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Insomnia and Morning Motor Vehicle Accidents:

A Decision Analysis of the Risk of Hypnotics Versus the Risk of Untreated Insomnia

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To the Editors:

Insomnia is a common clinical complaint encountered by primary physicians and specialists and involves extensive direct and indirect health care cost burden.[1] One major concern regarding sleep aids is the risk of "hangover" effect that may compromise performance in morning hours, including the safety of driving a motor vehicle. The United States Food and Drug Administration recently announced a warning for zolpidem regarding the potential morning driving risks after use.[2] However, the risk of motor vehicle accident (MVA) should be considered in the full context of the patient's clinical profile,[3] including the specific risk of MVA associated with sleep deprivation on any given night. Although experimental sleep restriction and deprivation in healthy subjects compromise performance including driving,[4] individual variability and uncertain relevance for patients with insomnia[5] make decision making challenging. Insomnia has been associated with increased accident risk in some[6,7] but not all[8] epidemiological studies. There is uncertainty about the risk associated with hypnotic use in that blood levels correlate poorly with risk.[9] Physicians and patients attempting to balance the risks and benefits of hypnotic use lack a structured framework, especially for the question of morning accident risk.

Here, we use decision analysis to explore the specific issue of morning MVA risk for patients with insomnia. The model is from the perspective of a patient deciding whether to take a hypnotic on a given night, although in practice, the process of weighing risks and benefits should be guided by discussion with prescribing providers. The framework of the model attempts to balance 2 key factors, which are as follows: (1) the risk of morning MVA associated with a "bad night" of sleep and (2) the risk of morning MVA associated with hypnotic use. Sensitivity analyses are shown for several representative clinical scenarios, including the important possibilities that one can still have a bad night of sleep even after taking a hypnotic (ie, hypnotic efficacy is not perfect) and that the interaction between

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AUTHOR DISCLOSURE INFORMATION

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having a bad night and having taken a hypnotic could have additive or multiplicative effects on morning MVA risk.

The simplified model begins with the choice of whether to use a hypnotic on a given night (Fig. 1), which affects the probability of a good versus bad night of sleep. We assume that a given night is either good or bad in regard to insomnia. Having a bad night and taking a hypnotic each increase the morning MVA risk by a scaling factor; these factors can be additive or multiplicative in the model. Taking a hypnotic reduces the probability of having a bad night. The true probability of morning MVA due to hypnotic use or due to a bad night from insomnia is unknown and likely varies substantially from person to person. The amount by which the risk of morning MVA is increased by hypnotic use is uncertain, with odds ratio values ranging from 1 to 9 for benzodiazepines.[10] Insomnia has been linked to sleep-related (but not total) MVA in some studies,[8] whereas in others, only non-car accidents were increased.[1]

We evaluated the relative decision preferences in the model across 3 clinical scenarios, including sensitivity analysis for the 2 variables most critical for clinical decision making (and most uncertain based on existing literature), namely, the risk associated with taking a hypnotic versus the risk associated with a bad night from insomnia. In each case, the risk was modeled as additive (left) or multiplicative (right). For sensitivity analyses, the risk multipliers for hypnotic or for a bad night of sleep were varied from 2-fold to 9-fold; the probability of a bad night (with or without hypnotic) was varied from 0 to 1.

Intermittent Insomnia: Good Hypnotic Efficacy

In this scenario, insomnia is intermittent (twice per week), and the hypnotic efficacy is good (10-fold reduction; Figs. 1B, C). Under these circumstances, the no-hypnotic choice is favored for most of the parameter space. However, when the hypnotic risk scaling is low (<3) compared with the risk of a bad night, taking a hypnotic is favored. The multiplicative model further favors the no-hypnotic decision. Two theoretical patients are shown as well, 1 of whom the risk of hypnotic and of a bad night of sleep both equal to 2, and 1 of whom the risk of a bad night of sleep is 2-fold higher (which might correspond, for example, to a case in which the clinical history revealed that untreated insomnia previously resulted in dozing off the next day). Each of these cases resides in the no-hypnotic space.

