

Crisis Connection

HALCION

Sweet Dreams or Nightmare?

The most popular sleeping Pill in the world faces a mounting challenge over its safety

When Officer Reg Browne walked into the room, 83 year-old Mildred Coats was stretched out on her bed clutching a cheery birthday card in her left hand. Several towels had been placed gently around her head to absorb the blood spilling from eight gunshot wounds. Anticipating a heated domestic dispute, Browne had donned a bullet- proof vest before leaving the sheriff's office in Hurricane, Utah. But he didn't get a chance to use it. The old woman's daughter, 57- year-old Ilo Grundberg, was waiting calmly to hand him a written confession. "I didn't kill her because I didn't love her," Grundberg explained. "I love her very much."

Grundberg was arrested, charged with second-degree murder, jailed and then moved to a Salt Lake City mental hospital for psychiatric testing. But she never had to stand trial. After examining her, a pair of court-appointed psychiatrists testified that Grundberg had been involuntarily intoxicated when she killed her mother. Like more than 7 million other Americans, she had been taking the prescription drug Halcion to help her sleep. Though the drug is intended only for short-term use, her doctor had prescribed it for much of the preceding year, and she had grown increasingly agitated and paranoid while taking it. Because she had no clear motive for the murder and little memory of it, the experts concluded she hadn't acted voluntarily. Prosecutors responded by asking the court to dismiss the case. On Feb. 7, 1989, Ilo Grundberg went free.

Out of custody and off the drug, Grundberg got herself a lawyer. In a \$21 million civil suit, she and her daughter, Janice Gray, charged that Halcion is a "defective drug" and that Upjohn, its Michigan based manufacturer, failed to warn regulators and the public of its "severe and sometimes fatal adverse reactions." The company responded that it was "in no way negligent" and that the murder was "in no way caused by the drug Halcion." But last week, on the eve of a trial that would have brought a long, public airing of Halcion's disputed safety record, Upjohn blinked. In a terse press statement, the company announced it had "reached a resolution" with Grundberg and that the "details of the resolution shall remain, confidential." The settlement spares the company what could have been a bruising battle with an unhappy customer. But it won't quiet the controversy surrounding the most widely prescribed sleeping pill in the world.

Sold in more than 90 countries, Halcion is Upjohn's second biggest money-maker (after the closely related tranquilizer Xanax). The drug is marketed under the name Somese in South America, Singapore and Malaya. It has annual sales of \$250 million-\$100 million in the United States alone. US pharmacists fill roughly a half million Halcion prescriptions every month. The US Food and Drug Administration (FDA) declared Halcion safe and effective in 1982, and many doctors and patients obviously like it. The question raised by the Grundberg case-one that sleep specialists have debated bitterly for more than a decade-is whether the drug is more dangerous than other drugs in the benzodiazepine family, a group that includes Valium and Xanax and such popular sleep aids as Dalmane and Restoril.

Halcion's critics say there is no question it poses special hazards. They claim it is more likely than similar drugs to cause such nervous-system disturbances as amnesia, anxiety, delusions and hostility. And they charge that neither Upjohn nor the FDA has done enough to protect the pill-taking public. "This is a very dangerous drug," says Dr. Anthony Kales, head of psychiatry at the Penn State University medical school. "No other benzodiazepine has such a narrow margin of safety. The only justification for keeping it on the market is to ensure the company's profitability. From a public- health standpoint, there is no reason at all."

Upjohn, for its part, maintains that Halcion is no more likely than any other sleeping pill to cause adverse reactions. "I don't think that we view the side-effect profile of this product as being any different from other benzodiazepines," says pharmacologist Robert Straw, Upjohn's director of project management. "The vast majority of studies back us up on that point." Many sleep specialists who have studied and prescribed the drug share that view. "If used properly," says Dr. Thomas Roth, chief of the division of sleep-disorders medicine at Detroit's Henry Ford Hospital, "this is a very, very safe hypnotic."

