EDITORIAL

ANALYSIS AND PERSPECTIVES

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Do No Harm: Not Even to Some Degree

Daniel F. Kripke, M.D.[1]; Robert D. Langer, M.D., M.P.H.[2]; Lawrence E. Kline, D.O.[1]

[1]Scripps Clinic Viterbi Family Sleep Center, La Jolla, CA; [2]Jackson Hole Center for Preventive Medicine, Jackson, WY

We are grateful to Dr. Bianchi and colleagues for summarizing questions about our recent paper associating hypnotics with excess mortality and cancer.[1] We are grateful to the *Journal* for this opportunity to provide organized answers to these questions.

In the absence of adequate randomized trials extending for years, it is clinically important to assess the long-term risks and benefits of commonly prescribed hypnotics, using the best data now available and employing the most conservative analytic strategies possible. We have done that. Dr. Bianchi and colleagues asserted that we confused correlation with causality. We did not. We took pains to be clear that ours was an observational study and that some residual confounding was likely. Nonetheless, the robust associations of hypnotics with mortality and cancer that we found, increasing stepwise with increasing exposure, and virtually unchanged with multiple strategies for control, command attention and reassessment of common practice.

It has been hard to report calmly that hypnotic use was associated with 3.60- to 5.32-fold mortality risks. It would be wonderful if somebody could prove it is not so—and the risk could be overestimated—but scientific ethics require us to report what our data showed and to explain the possible implications. Though the main responsibility for warning falls on the manufacturers who were informed of these risks years ago and on their FDA supervision, we physicians have a duty to warn also. We cannot hide risks, even if they might frighten patients out of taking hypnotics. Patients have a right to know.

Some suppose that the increased mortality of hypnotic users was due to their insomnia, and that insomnia might explain the 3.60- to 5.32-fold mortality excess. It is true that because of the IRB's interpretation of Pennsylvania law, we were unable to control explicitly for insomnia or depression. However, in our paper,[1] we referenced several studies which have found that insomnia is NOT associated with significant mortality. We know of no evidence that insomnia significantly predicts mortality when hypnotic use, comorbidities, and other confounders are adequately controlled. A new example is found in the recently published representative national sample from Taiwan, where those with sleep disorders had significantly less cancer incidence than those without sleep disorders among participants who had not received zolpidem, HR = 0.69 (0.62-0.78 95% CI).[2] Use of ≥ 300 mg/y zolpidem without benzodiazepines was associated with a cancer hazard ratio of 6.24 (4.13-9.43 95% CI), but even among the zolpidem users, those with sleep disorders had lower risk. Thus, sleep disorders could not conceivably explain the excess mortality or cancer associated with zolpidem prescriptions.

Our paper also referenced studies showing that depression does not confound the association of hypnotic use with mortality. In Belleville's Canadian sample, control for depression only reduced the hypnotics and tranquilizers mortality odds ratio from 1.40 (1.13-1.75, 95% CI) to 1.36 (1.09-1.70, 95% CI), which was not significant.[3] Depression was not even a significant mortality risk factor when benzodiazepine use and other covariates were controlled.[4] In the Taiwan sample, the cancer hazard ratio for depression was 0.68 (0.53-0.88, 95% CI).[2] Thus, confounding with depression could not explain mortality and cancer associated with hypnotic prescriptions.

What about sleep apnea as an explanation? Young and colleagues reported that apnea-hypopnea indices < 30 were NOT significantly associated with excess mortality in an adjusted model.[5] With AHI ≥ 30, the risk ratio was only 3.0 (1.4-6.3, 95% CI). The Sleep Heart Health Study had even more surprising results, wherein women (who use more hypnotics than men) had no significant increase in mortality associated with any level of sleep apnea. Among men, significant excess mortality was associated with AHI ≥ 30 only among those age ≤ 70 years.[6] Among both sexes of all ages combined, AHI ≥ 30 was associated with a hazard ratio of only 1.46 (1.14-1.86 95% CI). These apnea studies were not as extensively controlled for comorbidities as our study. Our hypnotic-associated risk ratios of 3.60 to 5.32 could not be caused by apnea risk ratios of only 1.46 or 3, even in the implausible event that all the patients prescribed hypnotics had AHI ≥ 30 but none of the controls.

