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HEALTH

FDA looks at link between medications, depression

Federal regulators warn that an array of drugs could play a role in spurring thoughts of suicide or other psychiatric symptoms.

By Melissa Healy

Los Angeles Times Staff Writer

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As symptoms of depression go, there is none much clearer than having thoughts of suicide.

But a spate of recent announcements from federal health officials suggests a surprising new interpretation of suicidal fantasies and the depression they are thought to signal: Sometimes, sadness, anxiety and self-destructive thoughts are not symptoms but side effects -- of medicine.

In this year alone, federal regulators have warned that a surprising array of drugs could play a role in spurring thoughts of self-destruction. Medicines that treat epilepsy, asthma and influenza are now under suspicion, as is one that helps smokers kick the tobacco habit.

The FDA stresses that it has established no direct causal link between these medications and suicidal thoughts in patients taking them. But in all the cases, regulators acknowledge they had one of two indicators of potential trouble.

In some cases, a review of a drug's early clinical trials turned up increased rates of suicidal thinking among subjects taking the medicine. In others, the tip-off came when the FDA observed an uptick of reports that patients taking a medication for some other condition developed symptoms of depression.

As a result, FDA officials and medical researchers now are scouring their data for clear signs that these drugs increase the risk of dangerous psychiatric symptoms. Moving forward, the agency will require developers of many new drugs to test for psychiatric side effects that could tip the balance between a new medicine's risks and benefits.

"We're trying to develop systematic strategies for looking . . . in a more rigorous way" for links between drugs and unintended psychiatric effects, said Dr. Thomas Laughren, director of the FDA's division of psychiatry products. "The difficulty is that we have such a primitive understanding of human behavior on a biological level . . . it is hard to predict which compounds are going to have psychiatric effects."

FDA warnings

The recent rash of advisories comes just four years after the FDA first suggested a connection. Prompted by reports that suggested children taking antidepressants were more likely, not less, to commit suicide, the agency in 2004 warned that antidepressants might actually increase the risk of suicidal fantasies and behaviors among children. That link is now in doubt, after recent studies showed a rise in youth suicide even as antidepressant use in that population has plummeted.

But the experience of coping with the anguished families of young suicide victims who took antidepressants has had a lasting effect on mental health professionals, researchers and federal regulators. If early-warning systems detect even a hint of psychiatric danger with a medication's use, government officials are inclined to alert first, study later.

"When they see a signal, even if they don't understand the genesis of that signal, that's a reasonable time to warn," said Dr. Robert Ward, a member of the FDA's pediatric advisory committee and professor of pediatric medicine and pharmacology at the University of Utah.

As it moves forward, the FDA hopes to detect such signals -- and warn patients and physicians -- *before* a drug enters wide use. One of the first drugs that will require testing for psychiatric side effects before it can be FDA-approved in the U.S. is rimonabant, an anti-obesity drug already used in some 20 other countries. After early clinical trials suggested patients taking the drug had increased rates of depression and anxiety, an FDA advisory panel voted last June to recommend a delay in market approval pending further study.

The FDA has asked rimonabant's maker, the French pharmaceutical firm Sanofi-Aventis, to use a new yardstick to detect and measure suicidal side effects. Scientists have long known that many drugs used to treat symptoms below the neck enter the brain also and that the receptors and chemicals on which they work in organs such as the heart, blood vessels or liver are present in the brain as well, although they may have different functions there. That these drugs might have an incidental effect on mood, then, "shouldn't be terribly surprising," Laughren said.

Abnormal behavior

Still, some of the bizarre reports prompting advisories were wholly unexpected. In Japan, where antiviral medicines such as Tamiflu and Relenza are widely used to shorten the duration and ease the symptoms of influenza, last year's flu season raised serious alarms.

In the span of several months, two 14-year-old patients taking Tamiflu -- a boy and a girl -- fell to their deaths from high-rise apartment buildings in suspected suicides, and two 12-year-olds on the medication were injured after falling from buildings. Delirium, hallucinations and psychotic behavior caused one child taking the drug to bolt into traffic to his death.

In all, an FDA advisory panel was told last November, there have been 25 deaths and 365 cases of abnormal behavior in children and young adults under 21 who took Tamiflu since it was approved for use in 1999. Although regulators underscored that hallucinations and bizarre behavior can be a consequence of the high fevers and brain inflammation that can come with influenza, they acknowledged they could not, without further scrutiny, rule out a link to Tamiflu.

"It came as a surprise to everyone," Ward said. "First the antidepressants raised people's concerns, and then they started to find these unusual suicidal behaviors with Tamiflu. It caused people to ask, 'Whoa, what is happening here?'"

Last month, the FDA notified physicians of the Japanese incidents (while also noting that "the contribution of Tamiflu to these events has not been established") and urged close monitoring of young patients with influenza, who might be taking an antiviral medication. In early April, GlaxoSmithKline, maker of the antiviral medication Relenza, voluntarily issued a similar notification to physicians.

On March 27, the FDA went on to announce it was investigating a "possible association between the use of Singulair," a pill used to treat asthma and allergies, and changes in mood and behavior, including suicidal thinking and suicide attempts. That warning came after the FDA's adverse-event monitoring system saw an uptick in reports about patients taking Singulair experiencing symptoms of depression, including thoughts of self-destruction. Although this monitoring system relies on voluntary reports from patients and physicians and does not establish causal connections between a drug and a reported "event," it is a key early detector of untoward side effects once a drug enters wide use.

Reports to the FDA also prompted a warning to healthcare professionals on Feb. 1 about Chantix, an anti-smoking drug approved in May 2006. As the medication gained a foothold among U.S. smokers wishing to quit, patients began telling physicians and the FDA of peculiar behavior, agitation, depressed mood and suicidal thoughts and actions.

By January, the FDA had concluded "it appears increasingly likely that there may be an association between Chantix and serious neuropsychiatric symptoms" and urged physicians to weigh that possibility when prescribing the drug, and to carefully monitor patients who take it.

One recent warning emerged not from spontaneous reports by patients and doctors, but from an internal FDA effort. Last year, after studies had shown an increase in suicidal thoughts and behavior among people taking certain drugs for epilepsy, the FDA conducted a broad review of clinical trials conducted on 11 anti-convulsive drugs.

The result was a Jan. 31 alert informing physicians of an established link between the 11 drugs and suicidal thinking and actions. As a group, patients taking any of the 11 medications were twice as likely to experience suicidal thoughts and actions as those who took a dummy pill. The heightened risk of self-destructive symptoms was evident as early as one week into treatment and continued throughout the 24 weeks of study.

Mind-body connection

Though such reports of psychiatric side effects defy prediction, researchers said that growing understanding of the connection between mind and body should lead the way to better guesses at which drugs may unexpectedly darken a patient's mood, and why.

"With every passing day, we've learned so much that there's a strong connection" between physical and mental health, said Dr. Hussein Manji, director of the Anxiety and Mood Disorders Program at the National Institute of Mental Health. "When you're depressed, a lot of things in your body don't work well. But conversely, both medical illnesses and certain medications can markedly make you depressed."

melissa.healy@latimes.com

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The information herein shall not be considered an endorsement of anyone discontinuing psychiatric drugs. If you are stopping taking medication it is advisable to reduce the dose gradually WITH EXTREME CAUTION, as it is difficult to predict who will have problems withdrawing. It is worth getting as much information and support as you can, and involving your doctor wherever possible. You will find withdrawal information here:

<http://www.mind.org.uk/Information/Booklets/Making+sense/Making+sense+of+coming+off+psyciatric+drugs.htm>

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