Study Finds Sleeping Pills Overprescribed

Physicians and insomniacs should wake up to the pills' hazards, says IOM panel

Sleeping pills, the most prescribed medication in the world, are more dangerous and less useful than either physicians or patients realize, according to a recent report by the Institute of Medicine (IOM)–National Academy of Sciences. Hazards associated with the most common pills are particularly unrecognized, the report says. At the same time, little evidence exists that the pills control insomnia, particularly when used for more than 2 weeks. In short, sleeping pills are prescribed far more often and with far less care than they should be.

The report, written by a panel under the direction of William G. Anlyan, vice president for health affairs at Duke, states that "sleeping pills should have only a limited place in contemporary medicine. It is difficult to justify much of the current" prescription practice, particularly in light of the general ignorance of why insomnia occurs and precisely how the pills act. "Given our current lack of knowledge, it would appear medically prudent to use hypnotics [sleeping pills] sparingly and carefully, prescribing only a small number of pills at a time." Currently, more than 25 million such prescriptions are written annually in the United States alone, and more than 8 million persons use the pills sometime during the year.

The panel is particularly concerned that persons are taking the pills for too many consecutive nights, beyond the period of proved effectiveness, and to a point where the hazards may be severe: "Physicians should rarely, if ever, prescribe hypnotic drugs for periods beyond 2 to 4 weeks." Clinical trials cited by the panel show that the effectiveness of most pills begins to drop off after 7 nights. Currently, most prescriptions are for 30 tablets or more, however. Refills are casually granted, and up to 2 million people may take the pills nightly for more than 2 months at a time.

Previously, the hazards from such extended use were thought to be more severe with some pills, namely barbiturates, than with others, particularly the newer and most frequently used pills, the benzodiazepines. Barbiturates are strongly addictive; they are also lethal in overdose (15 to 20 tablets) and they figure prominently in drug-related deaths and suicides. As a result, experts in the field of drug abuse, including President Carter's former adviser on drug policy, Peter Bourne, have suggested from time to time that barbiturates be banned, and that prescriptions be restricted to alternative sleeping pills. Bourne's recommendation, in fact, provided an impetus for the IOM study.

Far from giving its blessing to such a scheme, the IOM report concludes that, although barbiturates are indeed as hazardous as everyone thinks, the chief alternatives, benzodiazepines, may be just as risky, and in some ways may be even more risky than barbiturates. The most common benzodiazepine, for example, is flurazepam, which under the trade name Dalmane accounts for 53 percent of total sleeping pill prescriptions.

Report finds drug ad watchdogs in repose.

Dalmane, like other drugs in its class such as Valium and Librium, is addictive, although not as addictive as barbiturates; patients develop a tolerance for it more slowly. But the metabolite of Dalmane remains in the body far longer than barbiturate metabolites—for more than a single day, in fact. The consequence is that a patient using it on consecutive nights has a gradually increasing amount of the drug in his system; by the seventh night, patients have four to six times the amount present in their systems after the first night. The effects of the drug thus are increasingly felt during the day, contributing to greatly diminished alertness and hand-eye coordination, which may be important for driving. This side effect, which was discovered only recently, constitutes a significant drawback for Dalmane relative to barbiturates.

In addition, the panel reported, Dalmane may not have some of the attributes ascribed to it by its manufacturer, Hoffmann-La Roche Inc. Labeling in the Physician's Desk Reference and in the company's advertising, for example, claims, "Sleep laboratory studies have objectively determined that Dalmane is effective for at least 28 consecutive nights of drug administration." Nowhere, the IOM panel says, "do these advertisements reveal that the claim of effectiveness for 28 nights is based on studies of only ten patients and that hundreds of individuals with sleep complaints had to be screened to select these severe insomniacs for research purposes." Considering that millions of people are taking the drug, says panel member J. Christian Gillin, a sleep researcher at the National Institute of Mental Health, "to base such a claim on such a small sample and one that may not be properly selected to represent the broad spectrum of insomniac cases, is inappropriate." Adds panel member Frederick B. Glaser, a psychiatrist and head of the Addiction Research Foundation at the University of Toronto, "any scientist worth his salt would not go along with that kind of study to make that kind of claim."

Also, a major reported attribute of Dalmane and other benzodiazepines is that they do not suppress REM sleep to the degree that barbiturates do. REM sleep, which is characterized clinically by rapid eye movements, has been thought to be essential to long-term physical and mental health. The panel, however, says that such an assumption is at best unproved, and probably untrue: "It now appears that the overall effects of REM sleep deprivation . . . are, at most, slight and subtle." And though it may still be reasonable to pick the sleeping pill that least disrupts sleep, Dalmane may not be that pill. The panel notes that it disrupts stage 3 and stage 4 sleep, which may be just as significant.

Finally, and perhaps of greatest importance in judging the relative merits of barbiturates and Dalmane, the panel concluded that what was thought to be Dalmane's greatest attribute was, for all practical purposes, unimportant. Unlike barbiturates, Dalmane is not lethal by itself in overdose. But the panel discov-

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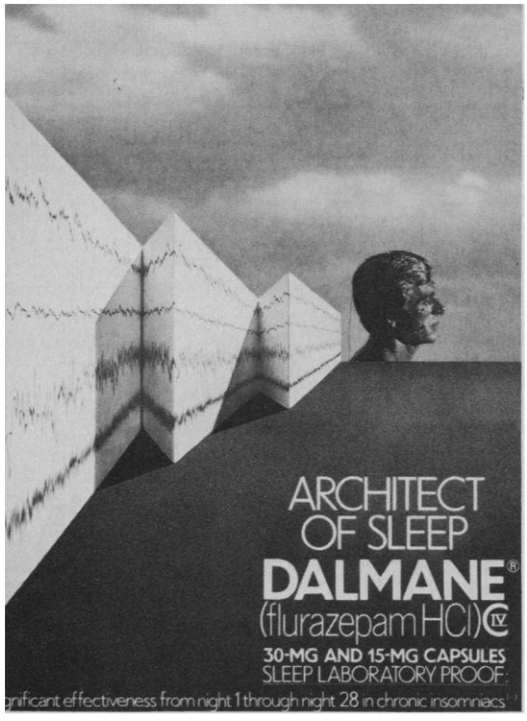

