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## Insomnia, Hypnotic Drug Use, and Patient Well-being: First, Do No Harm

Most sleep clinicians know the sinking feeling associated with encountering patients who are frantic about their inability to sleep. Such patients have often taken most hypnotics that we have heard of (and some that we haven't) and visited several other practitioners for this problem. They report being fearful that their insomnia is causing problems with daytime functioning and with health. They are often able to quote recent media reports associating "poor sleep" or "sleep disorders" with bad outcomes, including death. Indeed, North Americans regularly encounter news articles, Web alerts, direct-to-consumer advertisements, and evening news stories emphasizing the importance of a "good night's sleep." These alerts often feature medical sleep experts, and they frequently do 2 things that may be a disservice to the field of sleep medicine and to the consumers of these reports. The first is to blur the lines between sleep deprivation and insomnia, which are 2 very different entities with very different causes and outcomes. The second problem is that news stories proclaiming the deadly effects of "sleep disorders" often lump all sleep problems together. Some sleep disorders (notably sleep apnea) have well-documented, serious consequences, but others do not. We in the sleep community, in our struggle to gain recognition for Sleep Medicine as a legitimate entity, may have unwittingly undercut our credibility.

The end result has been what Moloney et al<sup>1</sup> call "the medicalization of sleeplessness." In an analysis of the National Ambulatory Medical Care Survey, Moloney et al reported approximately 2.7 million adult office visits for sleeplessness in 1993, which more than doubled to 5.7 million by 2007. Over the same 15-year period, insomnia diagnoses increased more than 7-fold. In 1993, approximately 2.5 million office visits resulted in a prescription for a benzodiazepine, compared with 3.7 million in 2007. Prescriptions for nonbenzodiazepine hypnotics have exploded, increasing about 30-fold from 1994 (540,000 prescriptions) to 2007 (16.2 million). Presumably many of these prescriptions for benzodiazepines and other hypnotic drugs were to treat sleeplessness.

In this issue of *Mayo Clinic Proceedings*, Kao et al<sup>2</sup> report that the risk of developing cancer was greater for individuals who were prescribed the most popular *nonbenzodiazepine* hypnotic, zolpidem, than for those who were not. There was also a small but statistically significant increase in cancer risk for those who took *benzodiazepine* hypnotics. The greatest risk was for oral cancer, followed by cancers of the esophagus, kidney, liver, breast, bladder, and prostate. This study has several strengths, including the large size of the study cohort, matched controls, and long duration of follow-up. However, an important weakness is that the investigators were unable to control for cigarette smoking, which is increased in those with insomnia<sup>3,4</sup> and has well-known carcinogenic effects. Nearly simultaneously, Kripke et al<sup>5</sup> reported increased mortality and incident cancer associated with hypnotic use in a large US cohort. In the study by Kripke et al, it was possible to control for smoking as well as for age, gender, body mass index, ethnicity, marital status, alcohol use, and prior cancer. Both studies demonstrated an increased risk in esophageal and prostate cancer in hypnotic users compared with nonusers, supporting the validity of each report's findings. Further, there was a "dose-response" effect in the study by Kripke et al, with those in the highest tertile of hypnotic use having a significant increase in incident cancer risk. This argues against the possibility of an increased cancer rate simply because those receiving hypnotics are, in general, less healthy because a fundamental premise of pharmacology is that sicker patients require lesser, not greater, doses of sedatives and hypnotics to achieve a given central nervous system effect. Given the marked increase in the use of hypnotics in this country<sup>1</sup> and worldwide in recent years, these reports are cause for concern.

What is going on? At least part of the explanation is that people with insomnia are not healthy people. They are more likely to smoke, to be obese, and to have chronic medical or psychiatric conditions.<sup>2-8</sup> Although the reports by both Kao et al<sup>2</sup> and Kripke et al<sup>5</sup> controlled for many confounders, it is likely that lifestyle factors and comorbidities of those with insomnia

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contribute to at least part of the increased risk. For that reason, we must keep in mind that association doesn't prove causality. Since it is not easily feasible to randomize people to be insomniac or not, this is an important factor to keep in mind whenever we are evaluating the associations between hypnotics and adverse outcomes. Thus, although chronic use of hypnotics is associated with motor vehicle crash,<sup>9</sup> infection,<sup>10</sup> suicide,<sup>11</sup> and death,<sup>5,12</sup> this association doesn't prove that these complications are caused by the use of hypnotics, although it does make it difficult to claim that hypnotics prevent these problems in insomniacs who take them.

That association doesn't prove causality is also an essential factor to consider in evaluating the associations between insomnia and adverse outcomes. Based on the reports by Kao et al, Kripke et al, and others, it is now time to recognize that studies that investigate the relationship between insomnia and its consequences may suffer not only from the confounder that insomniacs may be less healthy than those without insomnia but also from the possibility that the hypnotic drugs themselves may be harmful. Currently, such studies rarely control for possible adverse events associated with hypnotic use. (Indeed, since we lack an objective measure of "insomnia" and can actually demonstrate very few objective differences between those who complain of insomnia and those who do not, insomnia is sometimes actually defined by use of hypnotics.)

Why is it important not to overstate the evidence that either insomnia or hypnotics cause harm? Because nothing will keep you up at night like worrying that being up at night (or taking medications for it) will hurt you. Misattribution of consequences of insomnia and overvaluing of sleep can result in anxiety and tension, fueling and perpetuating insomnia. As I sometimes tell patients, "You can have performance anxiety about sleep, just the same as you can about the other thing that we are supposed to do in bed." Further, exaggerating the consequences of insomnia may undercut the well-demonstrated efficacy and safety of cognitive behavioral therapy (CBT).<sup>13-15</sup> As stated by Morin and Benca,<sup>13</sup> the aim of CBT "is to change factors that perpetuate insomnia, including . . . psychological factors (unrealistic expectations, worry, unhelpful beliefs), and physiological factors (mental and somatic tension, hyperarousal)." In other words, at least part of what needs to happen during CBT is that insomnia patients need to be disabused of the notion that insomnia has dire consequences or is the cause of most of their daytime problems. This is an important issue, given the number of people who are plagued by insomnia and the possible implications of its treatment with medications. As a sleep clinician on the front lines of insomnia treatment, my thinking about how to manage insomnia

has evolved quite a bit in recent years. Only 2 things are sure: (1) the more one worries about insomnia, the worse it gets, and (2) the evidence against chronic pharmacological treatment of insomnia is much stronger than the evidence in favor of it.

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