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Warning Urged on Stimulants Like Ritalin

By GARDINER HARRIS

GAITHERSBURG, Md., Feb. 9 — Stimulants like Ritalin could have dangerous effects on the heart, and federal regulators should require manufacturers to provide written guides to patients and place prominent warnings on drug labels describing these risks, a federal advisory panel voted on Thursday.

The panel's recommendation promises to intensify a long-running debate about whether the medicines are overused. Nearly four million patients take the drugs to treat attention deficit disorder and hyperactivity, and committee members said they wanted to slow explosive growth in the drugs' use.

The committee's action was unexpected. The Food and Drug Administration had convened the panel to help it determine how to research possible heart risks of the drugs. The agency had not asked the committee to address the drugs' labels, and agency officials seemed taken aback by the votes, saying they would not act on the committee's recommendations anytime soon.

"We don't think anything different needs to be done right now," Dr. Thomas Laughren, director of the Division of Psychiatry Products at the agency, said at a hastily arranged news conference after the meeting. "We think the labeling right now is adequate."

The committee voted unanimously to recommend patient guides, and it voted 8 to 7 to suggest that stimulant labels carry the most serious of the agency's drug-risk warnings — a "black box."

"I must say that I have grave concerns about the use of these drugs and grave concerns about the harm they may cause," said Dr. Steven Nissen, a cardiologist at the Cleveland Clinic and a panel member.

The votes came after F.D.A. medical officers described reports of 25 sudden deaths among people taking stimulants — the deaths were mostly children — and a preliminary analysis of millions of health records that suggested stimulants might increase the risks of strokes and serious arrhythmias in children and adults. The reports of sudden deaths never exceeded one in a million for any stimulant drug, although the F.D.A. usually receives reports of only a fraction of drug problems.

The preliminary analysis suggested that the stimulants might increase heart risks more than twofold. Such an increase may not be significant in children, whose heart risks are low, but could cause concern in adults, panel members said.

One of the drugs, Ritalin, has been marketed since 1955, and dozens of studies have shown it to be safe and effective. But no studies have been of sufficient duration or included enough participants to evaluate stimulants' long-term effects on the heart.

But the drugs' soaring popularity and increasing use in adults, panel members said, mean that the F.D.A. should study them more closely and warn patients and doctors about the potential risks to the heart.

Arthur A. Levin, director of the Center for Medical Consumers in New York City and a member of the panel, said that patients assumed that stimulants were safe, but that that confidence was misplaced.

"For us to sit around and talk about it, and for us to not make a very strong warning about the uncertainty of these drugs and their possible risks, would be unethical," Mr. Levin said.

Dr. Thomas R. Fleming, a professor of biostatistics at the University of Washington and a panel member, said stimulants might be far more dangerous to the heart than Vioxx or Bextra, drugs that were withdrawn over the past two years because of their ill effects on the heart.

The committee was composed largely of drug-safety specialists. Next month, the F.D.A. will ask another committee, mostly pediatricians and psychiatrists, to weigh the same issues. Such clinicians tend to focus on drug benefits and oppose warnings that might scare patients.

The vote by the drug-safety panel reflects changing notions about what the drug agency should do in the face of uncertainty. For decades, it generally refused to warn doctors about theoretical medical risks, even when there were strong hints of danger. But the committee said such silence was a mistake, particularly when millions took the drugs.

"Put yourself in our shoes," said Dr. Peter A. Gross of Hackensack University Medical Center in New Jersey and the panel's chairman. "Most of us see our role as protecting the public health. As often happens, the data we would like to see is not clear. In that setting, what we would like to see is a clearer warning."

But top F.D.A. officials said warning patients about theoretical risks might scare many away from needed treatment. "I think it's important not to minimize the benefits of these drugs," Dr. Laughren said.

Representatives of Johnson & Johnson, the maker of Concerta, and Shire, the maker of Adderall, two stimulants, said they would work with the drug agency on any label changes.

Dr. Todd Gruber, an executive of Novartis, which makes Ritalin, has said that Novartis has found no evidence that the drug raises the risks of heart problems.

Stimulants are the most widely prescribed medicine for childhood behavioral problems. Data presented at the meeting suggest that about 2.5 million children and 1.5 million adults are taking them. More than 30 million prescriptions for the drugs are written annually.

Several F.D.A. medical officers addressed the committee, and each suggested that the risks could be significant. Dr. Kate Gelperin, a medical officer in the Office of Drug Safety at the agency, began her presentation by telling the committee, "This morning I'm going to tell you a little bit about why the F.D.A. is so worried about these issues."

Dr. Gelperin noted that stimulants had long been known to increase blood pressure and heart rates. Other studies have shown conclusively that increased blood pressure leads directly to increased deaths from heart problems, she said.

Dr. Andrew Mosholder, also a medical officer in the Office of Drug Safety, said he reviewed the chemical structures of stimulants, and he noted that these structures were similar to drugs like ephedrine that had proven heart risks.

Dr. David Graham, another medical officer in the drug safety office, described the agency's preliminary analysis of millions of medical records that suggested an increased risk of strokes and arrhythmias.

"The number of arrhythmia hospitalizations really struck us as surprising," Dr. Graham said. "Arrhythmia is believed to be the pathway for sudden unexplained death."

In an interview after his presentation, Dr. Graham said, "There's smoke. Does that represent a fire? We want to answer that question."

After hearing the presentations, most committee members decided they should do more than simply make suggestions for further research.

"I want to cause people's hands to tremble a little bit before they write that prescription," Dr. Nissen said.

Psychiatrists and psychologists who treat and study attention deficit disorder and hyperactivity were deeply divided over the decision.

"I'm not saying a warning would be baseless, but if we're not careful we're going to engage in a Chicken Little scenario in which we sensationalize what is a very, very low-probability event," said Dr. Russell Barkley, a research professor of psychiatry at the State University of New York Upstate Medical University in Syracuse.

Others said that a black-box warning could prompt families to explore behavioral treatments as an alternative to drugs, which "would be a very good outcome for kids with A.D.H.D. and their families," said William Pelham, director of the Center for Children and Families at the State University of New York at Buffalo.

All agreed that parents of children on stimulants who have pre-existing heart conditions should consult their doctors.

Benedict Carey contributed reporting from New York for this article.