When the first benzodiazepines hit the market back in the early 1970s, they revolutionized the treatment of sleep disorders. These new agents were much less likely than the others then in use (the barbiturates) to cause death in overdose. But like the older drugs, they had a way of overstaying their welcome. People who took them at night were often too groggy to function efficiently, or drive safely, the next morning. The advent of Halcion seemed to solve that problem. Clinical trials showed that while it knocked people out in a hurry, it cleared the body so quickly that users experienced virtually no grogginess the next day. "Very reasonably, physicians jumped at the chance to have a benzodiazepine free of its major side effect," says Dr. Wallace Mendelson, director of the Sleep/Wake Study Program at the State University of New York, Stony Brook.

Belgium and Holland approved Halcion at doses of up to a full milligram in 1977, but the drug soon ran into trouble. Dr. Graham Dukes, a drug-policy expert who

was then vice chairman of Holland's drug-regulatory agency, recalls that by early 1979 a handful of users had reported "peculiar psychiatric changes." In television appearances and letters to medical journals, one Dutch psychiatrist, Dr. C. van der Kroef, described seeing some of his own patients become depressed or chronically anxious while taking the drug. He also described instances of amnesia, hallucinations, paranoia and verbal and physical aggression.

In August 1979 Dutch authorities suspended the drug's license for six months to study the problem, and the reports kept mounting. By the end of the year Dutch doctors had reported 1,100 such reactions. In early 1980, the Dutch government reauthorized a quarter-milligram dose but permanently banned higher ones; Upjohn chose simply to leave the Dutch market (Halcion was reintroduced there last year). Researchers who had studied the drug rallied in support of the company. In a letter to the British medical journal *Lancet*, a dozen experts noted that in trials involving 5,000 Halcion recipients, "no symptom clustering similar to that described by van der Kroef was recorded." **No FDA comment:** During these years, Halcion was making its way through the government-approval process in the United States. No one at the Food and Drug Administration is now talking about Halcion for the record, but publicly available documents reveal a long history of concern about the drug. In 1980 Dr. Theresa Woo, the medical review officer handling Halcion's application, wrote a series of evaluations recommending against approval. Citing the Dutch experience and results from Upjohn's own trials, she concluded that Halcion had a narrower margin of safety than other benzodiazepines (healthy young men were unable to tolerate as little as two milligrams) and was "associated with a greater number of adverse effects." When Woo's superiors decided to approve the drug despite her concerns, she argued for limiting the dose to a quarter of a milligram. But she eventually backed down, admitting that the "evidence for efficacy" was based primarily on the higher dose. Upjohn got its license in November 1982, and in early 1983 the half-milligram dose hit the American market.

Since new drugs don't always reveal their full character in initial trials, the FDA maintains a system of "post-marketing surveillance." Doctors and drug companies file brief reports, describing adverse reactions to the drugs they prescribe or sell, and experts within the agency monitor the reports for signs of unforeseen hazards. The spontaneous-reporting system is by all accounts a crude instrument. Many adverse reactions never get reported to the FDA, and those that do aren't always caused by drugs. A drug's record can also be skewed by such factors as its manufacturer's reporting practices, the kinds of patients who happen to take it, even the amount of publicity it receives. For all their limitations, though, spontaneous reports provide a vital early-warning system.

Dr. Peter Mendelis, a researcher at the FDA, tracked Halcion's adverse-reaction reports during its first year on the US market, and he perceived a troublesome pattern. The nervous-system side effects reported for Halcion "appear to have a singular intensity," he wrote in an unpublished manuscript in early 1984.

Americans were receiving only half the dose first approved in Holland. Yet their experiences- ranging from "purposeful activity without recall" to "personality changes," "inappropriate emotional expression" and "unaccustomed aggression" had a familiar ring.

