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Study Cites Increased Death Risk From Asthma Drugs

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Popular and long-acting asthma medicines such as Advair and Serevent pose a substantially increased risk of hospitalization and death to users compared with placebos, according to a new analysis of 19 studies on the subject.

The analysis also found that the increased risks of the long-acting bronchodilators affect a broad range of users -- more than doubling the rate at which asthma patients had to be hospitalized. Most experts have believed that the powerful bronchodilators are harmful only to a small number of people genetically predisposed to having a negative reaction.

"What we have here is a drug that increases the number of people who will die from the disease it is treating," said lead author Shelley Salpeter of Stanford University. "The long-acting bronchodilators can help reduce symptoms for many people, but we think the price in terms of serious side effects and deaths is unacceptable."

The Food and Drug Administration has voiced concerns about the widely used medicines, and last fall it required drugmakers to prepare stiff new warnings to the package label. But the new analysis, published in the journal *Annals of Internal Medicine*, raises the possibility that the drug should be taken off the market if it continues to be so widely used.

"The use of long-acting [bronchodilators] could be associated with a clinically significant number of unnecessary hospitalizations, intensive care unit admissions and deaths each year," the authors wrote. "Black box warnings on the labeling for these agents clearly outline the increased risk for asthma-related deaths associated with their use, but these warnings have not changed prescribing practices of physicians."

One of the long-lasting bronchodilators is Advair Diskus, made by GlaxoSmithKline. It brought in \$3.4 billion last year for the company, making it the nation's fifth biggest-selling drug, according to IMS Health, which tracks health data.

More than 3.5 million patients use the drug. In the new analysis, the authors estimated that Advair "may be responsible" for as many as 4,000 of the 5,000 asthma-related deaths each year in the United States.

Glaxo spokeswoman Mary Anne Rhyne disputed that figure and said the Centers for Disease Control and Prevention has found a decline in asthma-related deaths since the long-acting bronchodilators came on the market in the mid-1990s.

Rhyne said Advair has been recommended for use in treatment guidelines for asthma from the National Institutes of Health because it reduces symptoms and allows asthma sufferers to sleep through the night, exercise and generally resume normal lives.

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"The author's conclusions are inconsistent with a large body of evidence and experience of patients," she said.

She also said doctors have written more than 68 million prescriptions for Advair in the United States since 2001, so there is extensive experience with its benefits and risks.

The new generation of bronchodilators, known as long-acting beta-agonists or LABAs, have been both popular and controversial for some time. The FDA added a black-box warning about their risks in 2003, and last year additional concerns led to an FDA advisory panel meeting to discuss whether they should be taken off the market. The panel concluded that they should not.

As a result of the meeting, however, the agency demanded stronger language in the black-box warning and issued a public health advisory in November that said: "Even though LABAs decrease the frequency of asthma episodes, these medicines may make asthma episodes more severe when they occur. . . . LABAs should not be the first medicine used to treat asthma. LABAs should be added to the asthma treatment plan only if other medicines do not control asthma, including the use of low-or-medium dose corticosteroids."

The new meta-analysis looked at results of 19 trials that studied 33,826 asthma sufferers given either the long-acting bronchodilators or inactive placebos. (Slightly half of both groups were also taking inhaled steroids.) Salpeter said the results found that people on the long-acting medication were four to six times more likely to die of asthma-related causes than those on placebo.

Inhaled steroids, which have long been used to treat asthma, work by reducing the hypersensitivity in the lungs that leads to inflammation and narrowing of the airways. LABAs work by helping to relax the muscles around the airways in the lungs and thereby reduce wheezing. In addition to Advair, Glaxo sells another LABA drug, Serevent, and Novartis sells Foradil.

Glaxo and the FDA have long sparred over how to describe the potential risks of Advair and Serevent. When the agency said last November that the black-box warning needed to be made tougher, Glaxo publicly opposed the move. The tougher warning that the drug could increase the risk of asthma-related death was approved in March. It also said Advair should be prescribed only when other drugs have proved insufficient.

Some research has suggested that LABAs are more likely to harm African Americans than other groups.

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