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Evidence that New Hypnotics Cause Cancer (Draft 2)

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Summary

Fifteen epidemiologic studies have associated hypnotic drugs with excess mortality, especially excess cancer deaths. Until recently, insufficient controlled trials were available to demonstrate whether hypnotics actually cause cancer. The U.S. Food and Drug Administration (FDA) Approval History and Documents were accessed for zaleplon, eszopiclone, and ramelteon. Since zolpidem was used as a comparison drug in zaleplon trials, some zolpidem data were also available. Incident cancers occurring during randomized hypnotics administration or placebo administration were tabulated. Combining controlled trials for the 4 drugs, there were 6190 participants given hypnotics and 2535 given placebo in parallel. Restudy of on-line FDA files led to somewhat altered counts of incident cancers, which are currently being checked against an FDA case review. FDA files revealed that all 4 of the new hypnotics were associated with cancers in rodents. Three had been shown to be clastogenic. Combining these new randomizing trials provided equivocally-significant data that new hypnotics cause cancer. Together with the epidemiologic data and laboratory studies, the available evidence signals that new hypnotics may increase cancer risk. Due to limitations in available data, further review of case files for these trials and confirmatory research is needed.

KEYWORDS  hypnotics, cancer, eszopiclone, ramelteon, zaleplon, zolpidem
Introduction

To a varying extent, fifteen epidemiologic studies have indicated that increased mortality was predicted by consumption of hypnotic drugs (Ahmad and Bath 2005; Allgulander et al. 1987; Allgulander et al. 1990; Fukuhara et al. 2006; Hublin et al. 2007; Kojima et al. 2000; Kripke et al. 1979; Kripke et al. 1998; Lack et al. 2006; Mallon et al. 2002; Merlo et al. 1996; Rumble and Morgan 1992; Sundquist et al. 1996; Thorogood et al. 1992; Winkelmayer et al. 2007). Three studies have found no association between hypnotics usage and mortality (Brabbins et al. 1993; Hays et al. 1996; Phillips and Mannino 2005), but these had insufficient power to exclude modest risk ratios. In contrast, no epidemiologic evidence has been located that hypnotic drugs prolong survival. The excess mortality associated with hypnotics could not be attributed to comorbidities of insomnia, as excess mortality was not associated with insomnia (Kripke et al. 2002; Lack et al. 2006; Phillips and Mannino 2005).

Three epidemiologic studies observed that hypnotics consumption specifically predicted cancer deaths (Kripke et al. 1998; Mallon et al. 2002; Merlo et al. 1996). These studies controlled for numerous concomitant risk factors. Case-control studies found that benzodiazepine agonists were associated with ovarian cancer (Harlow et al. 1998; Harlow and Cramer 1995). An uncontrolled case series recently expressed concern about the carcinogenicity of zopiclone and eszopiclone (Stebbing et al. 2005). In a study monitoring 13,177 people who had taken zopiclone, a surprising 42% of deaths were from cancer (Hajak 1999). Zopiclone was reportedly denied U.S. approval due to indications of carcinogenicity (Anonymous 2005).
Despite epidemiologic association of hypnotics with cancer risk, observers have remained skeptical that hypnotic drugs actually cause cancer. Many thought that the demonstrated association was not causal, partly because there has been virtually no published comment on potential mechanisms and animal models of hypnotics-induced cancer. Also, it is widely believed that contemporary marketed hypnotics are safer than those popular at the time when most of the epidemiologic studies were done.

Randomized clinical trials are usually necessary to prove causality but are not always practical due to costs, duration or ethical concerns. The possibility of examining cancer causation has changed somewhat, now that three novel hypnotics have been introduced to the U.S. market, joining zolpidem, the market-leader. Several Phase 3 trials of unusual size and duration have been completed to document benefits and risks of long-term hypnotics treatment. For no single drug were the trials large enough to determine whether a specific hypnotic drug caused a significant increase in cancer. However, by combining data from 22 trials of several new hypnotics, accessible from the Food and Drug Administration (FDA) public internet site (2006b), a pilot examination of hypnotics cancer causality could be compiled. Such a compilation has many serious limitations, but there are no better data available from randomizing hypnotics trials regarding cancer risk, nor are better data likely to be available in the foreseeable future. It would seem that any data which may focus concern and stimulate further studies of a serious risk should be presented, despite the limitations.
Method

Material from the FDA Approval History and Documents for Sonata (zaleplon), Lunesta (eszopiclone), and Rozerem (ramelteon) were accessed from the Drugs@FDA web site (2006b). The older Approval History and Documents for Ambien (zolpidem) were also accessed, because zolpidem remained the 2005 market leader. Despite mention of an incident neoplasm associated with zolpidem treatment, this older material had insufficient information to ascertain what malignant neoplasms occurred in those studies or to evaluate the rate. The recent Approval History for Ambien CR (zolpidem tartrate extended release) did not include a new examination of toxicology (2006a). However, documentation of zolpidem as a comparison drug during the zaleplon trials was available, making it possible to include small trials of zolpidem in the compendium. For both ethical and practical considerations, the investigator could not seek access to original case records or research tabulations, but rather estimated the necessary information from the web-based Approval Histories and Documents, which provided summary data.