Alerted to these findings, Dr. Paul Leber, head of the FDA's Division of Neuropharmacological Drug Products, requested a more extensive study. For the next few years FDA staffers Diane Wysowski and David Barash compared Halcion's adverse-reaction reports with the reports for two other benzodiazepines, Dalmane and Restoril. The differences were startling. In a 1987 report, Wysowski and Barash noted that during its first three years on the US market, Halcion had racked up 8 to 30 times as many adverse-reaction reports as Dalmane and Restoril combined, even though it was still less widely used than either of them. Knowing how fallible the spontaneous reporting system can be, Wysowski and Barash had searched their data for biases. They corrected for differences in the companies' reporting habits, and they tested the possibility that different types of patients were receiving the different drugs. But they found nothing that could account for the patterns they were seeing.

Halcion's high complaint rate wasn't unique to the United States. Alarmed by similar reporting, French and Italian regulators forced the half-milligram tablet from their market in the spring of 1987. A few months later, Upjohn voluntarily lowered the recommended starting dose from a half milligram to a quarter in the United States. Under pressure from the FDA, the company also acknowledged in a revised package insert that "bizarre or abnormal behavior, agitation and hallucinations" might possibly be dose-related responses, not simply freak occurrences. By the summer of 1988, Germany had joined France and Italy in blocking the sale of the half-milligram tablet, and Upjohn had decided to stop producing it at all. The idea, says Upjohn pharmacologist Straw, was simply to "strengthen the concept of lowest effective dose."

The story might end there if a San Francisco novelist named Cindy Ehrlich had not received a prescription for Halcion in 1987. During the six months Ehrlich took the drug, she became depressed and anxious and ended up "convinced that the world was on the brink of nuclear war or invasion from space." In the fall of 1988, in a two- part article for California magazine, she told her story and went on to question the FDA's original approval of the drug. The piece prompted a flurry of publicity, plus yet another study of the adverse-reaction reports. At Leber's request, a team of FDA epidemiologists took another look at the spontaneous-reporting system. The number of Halcion users reporting severe nervous-system side effects was still going up, despite the lower recommended starting dose. So Leber convened an outside advisory committee to consider official action.

On Sept. 22, 1989, the FDA's Psychopharmacological Drugs Advisory Committee met outside Washington to hear the evidence. Dr. Charles Anello, the

FDA official who'd overseen the latest review, explained that his team had examined six years' worth of reports on six different side effects: amnesia, anxiety, confusion, hostility, psychosis and seizures. Depending on the reaction, Halcion had generated 8 to 45 times as many reports as Restoril. Like Wysowski and Barash, Anello's team had searched for factors that might have skewed -the results-and like Wysowski and Barash, they had failed to find any. There was nothing about the patients, nothing about the circumstances in which the drugs were prescribed, nothing about the reporting practices of the manufacturers that could account for Halcion's higher rates.

New labeling: The committee agreed that Halcion should carry a stronger amnesia warning (the label now states that amnesia "may occur at a higher rate with Halcion than with other benzodiazepine hypnotics"). But after hearing several Upjohn representatives dismiss the value of spontaneous reports and deny knowledge of any corroborating clinical evidence, the members voted not to require any other special measures. "Given the limitations of the information we had," committee chairman Daniel Casey explained after the meeting, "we did not sense [Halcion] had a special problem with side effects."

Naturally, Upjohn officials felt vindicated. "You've got to rely on science," says Thomas Webber, the firm's marketing director for central-nervous-system products. "Anecdotal evidence doesn't cut it." Straw adds that the firm has "not documented" unusual behavioral reactions in its large clinical trials. That's true. But critics say the relevant studies were not designed to detect unusual problems. In 1984, for example, researchers analyzed results from 45 Upjohn trials and found that Halcion was no more likely than other treatments to cause "excessive adverse reactions." But the analysts counted only the first side effect reported by any given patient (which, even with Halcion, is usually a morning hangover). By using that approach, says Dr. Frank Ayd Jr., one of the experts who defended Halcion during the 1979 Dutch controversy, the study failed to detect reactions that have since been "well documented."

