# Federal Government Faces Painful Decision on Darvon

*Darvon was prescribed 31 million times last year, despite the fact that aspirin works better.*

The federal government is considering whether to ban or sharply curtail the use of Darvon, one of the nation's most popular prescription painkillers. Citing recent evidence of many Darvon-related deaths, Secretary of Health, Education, and Welfare (HEW) Joseph Califano announced on 15 February that his department is conducting a full review of the safety and usefulness of Darvon. In the meantime, a warning about the drug's hazards and potential toxicity will be sent immediately to hospitals and physicians throughout the nation, Califano said. "It is imperative that these warnings be given . . . and that doctors think and count to ten before they prescribe these drugs."

Califano's action came in response to a petition from Ralph Nader's Health Research Group (HRG) asking HEW to ban Darvon as an imminent hazard to the general public, or to recommend its shift to a new schedule on the list of federally controlled substances. Califano denied the request to declare it an imminent hazard, but said that the Food and Drug Administration (FDA) would decide by 1 July whether to recommend a shift of the drug from Schedule 4, where it is currently listed, to Schedule 2, where narcotics with some therapeutic value are typically listed. If such a shift were made, Darvon would join ranks with methadone, cocaine, amphetamines, and barbiturates on the federal list of dangerous drugs. Telephone prescriptions would be prohibited and refills barred.

Such an action would have enormous general impact merely because Darvon is so widely used. In 1978 alone, physicians prescribed it 31 million times, making it the third most widely prescribed drug that year. Since Darvon was introduced in 1957 by Eli Lilly and Company, doctors have prescribed it more than 20 billion times, for everything from headaches to arthritis to dental pain to menstrual cramps to cancer pain. Doctors prescribe Darvon, or its generic equivalent propoxyphene, apparently secure in the belief that Darvon is a relatively mild, safe analgesic.

Actually, Darvon is a narcotic that induces the classic triad of psychological dependence, physical dependence, and tolerance. According to the results of most clinical trials, it is substantially less effective than aspirin and barely more effective than a placebo. It has been linked in recent years to more deaths than any other prescription drug. In several metropolitan areas, Darvon has been linked to more deaths than either heroin or morphine. It ranks near the top in drugs mentioned in emergency room visits. And, because it is so commonly prescribed and only 12 to 20 tablets are necessary to produce a lethal dose (perhaps 3 to 4 with a few stiff drinks), Darvon is a factor in hundreds of suicides each year.

Eli Lilly, which developed propoxyphene in 1953, would suffer the most under the Federal action and is fighting it vigorously. The company's role in the debate is important in several respects. Though its patent on the basic drug, propoxyphene, expired in 1971, Lilly is estimated to control more than 90 percent of the market through effective advertising and promotion and a new patent on a slightly different composition, Darvon Napsylate. The company reaped more than $70 million from Darvon sales in 1978 alone. If Darvon were shifted to the more restrictive schedule, business probably would fall off sharply; when amphetamines and methaqualones (such as Quaalude) made the same shift, prescription rates declined by about 50 percent.

Also, promotion of the drug by Lilly in the early years after its introduction is almost singly responsible for its widespread use and the current lack of understanding among physicians of its potential for abuse. The company developed the drug as part of a post-World War II search for nonaddictive narcotics and for years promoted it as the ideal alternative to codeine. According to Lilly's description of the drug in 1966, when 26 million prescriptions were being written annually (*excluding* hospital use), "When Darvon is given in therapeutic doses, euphoria is not observed, tolerances do not occur, and physical dependance does not develop." Lilly also used to claim that Darvon was equal in intensity and duration to codeine, had fewer side effects, and was especially valuable in treating migraines and menstrual pain.

Much of Lilly's promotion has changed since then, largely because the National Research Council (NRC) determined that most of these claims were untrue when it examined the efficacy of Darvon in 1969 for the FDA. Since this conclusion, the FDA and the Drug Enforcement Administration have been casting about for an effective way to get the new facts across. So far, their efforts have been only marginally successful, and physicians remain apparently uninformed of the true nature of the drug.

There now is a substantial consensus that Darvon is a narcotic, for example. William Beaver, an associate professor of pharmacology and anesthesia at George Washington University and an expert on Darvon, recently told a Senate subcommittee that "Propoxyphene is structurally related to potent narcotic methadone and is itself a narcotic in all pharmacologic and toxicologic respects." Kenneth Durrin, director of the office of compliance at the Drug Enforcement Administration, told the same subcommittee that "Propoxyphene is an abused drug and its abuse can and does lead to physical dependence." Several experts at the Haight-Ashbury Free Medical Clinics in San Francisco, in a study titled, "I've got a yen for that Darvon-N," report that Darvon can be used to effectively detoxify heroin addicts. Its potency is substantially less than that of methadone or morphine, but a 1200-milligram daily dose is said to be equivalent to 20 to 25 milligrams of morphine. Lilly conceded in 1972 that Darvon's "general pharmacologic properties are those of the narcotics as a group," but this remains in substantial part unrecognized by prescribing physicians. Old habits and associations die slowly.

The significance of the misunderstanding, according to Donald Jasinski, an expert on Darvon at the Addiction Research Center in Lexington, Kentucky, is that "by not calling Darvon a narcotic, Lilly was not informing physicians about its narcotic properties." Throughout the late 1950's and early 1960's, there was a debate about whether opium derivatives alone should be called narcotics, he said. Only recently has a scientific consensus developed that synthetic drugs such as


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Darvon that have the biological effects and abuse potential of narcotics should be called narcotics. In this sense, the law has lagged behind; for years, Lilly has successfully kept the World Health Organization and the drug enforcement establishment in the United States from controlling Darvon as a narcotic. "Lilly has been using the legal definition [of Darvon as a nonnarcotic] in a medical sense," says Jasinski.

