al have raised concerns about potential interactions between naltrexone-bupropion and monoamine oxidase inhibitors (MAOIs). To address this, we wish to emphasize that the prescribing information for naltrexone-bupropion combination globally, including in South Korea, clearly states that at least 14 days must elapse between discontinuation of MAOIs and initiation of naltrexone-bupropion. While our paper did not explicitly mention this, no patients in our study were prescribed naltrexone-bupropion concomitantly with any MAOIs, in line with established prescribing guidelines and medical practice. We acknowledge Wu et al's suggestion to thoroughly review participants' medication histories in future studies and wish to reassure readers that such reviews are an integral part of responsible medical practice. Additionally, our study explicitly states that patients with psychological disorders contraindicating the medication were excluded, which reflects adherence to prescribing guidelines and serves as a measure to minimize the risk of inappropriate use of naltrexone-bupropion in the study population.

Wu et al questioned the evidence supporting the cardiovascular safety of naltrexone-bupropion in individuals with obesity at high cardiovascular (CV) risk. However, it is important to clarify that our study was a six-month post-marketing surveillance study and was not designed to comprehensively evaluate cardiovascular safety outcomes. Consequently, the scope of our research did not include assessing the specific cardiovascular risks highlighted by Wu et al. The primary objective of our study was to provide real-world data on the safety and effectiveness of naltrexone-bupropion in a Korean population, not to serve as a cardiovascular outcomes trial. We emphasize that our findings should be interpreted within the context of the study's design and objectives.

We appreciate Wu et al's comments regarding the dose-response relationship observed in our study. As they noted, similar weight loss outcomes were observed between the 16/180 mg and 32/360 mg groups. However, it is crucial to understand that our study, a prospective, real-world, non-interventional post-marketing surveillance study, was primarily designed to evaluate the real-world effectiveness and safety of naltrexone-bupropion in clinical practice, not to conduct a rigorous dose-comparison analysis. Our findings offer valuable insights into the effectiveness of the 16/180 mg maintenance dose, which has been less extensively studied in previous trials. The comparable weight loss observed with this lower dose is a noteworthy contribution, suggesting its potential benefit for certain patients. While acknowledging the similar overall weight loss between groups, we also observed a greater proportion of patients in the 32/360 mg

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group achieving clinically significant weight loss thresholds (5%, 7%, and 10%). This suggests a potential dose-response relationship that warrants further investigation in future research.

This study contributes novel real-world data on the safety and efficacy of the lower 16/180 mg maintenance dose, highlighting its potential utility in clinical practice. These findings underscore the importance of individualized treatment approaches, where the optimal dose of naltrexone-bupropion is determined based on each patient's specific characteristics and needs, balancing efficacy and tolerability. Finally, as acknowledged in our study limitations, the inherent constraints of post-marketing surveillance, including the potential impact of dropouts, warrant consideration. While reflecting real-world challenges in obesity management, these factors underscore the need for future research to further explore the optimal dosing strategies for naltrexone-bupropion.

We appreciate the excellent suggestion to incorporate objective cardiovascular risk indicators such as high-sensitivity C-reactive protein (hs-CRP), blood lipid levels, blood pressure, and heart rate for a more comprehensive evaluation of the drug's safety and efficacy. We acknowledge that our study was limited in not analyzing these parameters, which represents an important area for future research. However, pivotal Phase 3 trials have already demonstrated significant weight loss and improvements in various cardiometabolic parameters with naltrexone-bupropion.[3–6] These include reductions in waist circumference, hs-CRP, triglycerides, LDL-C, and improvements in HDL-C, the LDL-C/HDL-C ratio, and quality of life. Additionally, significant improvements in fasting glucose, insulin, HOMA-IR, and A1C have been observed.[3–7] These findings provide robust evidence of naltrexone-bupropion's positive effects on cardiometabolic health and demonstrating its potential as part of a comprehensive obesity management strategy.

We appreciate the opportunity to clarify these points and believe that the totality of evidence supports the continued use of naltrexone-bupropion as a valuable tool in the management of obesity, with appropriate consideration of individual patient factors and adherence to prescribing guidelines.

Disclosure

The authors declared no conflicts of interest in this communication.

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