Aside from amnesia, the best-documented reactions are "rebound insomnia" and "rebound anxiety." Any sedative can leave a person feeling wired as it wears off and the body continues to fight it. But several controlled studies have found that Halcion causes harsher rebound reactions than slower-acting benzodiazepines. Dr. Ian Oswald of Edinburgh University found in 1982 that while a benzodiazepine called loprozepam left patients less anxious than usual by day, Halcion left them more so, especially after more than a week's use. Since then, Kales and his colleague Dr. Edward Bixler have shown that Halcion causes more daytime anxiety than Doral (quazepam). Researchers in Wales have obtained similar results by comparing Halcion with a drug called chlormethiazole. And Oswald has advanced on his earlier study. After randomly assigning 120 patients to Halcion or the benzodiazepine lormetazepam, Oswald found that the Halcion takers "became more anxious on self ratings, were judged more often to have

had a bad response by an observer, more often wrote down complaints of distress, and suffered weight loss."

That doesn't make Halcion a bad drug; some people no doubt prefer a little nervousness to the heavy hangovers other sedatives can cause. But if patients don't expect some rebound anxiety, they may perceive it as their own problem and return to the medicine chest for relief. Cindy Ehrlich, the San Francisco novelist, recounts that after two weeks on Halcion, "my heart pounded and I was on the verge of tears much of the time. The slightest danger, such as having to make a left turn in traffic, put me in a sweat." Her therapist, having heard only the good news about Halcion, never considered taking her off the drug. Instead, she added a prescription for Xanax, Halcion's close chemical cousin.

Delusions and strange behavior are less common problems than amnesia or anxiety. As a result, they're harder to study in controlled settings. No one has shown conclusively that Halcion users are more likely than people on other drugs to become paranoid or delirious or to wear overcoats in August. Upjohn may believe such reactions are flukes, no more likely with one benzodiazepine than another, but the company has never convincingly explained Halcion's remarkable ability to generate weird stories. The stories abound, not only in FDA surveillance reports but in the medical journals and in doctors' private conversations.

In one 1987 case report, Dr. John Patterson of Columbia, Mo., describes episodes of delirium, sleepwalking and amnesia in five elderly hospital patients who were receiving as little as an eighth- of-a-milligram dose. One man was "found attempting to perform somersaults in his room." Others wandered the wards or tried to flee the hospital in their pajamas. None of them remembered their escapades in the morning. Dr. Philip Westbrook, director of the Sleep Disorders Center at Cedars-Sinai Medical Center in Los Angeles, thought his mother-in-law had Alzheimer's disease until he learned she was using Halcion and martinis to help her sleep. "She became extremely anxious and confused, and her husband gave her more Halcion during the day to help her," Westbrook recalls. "I thought for all the world she had a rapidly progressing dementia until I saw the pill bottles. We took her off it and she recovered beautifully."

It probably isn't a coincidence that so many of these anecdotes involve older people. Studies by Dr. David Greenblatt, a professor of pharmacology, psychiatry and medicine at Tufts University School of Medicine, show that age has a lot to do with people's sensitivity to Halcion. In elderly patients, he reported recently, a given dose has roughly twice the effect it has on young adults. But Greenblatt sees no special risks to older patients as long as doctors prescribe the drug carefully.

If Halcion's role in bizarre behavior is still mysterious, its role in violent outbursts is more so. Drug-induced violence has never been documented in controlled, clinical studies. But Ilo Grundberg isn't the first person to lash out while taking

Halcion. Last year, when FDA analysts tallied the numbers of hostile acts reported in association with 329 different prescription drugs, Halcion ranked No. 1, followed by Xanax. In British Columbia a 63 year-old taxi driver with no history of mental illness ransacked a schoolhouse while taking Halcion. A San Diego man started setting fires. A woman in Virginia Beach, Va., shot her husband when he rebuffed her. And Ron Petty of Kalamazoo, Mich., a police officer with no criminal record, stabbed his wife in the heart, nearly killing her.

