LETTERS

Sleeping Pills and Insomnia

R. Jeffrey Smith's interesting review (News and Comment, 20 Apr., p. 287) of the Institute of Medicine (IOM) study *Sleeping Pills, Insomnia, and Medical Practice* (*1*) contains statements indicating some misunderstanding of the IOM committee's findings and recommendations.

In contrast to an implication in Smith's article, the IOM committee did not conclude that the benzodiazepine drug flurazepam (Dalmane) was physically "addictive." The IOM report stated, "Some benzodiazepines (diazepam but not, as yet, flurazepam) have been used in serious drug dependence of the barbiturate type" (*1, 2*). As for habituation to nightly use of sleeping pills—which some authors describe as a form of drug dependence (*3*)—the committee concluded, "Nightly reliance on drugs for sleep is equally likely to arise with either benzodiazepines or barbiturates." However, the IOM report explicitly eschewed the terms "drug dependence" and "addiction" in its discussion of this problem, in view of the limited information available about it. The committee was aware, anecdotally, of patients who have taken low doses of hypnotics for years without obvious adverse consequences. Research studies on this population are needed to assess benefits and hazards associated with long-term use of sleeping medication.

The committee's clinical suggestions for prudent prescribing included limiting the amount of medication (a few days to a few weeks) initially prescribed for carefully selected patients with *new* insomnia complaints. This approach was not intended to promote the abrupt withdrawal of hypnotics from patients who have already become reliant on regular use of sleeping pills. For these patients, the committee recommended frequent clinical reappraisal of diagnosis and vigilant monitoring "for development of either toxic side effects or risk factors which would make continuation of the drug hazardous (e.g., pregnancy, renal disease, alcoholism, depression"(*1*).

We also were troubled by the article's conclusion that the low likelihood of fatal results from ingestion of an overdose of flurazepam alone is "for all practical purposes, unimportant." The committee did discover that only a very small decline has occurred in the overall drug-suicide rate since 1970 (when the prescribing of barbiturate hypnotics began to be replaced by benzodiazepines). The drugs now being used in suicide are of several different types—analgesics, antidepressants, tranquilizers (benzodiazepines and others), and sleeping pills—predominantly in combination with each other and/or alcohol. From a public health point of view, therefore, the IOM committee observed that evaluation of a given drug's "safety" and efforts to control the availability of the drug "should not be based solely on the toxicity of a drug used by itself in overdose, but should take into account the dangers of combining different kinds of medication with each other and with alcohol" (*1, 2*). Nevertheless, from the point of view of clinicians who prescribe for individual patients, the relative safety in overdose of benzodiazepine drugs when taken alone is a significant advantage when a patient's suicidal tendencies are a possible source of concern.

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I would like to comment on Smith's article "Study finds sleeping pills overprescribed" because of our concern regarding several inaccuracies therein.

While the Institute of Medicine (IOM) report, in our view, lacked objectivity and fair balance in certain respects, the *Science* article omits data set forth in the report and, in some cases, appears to incorrectly interpret data, particularly that relating to the benzodiazepines in general and specifically flurazepam (Dalmane). The *Science* article also draws conclusions not present in the IOM report.

While the *Science* article states that "little evidence exists that the pills [hypnotics] control insomnia, particularly when used for more than 2 weeks," there is published clinical evidence which shows Dalmane to be effective in the relief of insomnia for longer than 2 weeks. As stated in the IOM report: "Of drugs marketed in the United States, only flurazepam has been shown to affect sleep for as long as 28 days of continuous use. . . . Most other hypnotics that have been studied in the sleep laboratory appear to lose their sleep-promoting properties within three to 14 days. . . ."

