EDITORIAL

ANALYSIS AND PERSPECTIVES

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Hypnotics and Mortality Risk

Matt T. Bianchi, M.D., Ph.D.[1,2]; Robert J. Thomas, M.D.[2,3]; Jeffrey M. Ellenbogen, M.D.[1,2]

[1]Sleep Division, Neurology Department, Massachusetts General Hospital, Boston, MA; [2]Division of Sleep Medicine, Harvard Medical School, Boston, MA; [3]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA

The risk-benefit balance of hypnotic medications remains an area of great clinical uncertainty, especially with long-term use. Issues of adverse effects on cognitive, psychiatric, and motor systems, together with risks of tolerance and dependence, necessitate caution even in short-term use. Several observational studies have even suggested hypnotics confer increased mortality risk. One recent study showed a strikingly increased mortality risk.[1] However, it contains several methodological and inferential limitations, the dissection of which may be instructive for providers and researchers for whom this complex and concerning topic is relevant.

Kripke et al. analyzed a large database of diagnosis codes and prescription records with linked indications.[1] They asked whether prescriptions for certain hypnotic sleep medications were associated with increased mortality over a 3-year observation period. From a database of over 200,000 individual outpatients seen between 2002 and 2006, about 10,000 had at least one hypnotic prescription, survived at least 3 months into the observation period, and did not already have a diagnosis of cancer. For each of these subjects, 2 controls were obtained from the remaining database, matched according to age, sex, smoking status, and observation period. The authors report 3.5-5.5 times higher mortality in the hypnotic group than the baseline 1.3% mortality of the control group.

The correlation of events in time does not necessarily imply a causal relationship. This is often referred to as the *post hoc ergo propter hoc* fallacy ("after this, therefore because of this"), and this fallacy remains an issue in modern clinical studies. Although the authors acknowledge this fallacy in the article's supplement, the discussion in the main text not only argues that hypnotics caused the deaths, but it also implies that limiting hypnotic use would prevent deaths. In prior work, Dr. Kripke challenged the critique that correlation is not causation by stating that the same criticism was applied to association data regarding smoking risks.[2] This argument is countered by the unfortunate reality that the literature is replete with examples of correlations in observational data that were not sustained in randomized prospective trials, as has been elegantly described by the work of Iaonnides.[3]

Beyond the flaw of implying causation from correlation in this instance, the study design contains several serious limitations. First, the groups were not matched for the most important confound in a study of hypnotic medications: the underlying sleep disorder. Given published literature that point to a key role of sleep disorders in the mortality risk associated with hypnotic prescriptions, we find it surprising that sleep diagnostic codes were not evaluated in this retrospective study based entirely on a diagnostic code database. In prior studies of hypnotics and mortality risk, it has been recognized that the drug-related risk and the underlying sleep disorder diagnosis are intertwined.[2] Moreover, one of the proposed mortality mechanisms discussed in this study is that hypnotics can exacerbate sleep apnea, which is known to cause motor vehicle crashes,[4] strokes, and heart attacks.[5] Failure to account for the critical confound of underlying sleep disorder likely contributed to an inflated mortality hazard in Kripke et al. By comparison, in the prior 24 related studies listed in their supplemental material, the median hazard associated with hypnotics was < 1.5, and only 4 studies reported values > 2.0. Failing to address the underlying sleep disturbance is a major design flaw equivalent to concluding that chemotherapy prescriptions increase mortality without taking into account the mortality associated with the underlying malignancy that prompted chemotherapy. Given that their main outcome was mortality risk, it is unfortunate that cause of death data was not available to support potential mechanistic links.

Another important limitation relates to comorbidities. Major illnesses that carry mortality risk burden were 1.5-2 times more common in the hypnotic group of this population, compared to the control group. While the authors attempted statistical correction for these differences, the severity of the comorbidities was not available and thus the groups could have differed in this regard. Also, the extent to which comorbid sleep disorders, presumably much more common in the hypnotic group, might have synergistic risks with the medical conditions remains unknown. Psychiatric comorbidities that may have contributed to morbidity and mortality were not available and may also have differed between groups, as sleep complaints are a fundamental part of most psychiatric disorders. Finally, alcohol consumption may have serious interactions with hypnotic medications, in addition to health and accident implications, yet the control for alcohol use was limited to self-reported "yes," or "no," or "unknown." Given the concurrence of alcohol use, sleep complaints, and psychiatric disorders, it is possible that the hypnotic group was overrepresented in alcohol consumption not captured by this simplified categorization. Imagine, for instance, a person occasionally having 1-2 drinks per week, being "matched" with someone consuming 5-6 drinks per night.

