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EDITORIAL

Who Should Sponsor Sleep Disorders Pharmaceutical Trials?

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WHO SPONSORS SLEEP DISORDERS TRIALS NOW?

At the current time, almost all trials of sleep disorders drugs are sponsored by the pharmaceutical industry. For example, in preparation for the State of the Science Conference on Manifestations and Management of Chronic Insomnia,[1] the Agency for Healthcare Research and Quality sponsored a systematic review of the literature.[2] Of 56 randomized controlled trials of drug treatments of insomnia which reported the funding source, all but 5 were apparently funded by the industry. These 5 may have been the only ones of 108 hypnotics trials considered in the meta-analysis which were not sponsored by the pharmaceutical industry. In contrast, in 4 psychiatric journals, of over 200 articles over 10 years, it was estimated that only 57% of trials were industry sponsored.[3] A slightly more recent analysis of the same journals found that among 397 trials, 60% were industry supported.[4] In gastroenterology, 48% of trials were not industry supported and 24% did not disclose funding.[5] In 5 high-impact medical journals, 36% had nonprofit sponsorship, the rest being not declared, industry sponsored, or mixed.[6] Obviously, the percentage of trials which were industry sponsored is much greater in the hypnotics field than in general medicine or psychiatry.

WHAT IS THE PROBLEM WITH INDUSTRY TRIALS?

In recent years, much has been written about the biases in clinical trials, which apparently arise from the financial interests of the authors and the trial sponsors.[7] For example, Bekelman and colleagues found that about one quarter of academic researchers had financial ties to industry, and more received gifts from industry.[8] In a comprehensive meta-analysis, they found that the odds ratio for finding results favorable to industry in industry-sponsored trials was 3.6 times as high as in non–industry-sponsored studies (95% C.I. 2.63-4.91). One might therefore infer that a high proportion of the industry-sponsored trials offered biased data presentation or biased designs. Another issue is that industry-sponsored studies have tended to compare the industry drug with placebo, whereas non–industry-sponsored studies were more likely to compare the drug with an alternative (see below). The goal of placebo-controlled trials is to show that the drug has some effect, not that it has a large or superior effect as compared to other alternatives. A further problem is that industry-sponsored studies with unfavorable outcomes are often never published.[9] This has certainly been the case among hypnotic studies, where a strong publication bias has been demonstrated.[2,10] Medical journals, often themselves dependent on drug advertising, risk becoming "a marketing arm" of pharmaceutical manufacturers.[11] It has been recommended that part of the solution should be more government-sponsored trials.[11]

In the literature on hypnotics, a variety of biasing practices have been evident. First, it has been shown that trials organized around a placebo baseline followed by drug treatment were biased from lack of counterbalancing. Parallel-placebo-controlled studies showed that participants in insomnia trials tend to remit without any pharmacologic agent (perhaps from spontaneous remission, suggestion, and hope; a regular schedule and imposed sleep hygiene; time after prior drug withdrawal in some cases, and so forth.) Therefore, much of the demonstrated improvement from baseline in sequentially-ordered trials had nothing to do with benefits of the drug evaluated. We still see this problem in the design and interpretation of studies today. Second, emphasis has been placed on the statistical significance of very small benefits. For example, the meta-analysis employed by the recent consensus conference on chronic insomnia concluded that hypnotics were "effective treatments," because of mean objective reductions of sleep latency of 11-12 minutes, even though (remarkably), the new benzodiazepine agonists were <u>not</u> found to increase objective total sleep time or to decrease wake after sleep onset significantly![2] Published industry trials have tended to celebrate small reductions in sleep latency, without conceding disappointment when total sleep time is increased little if at all by the hypnotic. Moreover, far from relieving diverse somatic symptoms, hypnotics significantly increase adverse symptoms.[2] Another recent meta-analysis concluded that the harm done by hypnotics outweighs the benefits, at least in an older age group.[10] It would be difficult to find an industry-sponsored publication which offers a balanced discussion of benefits and risks.

