

## Debate on Acne Drug's Safety Persists Over Two Decades

January 22, 2002, Tuesday  
New York Times  
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Health & Fitness

Can an acne drug cause teenagers to commit suicide? The question returned to the spotlight this month when a 15-year-old boy flew a small airplane into a Florida skyscraper. The boy, Charles J. Bishop, an unlicensed pilot, had a prescription for Accutane, which has been associated with suicide enough to cause the Food and Drug Administration to require a special warning label.

Toxicology tests by the county medical examiner found no Accutane in Mr. Bishop's system at the time of his death. But that finding may not end questions about whether the drug influenced the youth's behavior. Some think Accutane may affect mood weeks or months after a patient stops taking it. It certainly will not end a 20-year debate over how strictly this potent but potentially dangerous drug should be regulated.

Accutane, which since its introduction in 1982 has been prescribed for 12 million people worldwide, including 5 million Americans, is the only truly effective treatment for clearing up stubborn cases of severe acne, the emotionally debilitating kind that causes a rash of pus-filled lesions and leaves behind pitted scars. But the drug is also notorious for its devastating side effects. Twenty-five to 35 percent of babies whose mothers took it in pregnancy suffer malformations of the head, face and heart. Many more develop learning disabilities and other problems not obvious at birth.

The connection between Accutane and suicide is not nearly so clear. As of last month, based on MedWatch reports that doctors submit to the F.D.A., 140 Accutane users worldwide -- 94 in this country -- killed themselves while taking the drug or within a few months of stopping it. They ranged in age from 13 to 41. Another 257 were hospitalized with extreme depression or for trying to kill themselves. Because drug effects tend to be underreported, F.D.A. officials say the actual numbers may be higher.

Yet studies indicate that teenagers who take Accutane are no more likely to try to kill themselves than those who do not. The most extensive of these, financed by Hoffmann-La Roche, the drug's maker, and published in the October 2000 Archives of Dermatology, compared more than 7,000 Accutane users in Canada and Britain with more than 13,000 acne sufferers taking oral antibiotics. Accutane users were no more likely than the others to be depressed or suicidal.

Dr. Douglas G. Jacobs, a psychiatrist who has published extensively on suicide and is a consultant to Hoffmann-La Roche, says that every year about 11 of every 100,000 Americans commit suicide. If Accutane users took their own lives at the same rate, more than twice as many of them would have done so by now, he said.

F.D.A. officials acknowledge that there is no proof that Accutane causes depression.

But referring to the possible link, Dr. Jonathan Wilkin, director of dermatology at the F.D.A.'s Center for Drug Evaluation and Research in Rockville, Md., said, "We just simply believe that there is enough indication of an association that it is prudent for doctors to quite literally act as if there is a causal relationship."

Accutane, whose generic name is isotretinoin, is a synthetic molecule derived from vitamin A, which is involved in growth and maintenance of skin. The drug prevents pimples by shrinking the glands attached to hair follicles that, in acne sufferers, overproduce an oily substance known as sebum, which can clog pores. Accutane is one of Roche's top three selling drugs worldwide, with annual sales of more than \$700 million.

The most commonly reported side effects are dry skin and chapped lips, but in addition to causing birth defects, Accutane has been linked to fatigue, severe joint pain and blurred vision.

The notion that it might also lead to depression stems in part from studies in which people who consumed large doses of vitamin A and related molecules suffered symptoms of depression.

Dr. J. Douglas Bremner, a psychiatrist at Emory University, thinks it may be possible that Accutane causes depression by affecting the brain's frontal cortex. He is now using PET scans to examine the brains of 40 people who have just started taking the drug to look for signs of decreased functioning in the frontal cortex. Roche is also planning a study to see whether patients beginning Accutane treatment develop depression.

In the meantime, individual cases of teenage suicide by Accutane users continue to cause concern. Since B. J. Stupak, 17, of Menominee, Mich., shot himself to death a year and a half ago while taking Accutane, his father, Bart Stupak, a member of Congress, has worked to publicize his son's story and others like it.

Representative Stupak said his son, like many others, acted "out of the blue."

"One of the terms I've heard used to describe what happens is spontaneous suicide," he said. "They just take their own lives, and there's no sign of it coming, and it's just so hard to explain."

Dr. Jacobs argues that teenage suicides are notoriously difficult to see coming. "Many of them come out of the blue," he said, "but that doesn't mean there wasn't some underlying problem that was unidentified." Suicidal teenagers can be adept at hiding their despair, he said.

Adolescent depression and suicide, Dr. Jacobs said, stem from multiple causes, as diverse as self-esteem, family history and substance abuse, so it is "virtually impossible" to pin any case on a single trigger.

Mr. Stupak contends that Accutane is often needlessly prescribed to teenagers like his son, who did not suffer from the most extreme form of acne. He would like to see the drug taken off the market. "It's just not worth the side effects," he said.

Most dermatologists, however, still consider Accutane to be a miracle drug too useful to give up. Dr. David Pariser, a dermatologist in Norfolk, Va., and a member of the board of the American Academy of Dermatology, said that though the drug might possibly lead to depression in some patients, Accutane users very rarely reported feeling depressed. "Far, far more often, the main change you see is an increase in self-esteem," he said, "because the patient is no longer embarrassed to be out and around other people."

MedWatch reports describing mood changes, depression and suicide in patients taking Accutane have filtered in to the F.D.A. steadily since soon after the drug came on the market. Many reports have described cases in which patients became depressed or suicidal while taking Accutane, felt better when they stopped taking the drug, and then resumed treatment later, only to see their problems return.

By 1998, the agency had Roche revise the package insert to warn doctors about the possibility of suicide. Last year, the agency added a requirement that all patients acknowledge in writing that they are aware of the possible psychiatric side effects. And now, with each prescription, pharmacists must give out a Medication Guide that reports in lay terms that some Accutane users have become depressed, attempted suicide or actually killed themselves.

Over the years, the F.D.A. has also steadily strengthened its efforts to prevent Accutane-induced birth defects, an unambiguous problem that doctors consider far greater than the risk of depression and suicide.

One survey found that three of every 1,000 women who took Accutane became pregnant. Because that survey, by epidemiologists at Boston University's School of Public Health, relied on voluntary reports, experts believe the real number is higher.

At the F.D.A.'s urging, Roche has started a new program that requires doctors to put a bright yellow label on every Accutane prescription they write for a woman. The sticker assures the pharmacist that the patient has met all the qualifications for taking the drug: she has had negative pregnancy tests for two months in a row; she will continue getting pregnancy tests and counseling each month before having her prescription renewed and she has promised in writing to use two forms of birth control while taking Accutane.

But will the new rules be enough to prevent Accutane-induced birth defects? Dr. Nancy Green, acting director of the March of Dimes, in White Plains, N.Y., suspects not. "We're not completely satisfied," she said. Dr. Green would like the F.D.A. to require all doctors who prescribe Accutane, all pharmacists who dispense it and all patients who take it to register with the agency, as they must with thalidomide, which also causes devastating problems in the fetus.

Further tightening of the restrictions on Accutane is not out of the question. "We remain very concerned about birth defects and the potential suicide connection," said Dr. Steven Galson, acting director of the F.D.A.'s Center for Drug Evaluation and Research.