Big data reaps big rewards in drug safety

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Using the Food and Drug Administration's Adverse Event Reporting System (FAERS), a hospital electronic health records database, and an animal model, a team of researchers at the Icahn School of Medicine at Mount Sinai report that by adding a second drug to the diabetes drug rosiglitazone, adverse events dropped enormously. That suggests that drugs could be repurposed to improve drug safety, including lowering the risk of heart attacks.

The research is published online Oct. 9 in the journal *Science Translational Medicine*.

The approach is part of an emerging strategy known as systems pharmacology that integrates computer science, mathematical models, and animal models to examine how drugs work in cells.

Systems pharmacology shows that most drugs act by binding to targets that are part of complex networks within cells.

"Big data systems have a wealth of data, and when studied appropriately, can point to potentially safer combinations," said the study's lead author, Ravi Iyengar PhD, Dorothy H. and Lewis Rosenstiel Professor, Department of Pharmacology and Systems Therapeutics, and Director, Systems Biology Center, at the Icahn School of Medicine at Mount Sinai. "As an end in themselves, big data analyses must be considered preliminary, but findings can point to potentially safer combinations that can subsequently be tested in clinical trial," said Dr. Iyengar. "We may be able to use FDA-approved drugs to prevent adverse events."

In this study, investigators studied how drug combinations act through networks within cells, focusing on the diabetes drug rosiglitazone, an effective drug in controlling blood glucose. However, rosiglitazone has a serious side effect, increased heart attacks, which has restricted its use markedly.

Since most patients with diabetes take more than one drug and the FDA Adverse Event Reporting System (FDAERS) is freely available, investigators analyzed data from the FDAERS to see if second drugs could lower the rate heart attacks. In addition, investigators compared their results with Mount Sinai's electronic health records system.

Compared with many other commonly used second drugs, "we found that the drug exanatide, often given along with rosiglitazone to get better control of blood glucose, also very substantially reduced the heart attack rate in rosiglitazone users," said Dr. Iyengar. Using these findings, the investigators made some predictions of how these beneficial drug interactions might work in diabetic mice, finding that the heart attack rate declined.

"The beneficial effects of rosiglitazone and exanatide are not unique," explained Dr. Iyengar. " We found nearly 19,000 other drug combinations in the FDA database, where the second drug appears to reduce a wide range of side effects of the first drug. Other beneficial effects were demonstrated when lisinopril was added to a statin, where the rate of statin-associated rhabdomylosis, a kind of muscle tissue wasting, declined; when an H2 antagonist was added to SSRIs, it reduced completed suicide.

The research team stressed that the results are a valid starting point for developing clinical trials of safer drug combinations. To further drug safety, they urge researchers and clinicians to contribute to big databases, such as the Food and Drug Administration's Adverse Event Reporting System.

More information: "Systems Pharmacology of Adverse Event Mitigation by Drug Combinations," by S. Zhao et al. *Science Translational Medicine*, 2013.

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