Other significant clinical information on benzodiazepine and barbiturate hypnotics is not mentioned in the *Science* article, although it was covered briefly in the IOM report. As a class, benzodiazepines do not stimulate hepatic drug-metabolizing enzymes to any appreciable degree, and therefore do not interfere with concomitant drug therapies. Conversely, barbiturates do stimulate these enzymes and thus increase the rate of metabolism of a wide range of other drugs, including antidepressants and, particularly, oral anticoagulants. This phenomenon can result in decreased effectiveness of these drugs in patients receiving barbiturate hypnotics concomitantly; the clinical implications of these interactions should be clear.

Smith points out that barbiturates are highly addictive but then states that "Dalmane . . . is addictive, although not as addictive as barbiturates; patients develop a tolerance for it more slowly." Here he treats two distinctly different entities—tolerance (loss of effect at therapeutic doses) and addiction (physical dependence)—as if they were one and the same. While physical dependence has been reported with some benzodiazepines, such cases have usually been in patients who had received excessive doses over an extended period of time; the Dalmane package insert clearly states that physical dependence to Dalmane has not been observed or reported in patients receiving it. Furthermore, the IOM report states: "Among the disadvantages [of the barbiturates] are that tolerance [to their sleep-inducing properties] may develop quickly with regular nightly use." The preponderance of the medical evidence indicates that tolerance to the hypnotic effect of Dalmane does not develop over a normal course of therapy.

In two particular instances, the *Science* article appears to incorrectly interpret the data set forth in the IOM report regarding the relative safety of Dalmane versus that of the barbiturates in an overdose situation. That "Dalmane's greatest attribute [safety] was, for all practical purposes, unimportant" is not borne out by critical examination of the scientific

literature, nor can it be supported by the IOM report itself, which states: "It is unusual . . . for an overdose of a benzodiazepine alone to be fatal, and this particular safety aspect has been widely recognized. . . . When benzodiazepines have been taken alone in overdose . . . the outcome usually has been benign, even when the dose has been rather large." In contrast, the IOM report states: "Among the disadvantages [of the barbiturates] in suicidal overdose, coma and death can occur at relatively low doses (10-20 dosage units)."

The dangers of combining any drugs that act on the central nervous system in a suicide attempt should not be minimized, but as Greenblatt *et al.* (*1*) state: ". . . the severity of intoxication in cases of multiple drug ingestion probably depends largely on the type and quantity of *non-benzodiazepines* or other agents involved" [emphasis added].

An indication of suicides involving hypnotics, when used alone or in combination with alcohol or other drugs, appears in the April 1977 DAWN (Drug Abuse Warning System) report (*2*), in which the mortality per million pills prescribed is presented. The data relevant to the context of the *Science* article are shown in Table 1.

Table 1. Mortality, alone or in combination with alcohol or other drugs, per million pills prescribed.

Agent	Drug-related deaths per million pills
Secobarbital	11.6
Seco/Amobarbital	9.7
Amobarbital	8.5
Pentobarbital	7.8
Flurazepam	0.3

The suggestion that "The effects of [Dalmane] . . . are increasingly felt during the day . . ." has not been borne out by systematic evaluation of the daytime effects of Dalmane in *insomniac* patients. There is ample evidence that side effects of Dalmane, such as drowsiness, when they do occur, are generally seen early in therapy—between days 1 and 4, and most often on day 1 (*3*). If accumulation of the long-acting metabolite of Dalmane were to produce detrimental effects, one would expect to see an *increase* in side effects over time; this has not been the case in clinical experience in millions of patients.

That the accumulation of the metabolites of Dalmane contributes "to greatly diminished alertness and hand-eye coordination . . . [which] constitutes a significant drawback for Dalmane relative to barbiturates" has not been proved in the patient population for which hypnotics should be prescribed. One study has shown that, when both barbiturate hypnotics and Dalmane are administered to *insomniac* patients, no significant decrement in hand-eye coordination skills related to driving occurred, even when these performance parameters were measured after as many as 14 consecutive nights of drug administration (*4*). We encourage further research in this area, research which should employ the appropriate methodology and patient population.

