

Risk of depression dims hopes for anti-addiction pills

By MARILYNN MARCHIONE The Associated Press April 23, 2008

CHICAGO -- Two years ago, scientists had high hopes for new pills that would help people quit smoking, lose weight and maybe kick other tough addictions like alcohol and cocaine.

The pills worked in a novel way, by blocking pleasure centers in the brain that provide the feel-good response from smoking or eating. Now it seems the drugs may block pleasure too well, possibly raising the risk of depression and suicide.

Margaret Bastian of suburban Rochester, N.Y., was among patients who reported problems with Chantix, a highly touted quit-smoking pill from Pfizer Inc. that has been linked to dozens of reports of suicides and hundreds of suicidal behaviors.

"I started to get severely depressed and just going down into that hole ... the one you can't crawl out of," said Bastian, whose doctor took her off Chantix after she swallowed too many sleeping pills and other medicines one night.

Side effects also plague two other drugs:

* Rimonabant, an obesity pill sold as Acomplia in Europe, was tied to higher rates of depression and a suicide in a study last month. The maker, Sanofi-Aventis SA, still hopes to win its approval in the United States.

* Taranabant, a similar pill in late-stage testing, led to higher rates of depression and other side effects in a study last month. Its maker, Merck & Co., stopped testing it at middle and high doses.

The makers of the new drugs insist they are safe, although perhaps not for everyone, such as people with a history of depression. Having to restrict the drugs' use would be a big setback because it would deprive the very people who need help the most, since addictions and depression often go hand-in-hand, doctors say.

A bigger fear is that the whole approach may be in trouble. Researchers say blocking pleasure, especially the way the obesity drugs do, might take the fun out of many things, not just the harmful substances and behaviors these drugs target.

It may be possible to improve the drugs so they act more precisely. Chantix targets a different pathway - nicotine pleasure switches - and in a different way than the obesity

drugs, which aim at the same pathway that gives pot smokers the munchies. That is one reason many doctors are optimistic that any risks about Chantix will prove manageable.

But doctors are no longer talking about so-called "super pills" for a host of addictions.

"It certainly diminishes my enthusiasm" to see these side effects, said Mark Egli, co-leader of medicine development at the National Institute on Alcohol Abuse and Alcoholism.

The buzz started four years ago, when studies showed rimonabant helped people shed weight and keep it off longer than previous pills had. It also was being tested for smoking cessation. The Associated Press and other media reported extensively on prospects for a pill that might tackle two big problems at once.

Rimonabant won approval in Europe. But advisers to the U.S. Food and Drug Administration opposed it because of depression risks that became clearer with further study. Sanofi withdrew its U.S. application and said it hoped to resubmit after more research.

But in a new study last month, 43 percent of people taking rimonabant developed psychiatric issues versus 28 percent of those on dummy pills. One rimonabant patient committed suicide and one in the placebo group tried to. Unlike previous studies, this one did not exclude people who had depression in the past.

"I felt it was important to do an 'all-comers' study" to see how real-world patients might fare, said Cleveland Clinic's Dr. Steven Nissen, who led the work.

Sanofi now tells doctors to avoid giving the drug to people with a history of depression, said a company vice president, Dr. Douglas Greene.

"We are at the cutting edge of being able to manage this risk," he said.

Meanwhile, Merck had bad news from a study of its obesity drug, taranabant, which showed an increased risk of depression and other side effects among people taking medium and high doses.

"We're doing a lot to define this risk-benefit," including adding another year to all studies under way and going forward only with the lowest dose, said a Merck vice president, Dr. John Amatruda.

Others were less optimistic.

"The door is closing" on this approach, said Dr. James Stein, a University of Wisconsin-Madison cardiologist. If another study he is helping lead does not show benefit for rimonabant, "this drug's already slim chances of approval will be even more jeopardized," he said.

The situation is murkier with Chantix, which went on sale in the U.S. in 2006 and is sold as Champix in other countries.

The drug binds to the same spots in the brain that nicotine does when people smoke, causing release of a "feel-good" chemical, dopamine. Taking it is supposed to keep any inhaled nicotine from giving the same buzz.

In February, the FDA said a link between Chantix and psychiatric problems appears "increasingly likely." Pfizer added warnings to the drug's label and said that although a link had not been proved, it could not be ruled out.

But a Pfizer vice president, Dr. Ponni Subbiah, said nicotine withdrawal and even quitting smoking can cause mood swings and depression.

It is hard to know "what is causing what," she said. "We know that smokers are at higher risk of suicide than non-smokers, and heavy smokers are at higher risk than lighter smokers."

Some doctors agreed.

"Psychologically, just giving up this 'friend' that they've had many years in their life can be depressing," said Dr. Geoffrey Williams, co-director of the Greater Rochester Area Tobacco Cessation Center and a paid speaker for Pfizer.

Jeanne Morrison, 63, of suburban of Louisville, Ky., looked forward to giving up cigarettes when she and a friend went on Chantix. The friend did well, but Morrison lasted only 10 days on it.

"I got so depressed, I didn't want to go anywhere. I didn't want to do anything, and I'm a very high-energy person. It was a depression like I've never experienced in my life," she said. She also had "major, major nightmares. These would wake me up, and I would be absolutely shaking and sweating."

Several doctors said such reactions are rare, and that most patients do well on Chantix.

Morrison's doctor, psychiatrist Dr. Jesse Wright at the University of Louisville, said Chantix helped one of his schizophrenic patients, "who smoked like a smokestack," without worsening his psychological symptoms.

"The risk-benefit ratio is still very much on the side of use of the medication," Williams said. "The alternative, smoking, is extremely highly risky."