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New computer algorithm discovers drug side effects, interactions

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A week ago, you started a new prescription medication for acne. Today, you feel dizzy and short of breath and have difficulty concentrating. Your symptoms are not listed in the package insert as possible side effects of the drug, but why else would you be feeling so odd?

Unfortunately, there's no easy answer. Clinical trials are designed to show that a drug is safe and effective. But even the largest trials can't identify irksome or even dangerous side effects experienced by only a tiny proportion of those people taking the drug. They also aren't designed to study how drugs interact with one another in the human body — a consideration that becomes increasingly important as people age and their medicine cabinets begin to overflow.

Now researchers at the Stanford University School of Medicine have devised a computer algorithm that enabled them to swiftly sift through millions of reports to the U.S. Food and Drug Administration by patients and their physicians and identify "true" drug side effects. The method also worked to identify previously unsuspected interactions between pairs of drugs, most notably that antidepressants called SSRIs interact with a common blood pressure medication to significantly increase the risk of a potentially deadly heart condition.

The research, which includes a list detailing several dozen of the most prominent drug interactions, will be published March 14 in *Science Translational Medicine*. Russ Altman, MD, PhD, a professor of bioengineering, of genetics and of medicine at Stanford, is the senior

author of the research, and graduate student Nicholas Tatonetti is the first author.

"The average 70-year-old is taking seven different prescription medications," said Altman. "The FDA has a database for patients and physicians to report possible adverse drug events, but it's very difficult to uncover true side effects because people vary in their medical histories, conditions and drug regimens, as well as in age, gender and environment. Some researchers have gone so far as to say, 'No one will ever get useful information out of all of this data.'"

Although the FDA has its Adverse Event Reporting System for doctors, patients and drug manufacturers to use after the agency has approved a drug, many of the more than 4 million reports in the database are little more than anecdotal — there's no way to tell whether the fever, rash, dizziness, seizure or other unwanted reaction was a true side effect of the drug, a result of a combination of medications or even a simple fluke of circumstance (maybe the patient had a cold or other undiagnosed medical condition at the time of the event).

Tatonetti developed a way to run a kind of case control study within the data, matching up groups of people who were as alike as possible, with the exception of one drug variable — say, a hypertension medication. If significantly more of the people on the drug reported an adverse event, such as headaches or vomiting, than did those who were not taking the drug, it is likely that the medication was indeed the culprit. A similar method can be used to analyze the effects of pairs of drugs.

"It sounds obvious, but it's a nifty statistical way to eliminate bias," said Altman. "And we found that the more things you can match between the groups, like other drugs the people have in common, the more likely you are to also unintentionally match for variables you may not have even thought about but that may affect the result."

If they are on an antidepressant, you know they are more likely to be female, explained Tatonetti. If they're also taking a statin, you know they may have a high-fat diet, he added. If they've been prescribed medication for an enlarged prostate, you know they are male. "By matching up as many of these variables as possible, we're also controlling for gender, age, diet and many other things that may not be directly included in the FDA database," he said. "This increases the predictive power of the technique."

Tatonetti and Altman used the technique on the database from the FDA's Adverse Event Reporting System to discover previously unidentified side effects and drug interactions. They then tested their predictions by analyzing the electronic health records of patients at Stanford Hospital & Clinics. They confirmed that 47 new drug interactions identified in the AERS study held true when analyzing the records of "real" patients. In particular, patients receiving both an SSRI and a class of blood pressure medication called thiazides were more likely (9.3 percent) to exhibit prolonged QT intervals on an electrocardiogram than patients taking either medication alone (4.8 percent vs. 6.5 percent, respectively). Prolonged QT intervals are associated with increased incidences of spontaneous arrhythmias and sudden cardiac death.

The researchers have created two publicly available databases of their work, named OFFSIDES and TWOSIDES, respectively.

So far the OFFSIDES database includes an average of 329 new adverse events for each of the 1,332 drugs included in the system. (The average number of adverse events listed on a drug's package insert is 69.) The TWOSIDES database identifies 1,301 adverse events, resulting from an analysis of 59,220 pairs of drugs that cannot be clearly assigned to either drug alone.

"This is a testament to the value of huge data sets," said Altman. "They

allow us to throw out a lot of cases. When you start with millions of pieces of information, you can be pretty rigorous about weeding out those that don't match. And if you can arrive at even just a few hundred well-matched cases, that can give a good statistical comparison."

In addition to helping physicians to better tailor prescriptions for their patients, the database can also further drug discovery efforts by identifying medications with similar side effects. Previous research has shown that drugs with similar side effects may affect the same biological pathway, and may be useful for more than one clinical indication. For example, diazepam (marketed as Valium) and zolpidem (marketed as Ambien) share similar side effects and act on seven of the same protein targets, even though they're usually prescribed for different conditions.

"We're interested in understanding the biological effects of drugs in the body," said Tatonetti. "Can we connect these population-level outcomes to particular biological pathways? If so, we can learn a lot more about how drugs are acting in the body, and this in turn can help with drug discovery and in predicting possible future adverse events."

"This kind of pharmacoepidemiology is becoming increasingly important to understand how drugs work in the body," said Altman. "It can help a physician better and more safely tailor drug prescriptions to patients. It can also drive drug development and discovery by identifying shared biological pathways and targets among drugs with similar side effects."

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