The second problem with Lilly's early drug promotion relates to Darvon's therapeutic effectiveness. Contrary to Lilly's claims while the prescription pattern for the drug was first being established, Darvon is about half as potent as codeine, a related analgesic already listed on Schedule 2 as a controlled substance. Darvon has no particular value for migraines and menstrual pain and is in fact less effective than aspirin in treating these and other pain problems, according to data from clinical trials. Charles Moertel of the Mayo Clinic, for example, has compiled a list of 14 published clinical trials comparing aspirin and Darvon; aspirin was shown more effective in each one. Although several studies detected no statistical difference between Darvon and a placebo, the consensus now is that the drug is slightly more effective; it does, for example, have a positively sloping dose-response curve.

Lilly is well aware that Darvon, by itself, is not better than aspirin. Asked about this at the recent Senate hearings, Lilly spokesman Robert Furman said, "Aspirin is a truly remarkable drug." We are not, he said, claiming that it is better than aspirin. He emphasized, however, that several studies demonstrate that propoxyphene and aspirin together are more effective than the equivalent dosage of each drug separately, and, indeed, more than 80 percent of Lilly's Darvon tablets contain both propoxyphene *and* aspirin. In 1972, at the request of the FDA, Lilly mailed a notice to physicians that admitted Darvon was no more, and probably less, effective than aspirin; but once again, physician recognition and change in habit alteration have lagged behind disclosure of the facts.

One reason that recognition continues to lag could be Lilly's Darvon promotion program, which remains aggressive. Beaver, of George Washington University, notes that "The best ball point pen that I ever owned was given to me by a Lilly detail man and is emblazoned with the words, 'Darvon N-100.' " However, other drugs have not met with the same success, he says, so additional factors must be involved. The most important of these is the fact that up to one-third of the patients in clinical trials obtain relief from a placebo alone. Thus Darvon need not be very potent to have a pain-reducing effect. According to several experts, Darvon is an effective placebo because it is brightly colored and because it is prescribed. "Many patients have a psychological need to receive an analgesic which is available only on prescription," Beaver says. FDA Commissioner Donald Kennedy agrees that "a major advantage of Darvon is that it's prescribed." The placebo effect, he adds, is nothing to sneer at. A recent study that appeared in *Lancet*,* for example, states that the pain-killing effects of a placebo were reversed in clinical trial by a narcotic antagonist, naloxone, suggesting that a placebo, given adequate patient belief in its effectiveness, may trigger the same physiological changes that a real analgesic triggers.

A problem that results from Darvon's relatively low effectiveness, however, is that patients for whom it does not work—either as placebo or analgesic—may take higher doses to gain a greater effect. Lilly's basic and probably accurate defense of Darvon is that no one has died or suffered ill effects from using it at the recommended dosage. And estimates of the number of people who abuse it, by increasing the dose or combining it with liquor, are not entirely reliable. But it is well accepted that a significant number of people do abuse it, partly for a euphoric effect, and that some proportion of the more than 500 deaths related to Darvon each year are caused by abuse and addiction. Most experts appear to agree with Lilly's claim that the majority of these deaths are suicides. Darvon users have a marked tendency for hypochondria, chronic minor illnesses and emotional problems, and misuse of alcohol or other prescription drugs.

The critical uncertainty is the number of deaths that result from accidents and addiction, and not suicides. Lilly contends that the number is small, and as a spokesman put it, "If Darvon were suddenly to become unavailable, the problem would remain the same," meaning that people would turn to pistols or other drugs to accomplish the same end. If, however, the number of accidental or addiction-related deaths is large, Lilly is manufacturing a drug that is in practical use unsafe. This issue will be the focus of the HEW review; it may also be the hardest question to pin down.

—R. JEFFREY SMITH

*John Levine, Newton Gordon, and Howard Fields, "The mechanisms of placebo analgesia," *Lancet*, 23 September 1978, p. 654.

## BATF Decides Against Liquor Warning Label

After laboring for more than a year on the issue, the Bureau of Alcohol, Tobacco, and Firearms (BATF) in the Treasury Department has decided not to require a label on alcoholic beverages warning women that drinking during pregnancy may cause birth defects. The label had been sought by the Food and Drug Administration (FDA) as the result of mounting evidence of a "fetal alcohol syndrome"—a set of physical and mental abnormalities, including central nervous system problems and weight and growth deficiencies in children of mothers who drink heavily while pregnant. In deciding against the warning label, BATF acted against the advice of the FDA, the National Institute on Alcoholism and Alcohol Abuse, the Institute of Medicine, its own scientific consultant on genetics, and several associations for the retarded.

BATF did, however, agree to begin an educational campaign consisting of brochures, radio and television public service announcements, and school programs to warn teenage and older mothers of the dangers that drinking poses to their unborn children. The campaign is to be funded by the liquor industry, which presumably will find it in its own best interest: if public awareness about the syndrome, as measured in polls that BATF intends to take over the next 2 years, does not increase significantly, BATF says it may change its mind and require the label. Also, promoting awareness of the syndrome is said to be a means for liquor companies to indemnify themselves against damages arising from legal suits pressed by the parents of a syndrome victim.

BATF based its decision not to require a label on the paucity of data demonstrating the effects of the syndrome on babies of mothers who drink only moderately (less than 3 ounces of alcohol per day). Several experts in the field, however, including Judith Hall of Children's Orthopedic Hospital in Seattle, a consultant to BATF, have suggested that the effects of the syndrome in less than full-blown form may be present in the children of mothers who are light to moderate


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