

THERAPY

One plus one equals zero—drug combinations mitigate adverse effects

Adverse effects limit the use of many useful drugs. Addition of a second drug could suppress the adverse effects of the first, suggests a systems pharmacology study that integrated computer science, mathematical models and animal models.

Zhao *et al.* focused on the antidiabetic drug rosiglitazone, which is associated with an increased risk of myocardial infarction. Patients with type 2 diabetes mellitus are often treated with more than one drug; therefore, the researchers were able to perform big-data analyses of the FDA Adverse Event Reporting System (AERS) database to identify drug combinations that potentially mitigate the adverse effects of rosiglitazone.

Use of the glucagon-like peptide-1 agonist exenatide in combination with rosiglitazone was found to significantly reduce reports of myocardial infarction. Next, the investigators used a network biology approach to predict that exenatide might mitigate the adverse effects of

rosiglitazone by modulating clotting; experiments in a mouse model confirmed the network prediction.

“The beneficial effects of rosiglitazone and exenatide are not unique,” comments senior researcher Ravi Iyengar of Icahn School of Medicine at Mount Sinai, New York. “We found nearly 19,000 other drug combinations in the FDA–AERS database where the second drug appears to reduce a wide range of adverse effects of the first drug.” These findings show that integrating clinical and research informatics could be beneficial.

The team now hope to collaborate with clinicians to test the predicted beneficial effects of some of these drug combinations in clinical trials.

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Original article Zhao, S. *et al.* Systems pharmacology of adverse event mitigation by drug combinations. *Sci. Transl. Med.* 5, 206ra140 (2013)