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### Does a Meta-Analysis of Sleep Deprivation Studies Demonstrate Efficacy?

**To the Editor:** I read with great interest the recent meta-analysis by Boland et al on antidepressant effects of acute sleep deprivation.<sup>1</sup> These authors did a masterful job of documenting the world literature addressing sleep deprivation (wake therapy) as a possibly helpful treatment for depression. They report that wake therapy results in significant mood improvement about half of the time.

However, while they report response rates of those patients receiving wake therapy, I was unable to find in their article the likelihood of response to a comparator. Without a comparator, one might as logically conclude that the sorts of patients recruited into such studies spontaneously remit about half the time over the 2 to 4 weeks these studies were conducted. I therefore examined the 5 studies<sup>2-6</sup> they cite as randomized trials. (I did not include Smith et al<sup>7</sup> since this study states that it is a subset of Reynolds et al.<sup>3</sup>) Indeed, as Boland et al state, 51% (46/0.91) responded to antidepressant + wake therapy. However, 44% (37/85) responded to antidepressant alone ( $\chi^2_1$  [corrected] = 0.61,  $P > .1$ ), hardly a rousing endorsement for wake therapy. In light of those data, I cannot agree with Boland and colleagues' conclusion that "these findings support a significant effect of sleep deprivation."<sup>1</sup>(p e1020)

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Jonathan W. Stewart, MD<sup>a</sup>  
jws6@cumc.columbia.edu

<sup>a</sup>Clinical Therapeutics, New York State Psychiatric Institute, New York, New York

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**Drs Boland and Gehrman Reply**

**To the Editor:** We were happy to see Dr Stewart's comments, as one of the primary goals of our article<sup>1</sup> was to promote a continued dialogue about sleep deprivation as a therapeutic tool (ie, wake therapy) and model for the development of rapid and effective antidepressants. The author makes an important point, and while we highlighted the fact that the overwhelming majority of the studies included in our analysis did not include control groups, we did not examine the efficacy of comparison groups in the small number of studies that did randomize their subjects to comparison conditions. The data Dr Stewart provided are an appropriate and important contribution to this discussion.

We have 2 main points in response. First, it is difficult to define an adequate comparison group for sleep deprivation. It is not possible to blind subjects to condition since they know whether or not they are sleep deprived. Further, an appropriate comparator should be a condition that has the potential to exert rapid antidepressant effects akin to those produced by sleep deprivation. To our knowledge, no other treatment apart from ketamine produces such rapid effects, and head-to-head comparisons of sleep deprivation and ketamine have not been undertaken. In the randomized studies we included, there was also broad heterogeneity in duration of treatment, single versus multiple administrations of sleep deprivation, partial versus total deprivation, and variations in comparison medications (SSRIs as well as tricyclic antidepressants) that further muddy the picture of how sleep deprivation truly compares to known antidepressant treatments.

Our second point is related to the rapidity of the antidepressant effects of sleep deprivation. The studies cited by Dr Stewart assessed

the effects antidepressant medication *after several weeks of treatment*, not the next day. So, while it may be true that overall efficacy of wake therapy is not superior to medication, we are not aware of any evidence of placebo effects that can lead to a 50% response rate overnight. We concede that claims of the significant effect of sleep deprivation cannot be accepted without the understanding of the possible contribution of placebo and demand effects on outcome; however, we continue to see great promise in the continued examination of the mechanisms of the antidepressant effects of sleep deprivation in the service of developing rapid, effective, and longer-lasting treatments for depression.

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**Elaine M. Boland, PhD<sup>a,b</sup>**  
**Philip R. Gehrman, PhD<sup>a,b</sup>**  
 gehrman@upenn.edu

<sup>a</sup>Corporal Michael J. Crescenzo VA Medical Center, Philadelphia, Pennsylvania

<sup>b</sup>Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

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