Long-term sleep lab data mentioned on the next page of this Dalmane ad involved only ten patients.

ered that an increasing proportion of drug-related deaths involve alcohol; because both drugs are lethal in combination with alcohol, Dalmane does not offer any significant advantage in diminishing the overall number of deaths related to sleeping pills.

In light of these results, the panel swears off the barbiturate ban, and opts instead for corrections to generic problems in the medical and pharmaceutical communities. The reforms they suggest are cautiously stated but nonetheless bold for a group of physicians reviewing the practices of the profession. The panel notes, for example, that few medical schools offer training in sleep physiology. As a result, many physicians may not understand insomnia, and most are apt to exaggerate the importance of their patients' complaints about it. Were they to hear a lecture on the subject, they would doubtless hear that the sleep of patients who complain of insomnia is barely different from those who sleep normally, even when measured in sleep laboratories. An oft-quoted case in the literature is that of a woman with a 25-year history of insomnia who entered such a laboratory. In four successive nights, "she fell asleep quickly, slept more than eight hours per night, and had normal architecture of sleep stages," according to the IOM report. "Each morning, however, she reported that she 'didn't sleep a wink.' " Patients consistently exaggerate their insomnia, but doctors are not told this in school.

From medical school, the panel notes, the budding physician enters residency at a hospital. In hospitals, the predominant philosophy appears to be that both staff and patients are happier if patients are asleep. Studies show that half of all hospital patients are given sleeping pills. As Anlyan says, "It's easy for hospital physicians to get into a rut, leaving the standing order, sleeping pill of choice to be repeated at regular intervals." As the panel notes, "the casual prescribing of hypnotics in this environment may be expected to influence [physicians'] future use of these drugs."

From residency at a hospital, the by-now experienced physicians move on to private practice, in which—studies show—they derive most of their drug information from pharmaceutical sales representatives, drug advertisements, and the Physician's Desk Reference. Material in each on sleeping pills is occasionally misleading, the panel notes: "The committee finds information from these sources tends to be incomplete and of questionable value to the physician." One example is the current PDR listing for Dalmane, which claims that Dalmane is effective for a month of consecutive use. This listing is based on only two studies in sleep laboratories with five people each. Asked about this, a company spokesman admits that "perhaps this is not satisfactory." Also, no mention of Dalmane's long-acting metabolite was made until last year, 5 years after the characteristic became known. When the information was added, consequent adverse effects were not mentioned; the company instead brags that the drug is even more effective than known earlier. The listing warns only against operating machinery shortly after ingesting the drug and says nothing about the following day. The panel called this "deficient."

The agency with responsibility for policing such deficiencies is the Food and Drug Administration (FDA), to which the IOM panel extends its criticism. "Except in rare instances, the FDA is not legally permitted to screen advertising prior to its appearance, but it could be more vigilant and timely in insisting on 'complete labeling' (prescribing information) which is maximally useful in format and content to the physician," the panel states. In the agency's defense, Tom Hayes, chief of the FDA's psychopharmacology unit, says that the label for Dalmane is no better or worse than that permitted for other sedative-hypnotics. "It is characteristic that sleep lab studies involve a small number of patients," he says. Indeed, the FDA's recently published guidelines for such studies require long-term studies involving only 12 subjects. The Dalmane evidence is "typical of the sorts of data on duration that we've seen," Hayes says. After hearing sections of the IOM report read over the telephone, he adds that "it is conceivable that Dalmane's labeling should be stronger," to reflect more fully the long-lasting effects of the drug's metabolite.

Looking toward long-term improvements, the panel suggests that FDA will perform its watchdog role better only if it gets more outside advice, particularly from experts not connected with the drug industry. "Ways must be found to collect data and sponsor research which will supplement the information put forth by pharmaceutical companies in new drug applications and . . . marketing reports to the FDA." The scientific studies on which those data are based also need improvement. "There has been a failure to set high standards of interpretability, replicability, and general validity in the published studies. There is no adequate, independent peer review of protocols or healthy competition for support." In short, the industry has dominated sleeping pill research, and much of it is deficient. In particular, the panel notes, studies of the effects of sleeping pills on daytime performance have been funded by governments abroad; the United States should do some of the same.

The significance of this whole chain of events, the panel notes, is felt particularly by the elderly, who experience insomnia as a natural development of aging. Currently, they receive 39 percent of all sleeping pill prescriptions; among nursing home patients alone, the prescription rate may be as high as 94 percent. The practice is almost entirely unwarranted, the panel suggests. Moreover, the diminished alertness caused by the long-acting pills, such as Dalmane, may be confused with irreversible senility or dementia and lead to a host of other inappropriate treatments.

Still, the panel does not suggest that either barbiturates or benzodiazepines be more tightly controlled by the federal government. Instead, the IOM panel of physicians suggests that the profession heal itself. Office counseling and therapy are more appropriate but also more time-consuming alternatives to sleeping pill treatment. Dosages of many prescriptions could be reduced. And more generally, people should worry less about losing some sleep now and then. As panel member Glaser notes, "The problem is *not* life-threatening."

—R. JEFFREY SMITH