Title

“Rebound” is not an appropriate criterion for withdrawal insomnia11Dr Kripke's response (rebuttal) to Dr Mayer and Dr Rodenbeck's letter published in Sleep Med 2014;15:1169–71.

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“Rebound” is NOT an appropriate criterion for withdrawal insomnia

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Dr. Mayer’s interesting discussion of my letter in the September, 2014 *Sleep Med.* was helpful in clarifying problems with rebound criteria in the three studies on which I had commented [1,2]. Most important, “rebound insomnia” is not a suitable criterion for lasting insomnia after drug withdrawal, especially not when defined as insomnia exceeding baseline. Rather, I had stated that the three hypnotics produced lasting withdrawal insomnia, as demonstrated throughout the post-drug observations by the drug-withdrawn patients who experienced significantly worse sleep than those who had been randomized to parallel placebo treatments.

None of the studies I had discussed really fit into the dated definitions of rebound insomnia or withdrawal insomnia in the articles by Kales which Dr. Mayer cited. I happily recall my excitement when I first met Dr. Kales 47 years ago and learned of his innovative polysomnographic studies of hypnotics, which had yielded so much new information. Unfortunately, those articles by Kales and his definitions were based on rather brief longitudinal

measurements of baseline, drug treatment, and withdrawal intervals without any counterbalancing of orders or randomized parallel placebo groups. Since Dr. Mayer recognized that each of the three long-term studies I discussed had demonstrated that the placebo groups experienced improving sleep over time, Kales's longitudinal contrasts would be biased by confounding placebo remission and order effects with incremental drug benefits. Not all of the reductions in insomnia were attributable to the hypnotics cited in Kales's studies. Scientific methods must move on.

In 1977, the FDA advised that after early Phase II, clinical trials should include parallel randomized placebo or comparator groups, a necessary control for placebo remission over time [3]. Incidentally, "rebound" analyses did not appear in the FDA design recommendations. Each of the three trials I discussed did employ a parallel randomized-placebo design. Therefore, the primary endpoints should all have concerned contrasts between the randomized drug and placebo groups. It is a fine idea to control each participant's drug and withdrawal responses for their baseline levels by computing change scores or by employing baselines as covariates, provided that the primary focus is on the contrasts between the drug and placebo responses.

It is my hope that in the future, the referees and editors of sleep journals will insist on emphasis on the drug-placebo contrasts whenever that is the prospective design.

References

(1) Kripke DF. Hypnotics cause insomnia: evidence from clinical trials. Sleep Med 2014;15:1168-9.

(2) Mayer G, Rodenbeck A. Response to Dr. Kripke's letter. Sleep Med 2014;15:1169-71.

(3) Group Leader for Neuropharmacological Drugs F. Guidelines for the Clinical Evaluation of Hypnotic Drugs. Accessed 1977. Rockville, Maryland 20857, Bureau of Drugs, Food and Drug Administration.