Regular use of asthma drugs poses respiratory, cardiac dangers, Cornell, Stanford researchers find in study critical of drug industry.

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Physicians who prescribe the regular use of beta-agonist drugs for asthma could be endangering their patients, two new studies by researchers at Cornell and Stanford universities find. One study compiles previously published clinical trials to conclude that patients could both develop a tolerance for beta-agonists and be at increased risk for asthma attacks, compared with those who do not use the drug at all. The second study shows that beta-agonist use increases cardiac risks, such as heart attacks, by more than two-fold, compared with the use of a placebo.

Furthermore, the researchers say that their analyses lead them to suspect a conflict of interest among scientists who are supported by pharmaceutical companies that make beta-agonists, among the world's most widely used drugs. This conflict, they say, could be putting 16 million U.S. asthma sufferers in harm's way. Their statement comes as the American Medical Association is voicing its concerns that drug industry sponsorship of clinical tests is affecting the quality of research.

The first study (a meta-analysis, meaning a study of other previously published studies) of more than a dozen research papers on the respiratory effects of beta-agonists is published in the journal, Annals of Internal Medicine (May, 2004), by Shelley R. Salpeter, M.D., Thomas M. Ormiston, M.D., and Edwin E. Salpeter. The second meta-analysis pooled the results from 33 trials on the cardiac effects of beta-agonists, and is published in Chest (June, 2004), the cardiopulmonary and critical-care journal.

Edwin Salpeter, the eminent astrophysicist who is professor of physics emeritus at Cornell, has turned his interest to medical issues in recent years. He assisted his daughter, Shelley, by performing statistical analyses for asthma drug studies. Shelley Salpeter is a clinical professor of medicine at Stanford University School of Medicine and a physician at Santa Clara Valley Medical Center in San Jose, Calif., where Ormiston also is a physician.

Adrenergic beta-agonists, such as albuterol and terbutaline, work on receptors located on smooth muscles and inflammatory cells in the lungs. These bronchodilator medicines can relax the muscles around the airways that constrict during an asthma attack. Short-term use of beta-agonists has been shown to be helpful in reducing symptoms associated with acute asthma attacks. But continuous use of beta-agonists is a riskier proposition, the authors suggest in their Internal Medicine article.

"*Almost all the scientifically valid studies we examined associated continuous beta-agonist use by asthma patients with a decreased bronchodilator response to subsequent beta-agonist administration, and with increased airway inflammation compared to placebo use*," says Shelley Salpeter.

Continuous use of beta-agonist drugs cause asthma patients to develop a tolerance for the drugs, she adds, making beta-agonists less effective in true emergencies.

Edwin Salpeter questions why so many physicians ignore warning signs of beta-agonist overuse, and why drug companies continue to promote the products for continuous use. "We think the studies warning of adverse respiratory effects are getting lost among the dozens of poor-quality studies that missed the point," he says.

Most studies of continuous use of the drugs that showed favorable results were eliminated from the Salpeter-Ormiston-Salpeter meta-analysis because Cornell and Stanford researchers considered them to be scientifically flawed -- in part because they allowed the as-needed use of beta-agonists in the placebo groups of clinical trials.

Most of these "*poor-quality studies*" that were eliminated from the meta-analysis, the three researchers say, also turned out to involve conflicts of interest -- because the studies were funded by pharmaceutical companies, because researchers had financial ties to the industry, or both.

"*If you want to push continuous use of beta-agonists, you'll find plenty of published studies to back your point of view*," Shelley Salpeter says.

"*However, because of their flawed study designs, none of these trials were truly placebo-controlled and therefore should not be used to make valid conclusions about the safety of beta-agonists. We worry that physicians who recommend regular use of beta-agonists may actually be putting their patients at risk*."

To make matters worse, beta-agonist use in patients with asthma and chronic obstructive lung disease also increases the risk for adverse cardiac events (such as heart attacks) by over two-fold compared to placebos, the Cornell-Stanford researchers warn. Beta-agonists work on receptors found in the heart, to increase the heart rate and decrease the level of the essential element potassium.
These effects are the exact opposite of beta-blocker drugs, such as atenolol, that often are used in patients with heart disease to decrease their risk for heart attacks and congestive heart failure.

In the spirit of full disclosure, the meta-analysis authors say they have no ties whatsoever to the pharmaceutical industry. In the course of the meta-analyses, Ormiston and Shelley Salpeter received salary support from Santa Clara Valley Medical Center. Edwin Salpeter received no support from Cornell. He did the statistical analysis work, he says, "just for the fun of it, and because I want to see good science rise to the top."