Frequent Insomnia: Partial Hypnotic Efficacy

In this scenario, insomnia occurs more frequently (5 times per week), and hypnotic efficacy is reasonable (reducing insomnia to 1 night per week). Figures 1D and E show that the parameter space favoring hypnotic use is larger than the prior scenario (for additive and multiplicative risk), as expected, given the increased baseline insomnia risk. Considering the 2 theoretical patients as previously mentioned, although no-hypnotic is favored when the hypnotic and bad-night risks values are both set at 2, taking a hypnotic becomes favored when the risk of a bad night is raised to 4.

Nightly Insomnia: Lesser Efficacy Hypnotic

In this scenario, insomnia occurs nightly, and hypnotic efficacy is only modest (50% reduction). Figures 1F and G show similar decision boundaries to the prior scenario, except that the multiplicative model imposes an even further restriction on the decision boundary, requiring quite low risk of hypnotic to favor their use. The theoretical patient with equal risk values falls in the no-hypnotic range, whereas hypnotic is favored only for the additive model when the risk of a bad night is 4.

This modeling study provides a framework for balancing the MVA risk associated with hypnotic use against the MVA risk associated with sleep deprivation due to insomnia. Although the model is by necessity a simplification, the sensitivity analyses provide a context for considering competing factors that could influence clinical decision making in individual patients, for example, decision boundaries favoring hypnotic or not occurred within plausible ranges of the key parameters, namely, (1) the risk scaling value associated with hypnotic use, (2) the risk scaling value associated with sleep deprivation, and (3) hypnotic efficacy. This suggests that the risk-benefit balance for taking hypnotics in the specific context of morning MVA risk can be tipped by realistic patient-specific considerations.

Many factors affect MVA risk, some of which are non-sleep related (such as road conditions, route familiarity, trip duration, driving skill, experience, cell phone use, or texting), and some of which are sleep-related (sleep loss, drowsiness, attention, circadian phase, underlying primary sleep disorder). In addition, for those who take hypnotic medications, multiple factors influence medication blood levels (such as age, sex, weight, recent eating, cytochrome metabolism variations, and drug-to-drug interactions) and the vulnerability to the impairing effects of the medication (individual sensitivity, temporal dependence of tolerance, synergy with other sedating medications, alcohol, or sleep deprivation). Of note, the relationship between blood levels of hypnotic agents and MVA risk is highly variable.[9]

In our model, 1 important observation relates to how taking a hypnotic might interact with sleep deprivation from insomnia. As expected, when the model assumes a multiplicative effect, as is suggested by analogy to studies of alcohol and sleep deprivation,[11,12] the parameter space favoring hypnotic use is reduced. The scaling risk values might change from night to night. Such a change might occur, for example, after multiple bad nights, or if alcohol has been consumed, or if an unusually long or unfamiliar drive is expected in the morning. If there is no chance of a bad night with hypnotic use (ie, perfect efficacy), then the trade-off between the risks associated with hypnotic and those of sleep deprivation is a straightforward comparison of the risk scaling values.

Many variables factor into a patient's decision of whether to take a hypnotic on any given night. The recent Food and Drug Administration announcement raised 3 important considerations pertaining specifically to the risk of morning MVA; these are as follows: (1) risk of impaired performance the morning after taking zolpidem, (2) the impairment might not be subjectively recognized by the individual, and (3) women may be at greater risk. Multiple other risks have also been associated with immediate and/or long-term hypnotic

use,[13,14] including tolerance, dependence, cognitive complaints, and falls, and some authors have reported increased risks of cancer and death from even infrequent risk.[15] These epidemiological studies have limitations, and any potential risk considerations are balanced by literature suggesting risks associated with insomnia itself, including daytime functional/cognitive impairment, absenteeism, presenteeism, medical and psychiatric morbidity, and MVA.[4]

The estimates of risk values may derive from the clinical history and from published studies providing a range of plausible risks associated with hypnotics and with sleep loss.[8,10,16–18] At the individual patient level, certain clinical information may be informative to determine where on the spectrum of insomnia-related MVA risk a patient may reside, for example, if a patient has already reported near misses associated with sleep loss. The ultimate decisions about hypnotic use in general and on a night-to-night basis include multiple factors that should be discussed with patients to inform their decision making. Motor vehicle accident risk is only one of the many considerations when it comes to insomnia pharmacotherapy.

