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Do hypnotic drugs cause cancer, like cigarettes?

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Sivertsen and colleagues [this issue] have provided a new case-control study demonstrating epidemiologic association between usage of hypnotic drugs and cancer, particularly respiratory cancers. Evidence of dose-response and a similar time-course of hypnotic usage among cases and controls tend to reduce the likelihood of reverse causality as an important confounder in this study. An acknowledged limitation of the study was inability to control for cigarette smoking and obesity, two of the most important cancer risk factors, known to be somewhat associated with hypnotic usage in the population studied.

Sivertsen et al. review several previous studies that have found a similar association of hypnotics and incident cancer, often with lung cancer having one of the highest hazard ratios. In addition, another recent report demonstrated a significant association but argued that it was an artifact of cigarette smoking that they had not controlled [1]. Another study failed to find a significant association, but had not been able to control for hypnotic dosage [2]. An analysis observing significant associations of hypnotic usage 5+/week with lung cancer and melanoma found that only melanoma remained significant after adjustment for confounders [3].

To summarize, the preponderance of reports has favored an association of hypnotic drug consumption with new cancer, but the detailed results have not been entirely consistent. One worries that publication bias might have favored positive reports of significant association. The issues of confounding have not been fully resolved in any of these studies. Indeed, confounding probably cannot be excluded to everybody's satisfaction using any of the contemporary epidemiologic data bases. Thus, the issue of whether hypnotics cause cancer has not been resolved. To indicate causality, an epidemiologic approach would have to control all conceivable confounders with exceptional precision, analyze dosage and duration of hypnotic administration accurately, and have power to focus independently on each particular hypnotic considered.

The scientific question of causality is similar to that posed by cigarette smoking. Cigarette manufacturers have not undertaken randomized controlled trials of cigarettes of sufficient magnitude to prove whether or not their products are causing deaths and cancer. Thus, epidemiologic studies, especially the Cancer Prevention Study II (CPSII), were considered the gold standard evidence for the risks of cigarette smoking. After a few decades of study, public health authorities became ready to believe causation, even without adequate controlled trials. Although in that very same CPSII study, the mortality risks of heavy hypnotics use seemed almost as great as mortality risks associated with cigarettes when studied simultaneously in the very same Cox Proportional Hazards models controlled for dozens of confounders [4], the evidence for hypnotic causality was not considered conclusive, even though the hypnotics hazard ratios have usually been more persuasive for overall mortality than for cancer. Decades are passing while the scientific community thinks about the risks and hypnotic drug patents expire, but the U.S. FDA experts (and their world-wide colleagues) have not been ready to require warnings for the cancer and mortality risks associated with hypnotics. Note that the FDA requires warnings of less common hypnotic risks for which the epidemiologic evidence of association is far less developed than that for cancer or mortality and for which controlled-trials

evidence is non-existent. Evidently, the scientific community will not dare conclude that hypnotics cause human cancer without a different kind of evidence.

For drugs that have already been marketed extensively for many years, Mendelian randomization studies are an alternative retrospective way of exploring the causal risks of hypnotics. Mendelian randomization studies become increasingly practical as genomic assays become available for growing proportions of our populations. The Mendelian randomization strategy would be applicable for some of the older drugs with expiring patents, but what about the newest hypnotics?

The pharmaceutical industry would like to license a new generation of patented hypnotic drugs for which there will be no data for Mendelian randomization studies. Before licensing, drug regulators should require Phase III trials of sufficient magnitude to determine mortality and cancer risks. With authority under the 2007 FDA Amendments Act, the U.S. FDA could also require Phase IV trials of sufficient magnitude to determine mortality and cancer risks of already-approved drugs. The FDA should. Black box cancer and death risk warnings should be required until each marketed hypnotic might be proven free of such risks by large long-term controlled trials.

One would suppose that there are legislators whose family members have been stricken with cancer or died while taking sleeping pills. Wouldn't those legislators want the FDA to protect the remainder of their families? There is little sign. Those fighting for attention to hypnotic cancer risks gain the same respect as Don Quixote challenging windmills. In most of the world, the windmills are growing larger and seem to be winning! Yet, the winds of hypnotic regulation have been growing in the United States. Perhaps regulators will find sufficient courage to demand trials to resolve the questions of hypnotic risk or at least warn of evidence for cancer and mortality risks until the unlikely event that safety might be demonstrated.

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