People who take hypnotics are often worried about the consequences of poor sleep and motivated by desire to improve their next-day performance. The issue is confused by the well-known disparity between the small objective benefits of hypnotics for sleep and the somewhat larger subjective benefits.[2] Less well-known is the disparity between objective and subjective effects of hypnot-

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Table 1—Infection/Inflammation with Eszopiclone

	Placebo	Eszopiclone
Total N	195	593
infection	13	94
pharyngitis	10	59
rhinitis	9	42
sinusitis	11	25
Affected	43 (22%)*	220 (37%)*
Unaffected	152*	373*

*Chi-Square=14.9, p<0.0002, RR=1.68
raw data from Krystal et al., 2003[13]

ics on next-day performance. Participants in hypnotics trials often believe that their performance is benefited, when objectively, it is not. The older hypnotics literature contained far more objective evidence for hypnotic-induced next-day performance impairment than for improvement.[10] By a standard of improving objective next-day performance, most hypnotic trials have failed. The industry has responded with very large trials using subjective improvement as the endpoint, generally passing over the fact that their own shorter-term trials show that the subjective benefits cannot be validated by objectively improved performance. This leaves the clinician without data for whether by objective testing, the new hypnotics improve daytime performance or impair it over a period of months.

A concern is the lack of focus on adverse effects in industry-sponsored trials and the minimal discussion. Few sleep medicine clinicians discerned from the published hypnotics trials that the modern hypnotics tend to cause depression. Yet, an association with hypnotics (contrasted with placebo) in the development of depression was quite evident in the NDA data reported to FDA,[12] which presumably was more free of publication bias. To give some examples from an influential manuscript given priority publication in the journal *Sleep*, there were 2% dropouts due to depression in the eszopiclone group and none in the placebo group,[13] but the manuscript neglected to mention that this difference was statistically significant or that (as reported to FDA) there were 27 instances of depression overall in the eszopiclone group and only 3 in the placebo group (p~0.08, Fisher exact test, two-tailed).[13] Moreover, this manuscript listed incidents of infection, pharyngitis, rhinitis, and sinusitis in a table, but failed to emphasize that the combined categories related to infection and inflammation were 68% more frequent among participants receiving eszopiclone than placebo ($p < 0.0002$, see Table 1).[13] Incidentally, if the unpublished data (listed in the FDA NDA) concerning fever, cough, otitis media, and urinary tract infection with eszopiclone were added to Table 1, the risk ratio and statistical confidence of complications suggesting infection or inflammation would be even greater. Likewise, taking infection by itself, the risk ratio was greater. Overall, this manuscript detailed an overwhelming 84 significance tests related to benefits of the hypnotic but mentioned only one significance test related to risks. This imbalance of statistical reporting of benefits and risks was not because there was only one significant adverse effect in the trial data.

It is concerning that the preponderance of infection in participants randomized to benzodiazepine agonists in controlled trials, quite obvious in FDA NDA data, has never been discussed in the published hypnotics literature, so far as could be found. Infection is associated with other benzodiazepine agonists besides eszopiclone. Moreover, excess cancers among both human participants and laboratory rodents randomized to hypnotics in controlled trials has never been discussed in the published literature, though it is rather evident in the FDA NDAs.[14] Perhaps Scharf et al. presented the first hypnotics trial to mention the occurrence of cancers in the drug groups, though indeed this was certainly not the first hypnotics trial in which incident cancers have been observed.[15]

Similarly, over a dozen epidemiologic studies have reported an association of hypnotic use with excess mortality. A surprising feature of the latest epidemiologic study was that the risk ratio for zolpidem tended to be a bit higher than for older benzodiazepines.[16] No hypnotic manufacturer has attempted to refute the epidemiology by conducting trials to show that their product produces no excess mortality.

WHAT HAVE THE NIH AND THE VETERANS ADMINISTRATION BEEN DOING?

