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HYPNOTICS CAUSE INSOMNIA: EVIDENCE FROM CLINICAL TRIALS

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Many epidemiologic studies have found insomnia associated hypnotic drug use. It is often supposed that insomnia causes people to take hypnotics. The reciprocal that hypnotics might cause insomnia has rarely been considered. Randomised placebo-controlled clinical trials have now demonstrated that hypnotics do indeed cause insomnia.

Mayer et al. reported a 6-month clinical trial of ramelteon 8 mg. versus parallel placebo.[1] During subsequent placebo run-out, the placebo group had PSG-recorded TST of 383.0 min. ±SE 4.0, whereas the ramelteon group slept 372.9 min. ±SE 4.1. The difference in means was significant ($P<0.05$, one-tailed, my computation). By focusing on rebound insomnia compared to baseline (rather than to placebo) and by focusing on sleep latency, the authors claimed that "No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation." I would say ramelteon withdrawal insomnia (not rebound insomnia) was observed, since at the end of treatment, the placebo group was sleeping 380.1 min. and the ramelteon group 381.4 min., so there was hardly a ramelteon benefit from which patients could rebound.

A 12-week clinical trial of eszopiclone 2 mg. in older adults provided another example.[2] The abstract stated, "improvements occurred within the first week and were maintained for 3 months, with no evidence of rebound insomnia following discontinuation." I must disagree with the co-authors, who included several much-honored leaders of sleep research. Since the design of the study was a randomized, double-blind, placebo-controlled study in which the efficacy endpoints were the "subjective change from baseline" (e.g., in sleep latency), withdrawal insomnia would NOT require a sleep latency worse than baseline. We see in their Figure 2 that at the start of placebo run-out, sleep latency suddenly increased about 25 minutes in the group

withdrawn from eszopiclone, becoming several SEM greater than the sleep latency of the placebo group, and since the placebo group started with slightly higher sleep latencies at baseline, the inferiority to placebo in change scores would exceed 25 min. The change-score advantage of eszopiclone during 12 weeks of drug administration was 4.7 min. superiority to placebo, but the advantage of placebo during 4 weeks of drug withdrawal averaged 7.0 min.[3] The placebo-only advantage in sleep latency persisted throughout 28 days of placebo-runout. The eszopiclone-withdrawn group was also inferior to the only-placebo group in subjective total sleep time change for the first 3 days following drug discontinuation.

A subset of participants in the eszopiclone study wore wrist actigraphs. The authors stated there would be a separate report of the objective actigraphic data, but I have not located even an abstract, so it seems up to me to interpret the objective data available at www.clinicaltrials.gov under NCT00386334.[3] Actigraphically, mean improvement in TST over 12 weeks was 4.1 min. greater for eszopiclone than placebo, but the advantage decreased, so that by week 12, the placebo group had actually improved 0.9 min. more. After drug withdrawal, the placebo group's TST was 12.9 min. more improved than the eszopiclone group. Objectively, the disadvantage of eszopiclone during 4-week withdrawal was over 3 times as great as its advantage during drug administration! Similarly, placebo was 0.7 min. better than eszopiclone in sleep latency reduction over 12 weeks (13.2 min. superior by week 12), and placebo was 13.5 min. superior to eszopiclone in sleep latency reduction during withdrawal.

In a one-year trial of suvorexant 30-40 mg. using subjective outcomes,[4] the investigators proposed a drug-rebound criterion requiring exacerbation worse than the insomnia at baseline.

The study suffered from failed randomization, in that the group assigned to suvorexant had worse insomnia than the placebo group at baseline (less sTST, $P<0.05$ and more insomnia severity, $P<0.01$, two-tailed), creating a bias towards greater improvement in the suvorexant group due to regression to the mean. Failed randomization likewise biased against the placebo group after one-year drug withdrawal. The suvorexant-withdrawn group indeed had a higher percentage of TST rebound exacerbation than the group receiving only placebo ($P=0.057$), a difference which would have been significant, correcting for the failed randomization. Examining their Figure 2, we see that the group withdrawn from suvorexant had increased subjective sleep latencies during the entire 8 weeks of drug withdrawal observation, that this would be so even adjusting for the failed randomization, and that there was little evidence of insomnia remission even 8 weeks after withdrawal. This study demonstrated a lasting "return of insomnia" [their words, Figure 2] in the group withdrawn from suvorexant, leaving suvorexant-treated patients worse than the group maintained on placebo throughout. Comparing month 12 of suvorexant treatment with months 1 and 2 after withdrawal, the suvorexant-withdrawn group showed a worse drop in sTST after withdrawal and a greater increase in sleep latency ($P<0.0001$ all comparisons), as well as worse insomnia intensity ($P<0.0001$ and $P<0.05$) compared to those only treated with placebo. I must disagree with the co-authors (including much-honored leaders of sleep research) that "Abrupt discontinuation of suvorexant under double-blind conditions was not associated with ... significant withdrawal or rebound insomnia."[4]

In my opinion, these three placebo-controlled trials observed withdrawal insomnia throughout one, four, and eight weeks after hypnotic discontinuation, leaving patients who had received the hypnotic worse off than those randomized to placebo. The hypnotics CAUSED

insomnia, principally by prolonging sleep latency, and the harm lasted as long as observation persisted. Further research will be needed to examine if mechanisms causing this persistent post-hypnotic insomnia are more neuropharmacologic or behavioral. It is disappointing that withdrawal insomnia was caused by hypnotics of such different neuropharmacologic specificities.

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