Could excess comorbidities among hypnotic users account for our 3.60- to 5.32-fold hazard ratios? Let us recall the data. In our stratified analyses, we compared hypnotic users with controls having exactly the same classes of comorbidities, so comorbidity diagnoses were matched. Even had we not employed matching and alternative forms of adjustment to control for comorbidities, how could a 45% excess of comorbidities among the hypnotic users account for a 3.60- to 5.32-fold mortality hazard? It is true that we were unable to adjust for severity of comorbidities when they occurred, but since the diagnoses of comorbidities accounted for only a small amount of the mortality hazard, where is the evidence that severity of comorbidities or uncommon comorbidities could account additionally for a much larger portion of the mortality hazard?

No one has offered any explanation of how confounding could produce the significantly different hazard ratios we observed between hypnotics and different cancers. Sanofi Aventis

was cited in the *New York Times*, arguing that our 2.5 years mean follow-up was not long enough to study cancer initiation, but they have done no randomized zolpidem trials of 1 year or longer. Sanofi should be better satisfied with the new Taiwan study, with the high-dose zolpidem cancer hazard ratio of 6.24 observed after more than 8 years of follow-up.[2]

In answer to the query of Bianchi et al., one should not surmise that patients using drugs for occasional anxiety or allergic rhinitis "are dying at 4-6 fold increased risk," since we explicitly stated that such indications for the compounds studied were excluded. The low-dose mortality hazard ratio for participants with NO comorbidities was only 1.93, but the hazard ratio for all those taking 1-18 doses per year was 3.60. Higher hazard levels of 4- to 6-fold were only observed in subgroups with specific comorbidities, in which the lower limit of the confidence intervals was always < 4.0.

As the authors of the commentary know, objective performance testing generally does not demonstrate any restorative benefits of hypnotic agents, whether by neuroplasticity or otherwise. The more favorable subjective responses are best explained by the amnesic properties of hypnotics, like the waters of Lethe, erasing memories of poor sleep.

Our critics pointed out that our mortality hazard ratios were much higher than those of most (but not all) previous studies. We suppose that the higher hazard ratios were observed because we explicitly identified the hypnotic drugs studied, whereas almost all previous studies confounded risks of hypnotics with any risks of tranquilizers, antidepressants, and other unidentified compounds. Also, previous studies had largely failed to monitor the quantity of hypnotics prescribed during the follow-up intervals to confirm which participants did or did not receive hypnotics during the observation. Methodologic improvements in our study compared to prior work may have yielded more accurate estimates.

Since the multiple controls for comorbidities that we employed, along with control for age, gender, smoking, etc., only reduced the raw death hazard ratio in hypnotic users from 4.86 to 4.56, it is highly unlikely that other confounding could explain all of the excess mortality associated with hypnotics. Is there any scientific evidence that uncontrolled confounders could produce such large hazard ratios, or is that just the speculation of people groping for a way to avoid bad news? There is no evidence that the neoplasm-specific risks we observed can be due to confounding, especially recognizing the parallel study from Taiwan. Furthermore, our critics recognized that limitations in our study design leading to underestimation of the hazard ratios would, to some extent, counterbalance residual confounding that might have resulted in some overestimation of the hazard ratios.

We remind readers that there are now 21 published studies suggesting excess mortality or cancer associated with hypnotic use, with no published studies suggesting mortality reduction or cancer prevention. It is good to recognize the limitations of published studies, but the current weight of evidence does not favor prescribing even 18 hypnotic doses per year. We encourage others to conduct replication studies and hope that new investigators can learn from the limitations of past work and do still better studies. Perhaps others have the ingenuity to devise ethical randomization for drugs consistently associated with excess mortality and cancer. For hypnotics with unknown mortality and cancer risks, there is a pressing need for randomized clinical trials to explore long-term hypnotic safety.

We concede that it is theoretically possible that there is no hypnotic causality underlying our mortality association findings. However, we do not advise patients to bet their lives that suspicion of causality with associations as robust as these is entirely mistaken. Perhaps our critics agree, saying, "it remains plausible that hypnotics confer some degree of mortality risk." How much risk of death would they counsel patients to accept for the sake of using hypnotics? How much risk of cancer? Doesn't a mortality or cancer hazard ratio "some degree" exceeding 1.0 signify more harm than good? Do our critics suggest to "some degree" ignoring the ethics of "Do no harm"?

CITATION

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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Daniel F. Kripke, M.D., 8437 Sugarman Drive, La Jolla, CA 92037; Tel: (858) 222-2934; E-mail: Kripke.Daniel@ScrippsHealth.org

DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.