The data speak only to prescription content, not the actual patterns of hypnotic use. The authors argue that non-compliance in the hypnotic group or undocumented use of hypnotics in the

control group would each lead to underestimation of the effect size. We agree. But it is unclear why the authors disregarded the (likely) possibility that patients in the hypnotic group may also be taking undocumented over-the-counter or prescription agents for sleep, which would exaggerate any mortality risk, either through drug interactions or as a marker of severity of a sleep disorder carrying its own mortality risk.

The authors emphasize the dose-response relationship between frequency of use and mortality risk. Yet no statistics are provided to support that claim, and the overlapping confidence intervals raise the possibility that there may be little or no dose effect. Even if the hazard ratios are statistically different, the dose-response profile would be highly unusual: a steep and immediate risk elevation observed at sparse dosing—fewer than 1.5 pills per month—followed by less than 1.5 fold change in risk over the next 10-fold increase in dose. Furthermore, the antihistamine diphenhydramine conferred a similar risk as benzodiazepines, non-benzodiazepine ligands, and barbiturates, each of which have different mechanisms, different drug-drug interactions and different side-effect profiles. Furthermore, some of these medications are used for other common indications, such as anxiety, epilepsy, and allergic rhinitis. Are we to surmise that patients using occasional benzodiazepines for anxiety or using occasional diphenhydramine for allergic rhinitis are dying at 4-6 fold increased risk?

The authors argue that the absolute gain in total sleep time with sleep medications is modest. We agree. However, total sleep time may not be as important as continuity (which is not necessarily reflected in total duration). Further, the greater subjective than objective sleep time benefits reported by patients taking sleep medications may be partly due to our limited techniques of objectively quantifying sleep physiology through current conventions of sleep staging, rather than simply modest objective efficacy. This uncertainty extends to the question of whether pharmacological sleep recapitulates important or restorative aspects of normal sleep. For example, certain hypnotic agents impair cortical plasticity in animal models of sleep-dependent neuroplasticity.[6] Resolving whether hypnotic medications faithfully replicate natural sleep physiology remains an important area of ongoing investigation.

Reporting alarmingly high death risks from commonly used medications generates intense media coverage and raises public concern. This paper's discussion begins with the shocking claim that a half-million deaths in the USA in 2010 (about 25% of all deaths) may have been due to hypnotics. Given the numerous methodological flaws and logical fallacies of this paper, we find this claim to be irresponsible from scientific and ethical perspectives. From a Bayesian standpoint, extreme claims require extraordinary evidence. In this study, plausible arguments can be made that hypnotics are not causative for, and may not even be associated with, the observed mortality hazard.

Dr. Kripke is a long-standing critic of hypnotics.[7] To be clear, many of his concerns are shared by the community of providers who care for those with sleep complaints, including the authors of this commentary. For example, long-term use of hypnotics is not recommended. Short-term use should be employed with caution, controlling for circumstances that might lead to unwanted effects, including driving safety and psychiatric wellness. Tolerance and dependence may develop. Further, non-pharmacological treatments have been shown to be equal to, or more effective than, hypnotic medications.

In summary, it remains plausible that hypnotics confer some degree of mortality risk, and substantive clinical and scientific questions remain about their biological impact on sleep and risk-benefit balance. But alarmist claims from mediocre data serve only to distract and detract from the many serious questions and concerns lingering in the arena of hypnotic medications. We encourage practitioners to openly discuss with insomnia patients the risk-benefit balance of pharmacological and behavioral approaches, as well as no treatment—which itself may confer health risks.

CITATION

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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Matt T. Bianchi, M.D., Ph.D., Wang 720, Neurology Department, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114; Tel: (617) 724-7426; Fax: (617) 724-6513; E-mail: mtbianchi@partners.org

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Dr. Ellenbogen has received speaking fees from the American Academy of Neurology, Massachusetts General Hospital Academy, and the Massachusetts Department of Public Health. Dr. Bianchi has a patent pending on a home sleep monitoring device. Dr. Thomas is co-patent holder for electrocardiogram-based sleep technology, and for a carbon dioxide delivery device used to treat central/complex apnea, and he receives consulting fees from DeVilbiss.