Night rage: Petty recalls taking two half-milligram Halcion tablets (twice the dose his doctor had prescribed) at about 11 p.m. on Feb. 24, 1984. He also recalls getting in his car at about 2 a.m. and driving 30 miles to the Battle Creek apartment where Jennifer Petty Bradley, then his wife, was staying while they were separated. But he says he has no recollection of breaking down the door with a tire iron, finding her with another man and attacking her. Petty was convicted of assault with intent to commit murder and sentenced to n. After seeing a television magazine show in which Cincinnati pharmacologist Martin Scharf described Halcion's possible side effects, Petty grew more convinced that the drug had fueled his middle-of-the-night rage. He contacted Scharf, hired a lawyer, got a retrial and eventually won his freedom. He now works as an electrician.

Scharf, who has served as an expert witness in several such cases, has little doubt that the drug sometimes turns repressed anger into homicidal rage. Some users' actions are "completely unusual in contrast to their normal behavior," he says. But Scharf's is a minority view. Most experts resist the notion that Halcion can steal a person's volition. "I do believe that benzodiazepines can be dangerous drugs," says University of Chicago psychiatry department chairman Dr. Stuart Yudofsky, a neuropsychiatrist who studies aggression. "They can affect memory. They can affect concentration. They can affect attention. They can affect mood. They can affect spatial perception and discrimination. But I don't believe that they cause people to murder other people." Far more people become violent on alcohol than on Halcion, Yudofsky says, but we don't excuse their behavior and blame the distilleries. If we did, he says, "the implications would be unimaginable."

Upjohn's critics have assumed wrongly that the only acceptable risk is no risk at all. Halcion may pose dangers not found with other drugs. But for many people, it has clear advantages over its longer-acting relatives. And horror stories aside, it's far less dangerous than a barbiturate. "The general public is expecting a drug that doesn't cause any side effects," says Mark Mahowald, director of the Minnesota Regional Sleep Disorders Center at Hennepin County Medical Center and president-elect of the American Sleep Disorders Association. "If you take a medication, you are implicitly accepting a risk."

Still, the FDA has been slow to ensure that users really understand the drug's potential hazards. Nowhere does the label note that Halcion generates more

adverse-reaction reports than any other benzodiazepine. Nowhere does it stipulate that the drug becomes largely ineffective after two weeks' use. The Public Citizen Health Research Group, a Washington-based consumer-interest organization, has petitioned the FDA to request those changes.

The question is whether doctors would even notice them. Many of Halcion's horror stories involve patients who were prescribed excessive doses-and who were kept on the drug long after they should have been taken off. Halcion is approved, labeled and promoted only for the short-term management of insomnia. Yet Ilo Grundberg took it for months at a time, and her physician raised her dose when its effect dwindled. "These really bad cases result from doctors continuing to do something that's damn stupid," says one federal health official who insists on anonymity. "If a patient doesn't do well on a medication, stop it."

Upjohn, for its part, has also done less than it could have to promote caution. It has resisted labeling changes and has attacked unflattering research rather than face its possible implications. It has also worked assiduously to prevent full public disclosure of the data on reported side effects. As the Grundberg trial approached, the company tried to copyright and seal documents that it admitted contained no trade secrets. "It appears," US District Judge J. Thomas Greene wrote in rejecting the move, "that Upjohn intended to use the copyright laws to thwart accessibility to the public of information ... which may be offered into evidence in court proceedings."

The lesson for consumers should be clear. Sedatives are powerful drugs-and Halcion, for all its advantages, is not the elixir its name implies. Neither Upjohn nor the FDA nor your doctor can guarantee it's right for you. So think before you swallow.

NEWSWEEK
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