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LETTERS TO THE EDITOR

Response to: Real effect vs placebo effect

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We thank Dr. Hunasikatti for his commentary[1] on our study titled "Effects of trazodone versus cognitive behavioral therapy in the insomnia with short sleep duration phenotype: a preliminary study."[2] Trazodone, a heterocyclic antidepressant in low doses of 25 to 150 mg, has been the second most widely prescribed medication for sleep for the last 20 years in the United States.[3] In fact, a recent study showed that trazodone has been prescribed in increasing trends in the last 10 years.[4] Only in 2018, there were 24,000,000 prescriptions for low-dose trazodone in U.S. adults.[4] Hence, the following question arises: Why do so many physicians and patients use this medication although it is not approved by the U.S. Food & Drug Administration, not recommended by scientific organizations, and not promoted by industry? A critical issue is that trazodone, despite its widespread use by the U.S. public as prescribed off-label by their physicians, has remained grossly understudied in randomized clinical trials (RCTs) for insomnia; thus, trazodone lacks evidence from RCTs.[5] This concern was one of our motives to initiate this small pilot study.

The lack of evidence and guideline indication for trazodone did not stop Morin and colleagues[6] from investigating its therapeutic effect as a second-stage agent in a sequential RCT with hundreds of patients. Interestingly, their large RCT showed that cognitive-behavioral therapy for insomnia was most effective in reducing sleep latency and wake time after sleep onset and in increasing sleep efficiency, whereas medications had their strongest effect on increasing total sleep time, particularly when patients were switched from zolpidem to trazodone.[6] The investigators concluded that "[G]iven the emerging literature on insomnia phenotypes and the higher risk for cardiovascular morbidity among individuals with insomnia and short sleep duration, such findings could guide the development of personalized therapies for insomnia management."[6]

In summary, we would agree with Dr. Hunasikatti's concern[1] about the use of trazodone in our small pilot study if our sample had comprised at-risk individuals for whom trazodone contraindications existed; with this not being the case, "lack of evidence" arising from multiple reasons and sources, including physicians' preferences or industry interest, should never stop scientific inquiry. Leaving trazodone underinvestigated, despite promising results, and grossly prescribed should be a matter of public health concern for the National Institutes of Health and the U.S. Food & Drug Administration.

Insomnia with objective short sleep duration was proposed by our group as a novel phenotype associated with activation of the stress system, particularly the hypothalamic-pituitary-adrenal axis, significant cardiometabolic and neurocognitive morbidity, and, possibly, better response to biologic treatments.[7] Comparing the effectiveness of a pharmacologic agent that seemed to decrease the activation of the hypothalamic-pituitary-adrenal axis and increase total sleep time with that of cognitive-behavioral therapy for insomnia, the first-line recommended treatment, was one of the goals of our preliminary study. Our results are interesting but far from conclusive, as indicated in the title of our report. Notably, 4 studies consisting of retrospective secondary analyses of previously published RCTs have found lower insomnia remission rates after cognitive-behavioral therapy for insomnia in the insomnia with objective short sleep duration phenotype than in the insomnia with normal sleep duration phenotype,[8–11] and 3 other studies have found equivalent insomnia remission rates in these 2 phenotypes.[12–14] Similarly, despite this preliminary evidence, the issue of the relative efficacy of cognitive-behavioral therapy for insomnia in our proposed insomnia phenotypes remains inconclusive but should fuel scientific inquiry for well-designed, adequately powered, prospective RCTs using a personalized medicine, phenotype-matching approach.

Dr. Hunasikatti[1] also noted our choice of measure and cutoff point for total sleep time when classifying the insomnia with objective short sleep duration phenotype. The answer is clearly indicated in the "Methods" section of the article and discussed in the following manner:

> *In this study, we used the cut-off of less than 7 hours via actigraphy, which was the closest meaningful cut-off to the median of 6.8 hours. This is higher than the cut-off of 6 hours, which was the median PSG sleep duration in physiological studies and in large random general population samples. It is to be expected that the median value of TST will differ based on the method used (i.e., actigraphy tends to overestimate TST when compared to PSG), population studied (i.e., general random sample versus clinical or volunteer), and age of the sample. We have emphasized that the previously suggested cut-off of 6 hours for the ISS phenotype has been used as an internally valid marker of the severity of insomnia and not as a recommended optimal sleep duration for the general population.*[2]

These statements and approach should have resolved any concerns and is consistent with our early proposal that an important research agenda for insomnia phenotyping was to "replace the expensive, inconvenient, and impractical in-lab

sleep measures with easy-to-use, inexpensive, home-based objective sleep measures."[7] Future studies should validate actigraphy and other wearable technology, not just to accurately estimate specific polysomnography parameters as has been traditionally done but also to provide reliability and validity for specific cutoff points needed to identify individuals who are short sleepers despite adequate opportunity for sleep and, thus, individuals with the insomnia with objective short sleep duration phenotype.

The results of our small pilot study are interesting, obviously stimulating, but far from conclusive. We cannot agree more with the final statement by Wong and colleagues[4] in their *Journal of the American Medical Association* article that "[M]ore studies evaluating the efficacy and safety of trazodone for insomnia are warranted" and with the conclusive statements by Morin and colleagues[6] in their *Journal of the American Medical Association Psychiatry* article: "Additional studies are needed to validate best treatment algorithms for insomnia disorder, and rather than randomizing patients to treatment options, perhaps a more effective strategy would involve a personalized approach matching patients with their preferred treatment, while also taking into account their insomnia phenotypes (ie, presence of hyperarousal and TST)."

CITATION

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. The authors report no conflicts of interest.