Citing the relatively small number of patients (ten) involved in the sleep research laboratory studies in which Dalmane was proved effective for 28 nights, the IOM report inferred that the data derived from these studies may not be valid. Sleep research laboratory studies permit accurate, objective measurement of the architecture of sleep; these measurements are exceptionally reproducible across studies. Clinical researchers and biostatisticians recognize that the more precise the measurement being used for evaluation, the fewer patients need be evaluated. The relatively small "*n*" involved in these studies does not, therefore, in any way invalidate the data derived from sleep laboratory research, since this method permits precise, accurate measurement of the actual efficacy of hypnotic medications.

The selection of patients for these studies was based on strict inclusion criteria, one of which was a willingness to spend many nights in a sleep research laboratory, and the most important of which was the presence of clinical insomnia *measurable* by sleep research laboratory techniques. The strict protocols followed in these trials are indicative of the objectivity for which the researchers strove, not of biased or slanted screening techniques, as was inferred.

We strongly support the IOM report's recommendation to initiate new, more sophisticated, multidisciplinary research on the efficacy and safety of hypnotics. However, the statements in the IOM report that "ways must be found to collect data and sponsor research which will supplement the information put forth by the pharmaceutical companies in new drug applications and . . . marketing reports . . ." and "the industry has dominated sleeping pill research" suggest that the data gathered to date have been biased in favor of the industry. This insinuation is unwarranted and unjustified. We contend that objective sleep laboratory research, combined with subjective studies of hypnotics has provided the best *available* methods for determining and replicating data on the efficacy of these drug products.

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5. I thank D. H. Barlekamp, C. Blicharz, and D. Chen-Cohen for their invaluable assistance in preparing this manuscript.

Anlyan *et al.* now state that many patients can take hypnotics for years without "obvious" adverse effects, but the IOM report—signed by the full panel including Anlyan—contains many statements to the contrary. "Some chronic insomniac patients receiving prolonged treatment with hypnotics appear to sleep worse than similar patients without hypnotic therapy" (p. 93); "in long-term use, the side effects and risks of benzodiazepine hypnotics are likely to increase" (p. 142); "the consensus of sleep disorders specialists seems to be that hypnotic drugs should not be the primary form of treatment for patients with persistent insomnia" (p. 138).

As to the point about addiction raised by both Anlyan and Roche, the IOM report says flatly, "Although physical addiction to benzodiazepines is not as major a medical problem as it is for other classes of sedative-hypnotics, there has been growing concern in medical circles about dependence on these drugs. It has been estimated that ingestion of 3 to 5 times the hypnotic dose for one month may pose withdrawal seizures" (p. 28); "with any hypnotic, patients should be advised of the potential for the development of habituation in the form of nightly reliance on sleeping pills" (p. 139).

Roche makes a questionable distinction between tests of motor coordination following flurazepam use among *insomniac* and *noninsomniac* patients, because few of the millions who take flurazepam have classic insomnia. Moreover, contrary to an implication in Roche's letter, motor coordination *has* been tested among insomniacs, and found to affect coordination. As the IOM report states (p. 165), two British researchers determined that "30 mg of flurazepam manifested definite impairment

of visual-motor coordination" in "anxious, insomniac patients."

Finally, Roche selectively omits six words from a sentence in the IOM report quoted in the third paragraph of their letter; the words point up what the IOM committee considered to be inadequate proof of Dalmane's efficacy in long-term use. The full sentence as written by the IOM panel reads, "Of drugs marketed in the United States, only flurazepam has been shown to affect sleep for as long as 28 days of continuous use, *and then only in 10 insomniac subjects*" (emphasis added).—R. JEFFREY SMITH

Smith's review of the Institute of Medicine (IOM) report on sleeping pills concludes with a quotation from panel member Frederick B. Glaser that insomnia, "is *not* life threatening," but the actual report reached no such conclusion. Our data (*1*), cited in the IOM report, and other studies (*2*), have shown that people who sleep less than 7 hours a night or who complain of insomnia have substantially increased mortalities. For example, men who reported they usually got less than 4 hours of sleep a night had 2.8 times the mortality of age-matched men who reported 7 to 8 hours of sleep (*1*). Controlling for reported sleep duration and insomnia, moreover, subjects who reported taking sleeping pills "often" had 50 percent greater mortality.

