Medical Xpress

Dangerous side effect of common drug combination discovered by Stanford data mining

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A widely used combination of two common medications may cause unexpected increases in blood glucose levels, according to a study conducted at the Stanford University School of Medicine, Vanderbilt University and Harvard Medical School. Researchers were surprised at the finding because neither of the two drugs — one, an antidepressant marketed as Paxil, and the other, a cholesterol-lowering medication called Pravachol — has a similar effect alone.

The increase is more pronounced in people who are diabetic, and in whom the control of blood sugar levels is particularly important. It's also apparent in pre-diabetic laboratory mice exposed to both drugs. The researchers speculate that between 500,000 and 1 million people in this country may be taking the two medications simultaneously.

The researchers' study relied on an adverse-event reporting database maintained by the U.S. Food and Drug Administration and on sophisticated electronic medical records used by each of the three participating institutions. They used data-mining techniques to identify patterns of associations in large populations that would not be readily apparent to physicians treating individual patients.

"These kinds of drug interactions are almost certainly occurring all of the time, but, because they are not part of the approval process by the Food and Drug Administration, we can only learn about them after the

drugs are on the market," said Russ Altman, MD, PhD, professor of bioengineering, of genetics and of medicine at Stanford.

Although some physicians and researchers have questioned the usefulness of the databases to change medical practice, this study underscores their importance.

"It's very exciting because we were led to this conclusion by mining data that already exists, but of which many people were skeptical," said Altman. "Physicians tend to think of electronic medical records as ways to better track data about single patients, but there's another really important component to them — their utility in looking at population effects. The information is there to change health-care practice in a meaningful, substantial way."

Altman, the Guidant Professor for Applied Biomedical Engineering and the chair of Stanford's bioengineering department, is the senior author of the study, which will be published online May 25 in *Clinical Pharmacology and Therapeutics*. The first author of the research, Nick Tatonetti, is a graduate student in biomedical informatics in Altman's laboratory.

It's not uncommon for medications to have effects together that they don't display alone. However, because most drugs are tested and approved independently, it can be difficult or impossible for clinicians to predict the effects of drug combinations. To learn more, the FDA encourages physicians to report any adverse events a patient may have to their Adverse Event Reporting System, or AERS. Such reporting is voluntary, however, and relies on a patient or a physician noticing that something unusual has happened. It also often doesn't include any follow-up to identify the cause of the event or symptom.

Altman and his colleagues used a technique called latent signal detection

to identify random pairs of drugs that caused diabetes-related symptoms, such as altered blood sugar levels. To do so, they began by looking in the AERS for individual drugs known to cause side effects reminiscent of diabetes, such as high blood sugar. They then amassed a profile of symptoms related to hyperglycemia, including fever and fatigue, which occur in patients receiving these drugs.

"We were able to create a symptomatic 'fingerprint' to predict glucose-altering drugs," said Altman. "We then looked for that fingerprint in people who were receiving pairs of drugs not known to affect blood sugar levels." The researchers found four pairs of drugs that seemed to cause such symptoms only in combination; they concentrated on Paxil and Pravachol because they are so commonly prescribed.

"Between 13 and 15 million people in this country have prescriptions for these drugs," said Altman. "By extrapolating from the electronic medical records at Stanford and elsewhere, we can predict that between 500,000 and 1 million people are taking them simultaneously."

However, despite the suggestive nature of the symptoms, none of the patients in AERS who were taking the two drugs were directly reported to have hyperglycemia. To demonstrate a direct connection, the researchers turned to electronic medical records at the three participating institutions. They found that 135 non-diabetic people who had prescriptions for both of the drugs experienced an average increase in their random blood glucose levels of 19 mg/dl after beginning treatment. They also found that 104 people with diabetes experienced an even greater average increase: 48 mg/dl after being prescribed both drugs.

The increases are significant because people with two consecutive, fasting blood glucose levels of 126 mg/dl or higher are considered to be diabetic, and people with levels between 100 and 125 mg/dl are considered to have impaired fasting glucose levels and to be pre-

diabetic.

"Understanding and mitigating the effect this pair of medications has on blood sugar could allow a person with diabetes to better control his or her glucose levels, or even prevent someone who is pre-diabetic from crossing that threshold into full-blown diabetes," said Altman.

The researchers then looked at the effect of the two medications in laboratory mice fed a high-fat, high-calorie diet. After several weeks on such a diet, the mice typically become insulin resistant and are considered to be pre-diabetic. They found that the pre-diabetic mice experienced an increase in fasting glucose levels after several weeks on the diet. Neither medication alone increased this baseline level. But when they were given Paxil and Pravachol together for three weeks, the glucose levels of the mice increased dramatically — from about 128 mg/dl to 193 mg/dl.

Altman pointed out that the bioinformatics studies of the databases allowed the mouse experiments to be very focused and targeted. As a result, they were completed more quickly and less expensively than traditional drug screening studies in animals.

The researchers are now applying similar detection methods to identify drug combinations that affect things other than blood glucose levels. The challenge, Altman said, is to triage and prioritize the many intriguing results.

"Post-marketing surveillance of drugs has traditionally been very difficult," said Altman. "The FDA is doing the best it can, but it may be time to embrace some new bioinformatics methods. This study shows that we can identify previously unsuspected issues that may affect hundreds of thousands of people around the world." Stanford is organizing a group of faculty dedicated to using population-based data to

make biomedical discoveries.

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