For all randomized, placebo-controlled trials of each hypnotic compound, the number of incident cancers reported among participants randomized to that hypnotic was tabulated, along with the matching number among those receiving randomized placebo. So far as possible, results from open-label nonrandomized portions of the trials were excluded. Because data were selected only from studies randomizing participants to a hypnotic or to contrast placebo, it is assumed that all cancer susceptibility factors affecting the contrasts such as age, gender, and
duration of exposure were balanced by randomization. The FDA documents contained disagreements among observers, ambiguities, and contradictions about the numbers of incident malignancies, but the tabulations were made to the author’s best estimation. For example, the ramelteon documents stated in several places that no cancers occurred in the placebo group, but a case of lung cancer occurred in a cross-over study in which a participant had received several doses of ramelteon and finally received placebo, so that in one table, that cancer was assigned to placebo (2005). All cross-over cancer cases (because these could not be reliably allocated either to hypnotics or to placebo) were omitted from the tabulation of parallel studies. Listings of neoplasms of undetermined malignancy were tabulated separately, since the reports sometimes lacked conclusive pathologic documentation of the nature of incident neoplasms. Clearly-benign neoplasms were not tabulated. Unfortunately, tabulating the total numbers of hypnotic-exposed and placebo-exposed subjects required some estimation, even leaving out some small Phase I trials. Age ranges were not always available. Accurate exposure distributions were not generally available, but an attempt was made to estimate durations of drug (or placebo) exposure, arbitrarily assuming that dropouts received half of the planned doses.

The Fisher Exact Test was used to determine if the number of cancers in combined drug and placebo groups differed significantly. The significance criterion selected was p<0.05, one tailed, recognizing that warnings or regulatory action might be advisable before there is 95% scientific confidence that a drug is carcinogenic. One-tailed significance values were recorded, because the FDA and the sponsors considered cancers as risks, whereas no anti-cancer benefits were hypothesized, and both animal data and the prior epidemiology predicted the direction of
the effect which the investigator was seeking to verify.

The author has learned that following submission of an early draft of this manuscript to the FDA, the FDA conducted a case review. The results of the FDA's case review have been requested, and detailed results of the author's review of on-line data will be delayed in the hopes that the FDA's case review will be disclosed.

Data regarding infections in the human trials and experiments in rodents to explore genotoxicity and carcinogenicity, described in the Approval Documents related to each hypnotic, were briefly reviewed.

Results

For zaleplon, eszopiclone, ramelteon, and zolpidem each taken individually, the rate of malignancies and the rate of total neoplasms was higher in the hypnotics groups than in matching randomized placebo groups. Further details should be checked against the FDA's case review.

It appeared from compilations of the trials (including trials in the NDA for zolpidem) that eszopiclone, zaleplon, and zolpidem all produced substantially higher rates of adverse effects described as colds, naso-pharyngitis, sinusitis, infections, or viral infections. The infection data for ramelteon was unclear, because the most comprehensive tabulations may have included
events during open-label administration which were not comparable to the placebo exposures.
Discussion

As compared to matching placebo, trials of the most contemporary hypnotics in combination observed that participants randomized to hypnotics had a higher rate of incident malignancies and a higher rate of incident cancerous plus possibly-malignant neoplasms. These combined data offer the first evidence from randomized trials that hypnotics cause human cancer. That these drugs apparently caused cancer in animal screening added credence to clinical trial evidence that hypnotics cause cancer. That use of hypnotics predicted cancer in epidemiologic studies likewise supported the clinical trial compilation.

The trials compiled, of durations from 1 day to 6 months, were so brief that de novo development of cancers might seem implausible to the FDA (personal communication), suggesting that either biases in ascertainment or errors in tabulation may have occurred. The shortest study with reported cancer occurrence was 14 days, and most were 35-day or 6-month studies. On the other hand, experimental observations should not be disregarded merely because they seem inconsistent with contemporary suppositions.