Although these statistical associations among short sleep, sleeping pill use, and increased mortality are highly significant, the causal factors have not been established. Specifically, we do not know whether either treatment of insomnia with sleeping pills or avoidance of sleeping pills can prolong life.

The IOM study emphasized that the benefits and risks of sleeping pills, particularly their long-term risks, are unclear. Since adequate assessment of sleeping pill benefits and risks has not been available to physicians, to the Food and Drug Administration (FDA), or to the manufacturers, it is not surprising that their activities have lacked firm scientific rationales. When the common patient complains of trouble sleeping, nobody really knows what should be done. Our lack of knowledge should not be blamed primarily on the manufacturers, since they have financed almost all recent clinical sleeping pill research.

How could we lack essential knowledge about such widely used drugs?

As an aged class of drugs, the sleeping pills seem to have been abandoned by contemporary psychopharmacologists for romances with the younger antipsychotics, antidepressants, lithium salts, and so forth, just as in the 1950's and 1960's, the old-fashioned and modest technologies of solar heating and windmills were abandoned because of fascination with nuclear energy. Youth triumphed over sober policy! These were worldwide phenomena not limited to the United States. Widespread use of sleeping pills also occurs in socialist countries, which tends to exclude advertising and the profit motive as major factors in sleeping pill misuse.

A few examples demonstrate the extent to which our research establishment is failing to monitor sleeping pills, even though many new compounds are being introduced. The IOM found that only a handful of small clinical studies of sleeping pills have been sponsored by government and philanthropic agencies in recent memory; the IOM cited no long-term, randomizing studies of sleeping pills whatsoever done in the United States. The President's Commission on Mental Health failed to contemplate any clinical research on sleeping pills (*3*), and sleeping pill research has not even been mentioned in recent government research plans (*4*, *5*). Bibliographic efforts have also been neglected. The National Institute of Mental Health's *Psychopharmacology Bulletin* omits most clinical trials of sleeping pills from its psychopharmacology bibliography, yet the National Institute of Neurological and Communicative Disorders and Stroke has withdrawn its support from sleep bibliographies compiled at the University of California at Los Angeles. I would hope that White House support for the IOM study augurs a government effort to reevaluate sleeping pill use.

To establish guidelines for treating patients with insomnia, we need an organized, government-sponsored program of clinical trials both of sleeping pills and of alternative treatments. A research effort proportionate to the health problem should be developed. It is estimated that there are about 27 million hypnotic drug prescriptions filled yearly in the United States, not counting the use of diazepam as a hypnotic (*6*). Since some studies suggest that diazepam may be used as a hypnotic as often as flurazepam (*7*)—diazepam is also prescribed for other purposes—total annual outpatient prescriptions used for sleep induction probably exceed 35 million. Including the costs not only of these prescriptions but also the costs of the physician visits, laboratory tests, and so forth, associated with them and including the costs of hospital dispensing, I estimate the total health effort devoted to insomnia exceeds $500 million annually. Since the United States spends 4 percent of health costs on research (*4*), a proportionate research program for sleeping pills should receive at least $20 million yearly. My estimate of the excess deaths associated with sleeping pill use would also support a research program of this magnitude, while estimates based on the mortality associated with insomnia indicate need for an even larger research program.

In summary, the most important conclusion of the IOM study was that there is insufficient knowledge of how insomnia should be treated. We need to discover effective ways of reducing the mortality associated with short sleep, with insomnia, and with use of sleeping pills. Only when adequate scientific knowledge is available to establish which treatment approaches are safe and effective can we expect the FDA and pharmaceutical advertising to promulgate such approaches among our nation's physicians.