Some years ago, an NIH CRISP search was used to establish that hypnotics were the only class of commonly-used psychotropic drugs for which NIH funded no controlled trials focused specifically on the effectiveness of marketed drugs.[17] In a recent CRISP search with keywords "hypnotic" and "trial," the author could find no results suggesting R01 funding of a trial of a prescription hypnotic compared to placebo or to another prescription hypnotic. There were a few funded contrasts with alternative treatments such as cognitive-behavioral therapy or melatonin and one trial combining a hypnotic or placebo with an antidepressant. Approved hypnotics were studied as contrast treatments but were not the major focus. The Veterans Administration (VA) record is similar. It can be argued that since the manufacturers tend to do placebo-controlled trials, it is more important for NIH to study the contrasts with alternative treatments. Unfortunately, the balance of benefits and risks of hugely popular marketed hypnotics, particularly using objective data, and particularly focusing on adverse effects, remains to be adequately studied.

Similarly, an NIH CRISP search for grants with key words "RLS" and "trial" disclosed no NIH-sponsored trials of prescription drugs for primary restless legs syndrome.

The situation is somewhat better for treatment of sleep disorders such as sleep apnea and narcolepsy, where NIH research on sleep disorders treatment has been a bit more forthcoming. Historically, however, and perhaps still today, treatment with hypnotics impacts more people (many millions) and costs more money than all the rest of sleep medicine put together.

WHAT ABOUT PRIVATE FOUNDATIONS?

In some areas of medicine, private foundations such as the American Cancer Society, the American Heart Association, the MacArthur Foundation, the Howard Hughes Medical Institute, and the Stanley Foundation have leadership roles in medical research. Regrettably, the large private foundations have not been substantially active in promoting independent critiques of hypnotic medications.

WHAT SHOULD NIH AND THE VA BE DOING?

NIH or VA sponsorship of major hypnotic trials is needed to more carefully study potential adverse effects of hypnotics such as daytime impairment, infection, cancer, and death and the resultant balance of benefits and risks. At least several thousand

participants will be needed for adequate power. Objective as well as subjective assessment of health and performance effects is needed. Although possibly more difficult to perform, a study of several years of hypnotic vs. placebo administration might be particularly informative. For issues such as cancer and mortality, studying a smaller number of participants for a longer period of time may make for a more cost-efficient and clinically relevant study. A planning conference and pilot studies might be needed before initiating a major trial.

The NIH sponsors numerous trials of aspirin and other minor pain relievers, vitamins, and foods, but generally ignores hypnotics. A skeptic might argue that aspirin, vitamins, and foods save or cost lives, whereas hypnotics do not do very much. To the contrary, some studies have argued that long-term hypnotic usage improves general health, whereas other reports suggest that they shorten lives. The public needs to know which is correct.

CONCLUDING REMARKS

In 1979, an Institute of Medicine committee reported, "Nearly all investigations into prescription drugs and insomnia conducted in the United States have been sponsored by drug manufacturers. In the United States, there is no independent clinical research, supported either by the government or by philanthropic foundations, with which to seek answers to legitimate public health questions about hypnotic drugs. Although various agencies of the Public Health Service (especially the National Institute of Mental Health) have supported studies of sleep physiology and sleep disturbances associated with such specific mental disorders as depression or schizophrenia, the amount of clinical investigation directed toward treatment methods for insomnia has been negligible."[18] They concluded, "The committee finds that there is a need for research and clinical evaluation of hypnotics that is independent of drug manufacturers. . ."[18] The Institute of Medicine recommendations are as valid today as they were in 1979. Considerable progress has been made in studying insomnia, but there remains little research on hypnotics that is independent of drug manufacturers.

It has been hard to persuade scientific review committees to place a high scientific priority on studies of a class of drugs in use for over a hundred years. Scientific disinterest in hypnotic effects is exemplified by a review of 621 clinical trials published in the *Archives of General Psychiatry*, in which not a single trial of an hypnotic was found.[19] Perhaps leading journals, the NIH and the VA, like to focus on major medical advances. There is less enthusiasm for studying an older class of drugs which may do more harm than good. Yet, the public desperately needs an equipoised assessment of hypnotic benefits and risks, so the NIH and VA leadership need to rearrange priorities in order that these public health needs are satisfied.

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