The evidence suggested but did not prove that carcinogenicity might be a property shared by all 4 hypnotics. The trials of each hypnotic were insufficient in size to determine if each hypnotic by itself caused cancer. Similarly, the available data were not sufficient for contrasts among the 4 hypnotics for the rates of cancer incidence. Moreover, because of differences in the age groups and various other cancer risk factors of trial participants, a nonrandomized
comparison among the 4 hypnotics would not be valid.

FDA reviewers initially had recommended nonapproval in some instances because of data suggesting carcinogenicity, but all 4 hypnotics ultimately received final approval. Evidently the sizes of the human trials for each drug by itself were not sufficient to provide FDA convincing proof of carcinogenicity. Also, the incident cancers during double-blind administration were mostly or all basal cell skin cancers, which may not have seemed impressive to FDA reviewers. Parenthetically, basal cell skin cancer was reported in rats given zaleplon (1999). However, the cancers in the open-label and cross-over intervals included cancers of the brain, lung, bowel, breast, and bladder, and the neoplasms of uncertain malignancy were likewise widely distributed.

This compilation had many gross limitations. First, the pre-approval drug trials were not planned as trials of carcinogenicity, and the Approval Documents were not focused to document cancer outcomes. Even in combination, the size of the trials was hardly robust for cancer detection. This investigator did not have access to complete research protocols, the raw case reports, data bases documenting risk factors and outcomes for each trial participant, or comprehensive summary data. Because of some lack of clarity in the Approval Documents and because of differences of opinion and contradictions recorded between various observers, it is quite possible that this compilation contains imprecise tabulations or mistakes in interpretation. To recheck this compilation, it would be desirable to cross-reference our conclusions versus the FDA review of the case reports. A more ideal statistical assessment would include data on the
duration of exposure and other risk factors such as age and gender. Since additional time has elapsed, it may further be now possible for FDA to resolve some of the ambiguities concerning which incident neoplasms were malignant. Nonetheless, it seems implausible that reinterpretation will erase the preponderance of incident malignancies among participants given hypnotics.

A limitation of this compilation was the concatenation of trials which were diverse in design and duration and which involved different hypnotics. The data for the 4 drugs were combined because they represented the newest hypnotics which had most recently appeared in the U.S. market, and for which large trials were therefore available. Were adequate data available, a compendium of more similar trials would be preferred. A single trial of a single hypnotic large enough to evaluate cancer as an endpoint would be preferred.

Since ramelteon does not act on benzodiazepine receptors, it might seem surprising to observe that its association with cancer was similar to that of benzodiazepine agonists, but so it appeared. Ramelteon, eszopiclone, and zaleplon were all clastogenic, which may be a common mechanism of carcinogenesis. Eszopiclone, zaleplon, and zolpidem appeared to promote infections, including viral infections. This may have indicated suppression of immune function. Either suppression of immunity or viral infections per se might increase cancer development.

Because the FDA requires manufacturers to report adverse as well as favorable clinical trial outcomes, the FDA NDA documents for these four hypnotics may offer a less biased
presentation than might review of the published literature, where publication bias is serious (Buscemi et al. 2007; Glass et al. 2005). I have not noted that the occurrence of any of these cancers has been previously published, although several of the trials have been published. Since these NDA data were compiled, and not included in the Tables derived from FDA on-line data, two publications have additionally reported three cancers occurring in clinical trials in indiplon groups, but none were reported in the parallel placebo groups (Roth et al. 2007; Scharf et al. 2007).

This report should not imply that we can have confidence from controlled trials that new hypnotics caused cancer as compared to placebo. The tabulation process should not be considered that reliable until the review of case reports is made available. Were adequate data available, a multivariate statistical analysis such as a Cox multiple-hazards model would be desirable.

Because the compilation of cancer incidence awaits FDA confirmation, both for the number of cancers and for the durations of exposure and other risk factors, because the compilation mixes diverse studies of several drugs, and because the number of cancers observed during controlled hypnotics trials remains small, this preliminary analysis should be viewed as an investigative step, rather than sufficient proof that modern hypnotics cause cancer. The data warn us that further investigation is needed, including re-examination of these data by the FDA or European agencies. Expanded clinical trials with a specific focus on cancer incidence are needed. One might suppose that drug manufacturers would wish to prove that their products are
safe from cancer risk. If they have insufficient confidence in their products to undertake adequate studies, the public interest demands that the U.S. National Institutes of Health and similar agencies determine the risks or safety of contemporary hypnotics. Meanwhile, the likelihood of cancer causation is sufficiently strong now that physicians and patients should be warned that hypnotics possibly place patients at higher risk for cancer.
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Competing Interests

Dr. Kripke has no competing interests, other than a desire to confirm and extend previous work of his research group. He has been a long-time critic of hypnotic safety, e.g., in his non-profit web site, www.DarkSideOfSleepingPills.com.

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