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I hope other practicing physicians read Smith's excellent article on the Institute of Medicine's report on the overprescribing of sleeping pills. The inaccuracies and misleading statements in the Physician's Desk Reference (PDR) and in advertising are but one facet of the pill-pushing propensities of the pharmaceutical industry and the creation of a pill-popping society.

Practicing physicians are subject to a continual barrage of advertising as new drugs are marketed in rapidly increasing numbers. The PDR becomes thicker each year. Detail men tout pills in physicians' offices, each claiming a superior product, handing out impressive documents (and samples) to prove it. National, state, and specialty medical meetings are three-ring circuses where pharmaceutical houses intensively push their

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products. Each drug advertisement in medical journals claims superior results. Competition is fierce.

The most recent peddling medium for drugs is the program for continuing medical education foisted on physicians by state licensing boards on the premise that better medical care will result. Drug manufacturers are making hay by offering an array of films, programs, and tapes giving "CME credit," but which are basically sales gimmicks. Most of these "educational" films are made by cooperative medical school faculty members and are accepted by physicians as scientific and objective. The "science" of marketing apparently has reached its peak of development in the selling of drugs to my sophisticated, educated, gullible colleagues. As physicians swallow more pharmaceutical company propaganda, patients swallow more pills.

Propaganda + physician + patient + prescription = profit is a highly successful formula.

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Nuclear Risk

In support of Richard L. Meehan's editorial "Nuclear safety: Is scientific literacy the answer?" (11 May, p. 571), I should like to ask, Where are the crowds of protesters clamoring to close down O'Hare airport? Or the jet aircraft manufacturers? Where are the banners and slogans to shut down the automakers of Detroit? . . . the cigarette factories of the South? It's interesting that the actual statistics of 273 killed in one jet crash, 300 or more highway fatalities in one weekend, and uncounted, documented deaths from emphysema and heart problems have not caused more than a slight ripple in public opinion.

In spite of all the outcry, the nuclear generating industry record is *no* fatalities after 20 years of operation. From the Three Mile Island incident the government and independent experts have estimated the possible increase in cancer mortality resulting from radiation releases to be 3 to 4 per 100,000 individuals compared to an expected 4000 to 5000 cancer deaths in the same population from other causes (*1*).

Nuclear safety—yes, no argument, it must be examined, maintained, and worried about. However, the hysteria of much of the media and the American public about *possible* nuclear risks should be tempered by the realization of the *demonstrated* greater risks we daily accept. Why do we accept some risks and reject others? I don't know, but, when the people in the loud antinuclear groups and lobbies stop smoking and traveling in airplanes and cars, then perhaps I will have more respect for their position on the risks affecting my life.

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Continuation Methods

The article "Continuation methods: new ways to solve equations" (Research News, May 4, p. 488) was an extremely effective presentation of new and difficult mathematical ideas to a general audience. Gina Bari Kolata stresses the new continuation methods; it can be pointed out that the older "simplicial" methods mentioned there are in fact actually competitive and useful in solving hard problems, and both approaches are still evolving. The basic idea of continuation has a certain simplicity shown in the article which may be more readily communicated to many scientists. In any case, continuation can be thought of as an alternative way of explaining and implementing some of the ideas of Scarf and Eaves though their work uses simplicial methods for implementation.

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I enjoyed reading Kolata's article but believe she is not justified in asserting that the older simplicial methods of Scarf and Eaves are much more difficult to implement than the newer differentiable continuation methods. It seems to me that both methods need further study and computational experience.

One problem is to see how machine algorithms can be developed which unify the simplicial and differentiable approaches. Perhaps an even more important problem is to make a study of the "complexity" of these methods; that is, find a theory of speed of computation for path following algorithms.

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BOOKS RECEIVED

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