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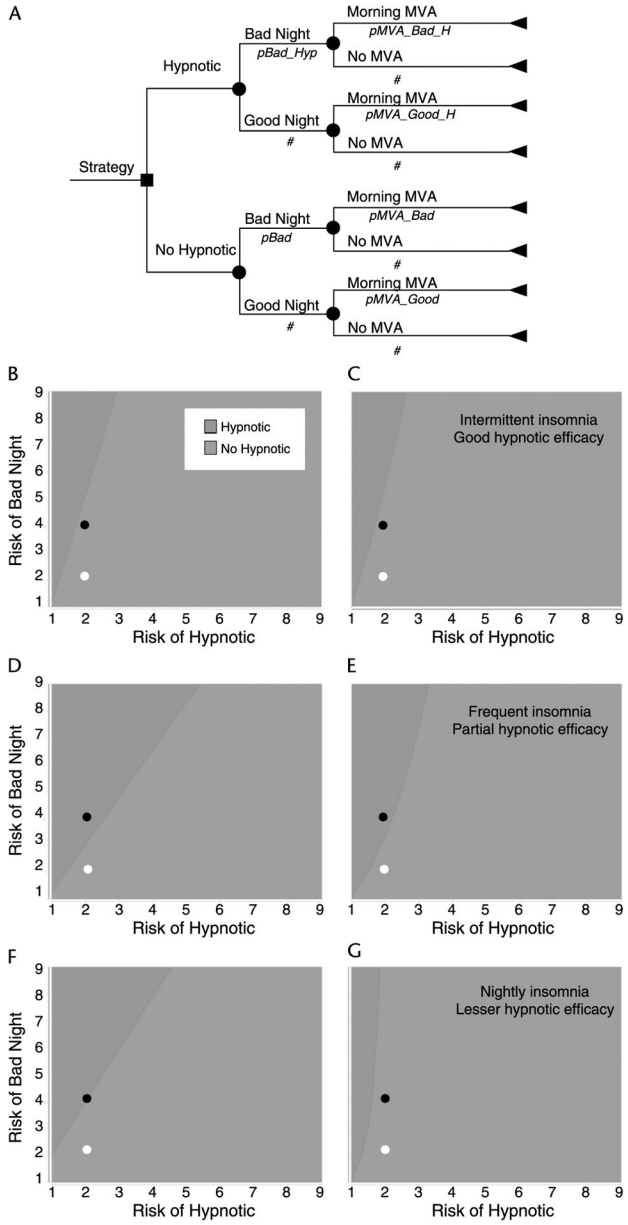

FIGURE 1.

Decision model schematic. A, The choice node (square) is followed by chance nodes (circles) and the terminal (outcome, triangle) is MVA or not. Descriptive labels (above the lines) and probabilities (below the lines) are given (#, converse probability). pBad and pBad_Hyp are probabilities of a bad night without or with a hypnotic. pMVA_Good and pMVA_Bad are probabilities of morning MVA based on the night(no hypnotic), whereas "_H" correspond to with hypnotic use. B-G, The 2-way sensitivity analysis of favored choice (hypnotic or no hypnotic) for 3 scenarios (see text) based on either additive (left) or multiplicative (right) MVA risk from a bad night and from takinga hypnotic. In each panel, the circles are the example cases in which the risks are equal (factor of 2; open circle) or

when the MVA risk from a bad night is twice that of the hypnotic risk (factor of 4; filled circle).