Drug data reveal sneaky side effects

Mining of surveillance data highlights thousands of previously unknown consequences when drugs are taken together.

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14 March 2012

An algorithm designed by US scientists to trawl through a plethora of drug interactions has yielded thousands of previously unknown side effects caused by taking drugs in combination.

The work, published today in *Science Translational Medicine*[1], provides a way to sort through the hundreds of thousands of 'adverse events' reported to the US Food and Drug Administration (FDA) each year. “It’s a step in the direction of a complete catalogue of drug–drug interactions,” says the study's lead author, Russ Altman, a bioengineer at Stanford University in California.

Although clinical trials are often designed to assess the safety of a drug in addition to how well it works, the size of the trials needed to detect the full range of drug interactions would surpass even the large, late-stage clinical trials sometimes required for drug approval. Furthermore, clinical trials are often done in controlled settings, using carefully defined criteria to determine which patients are eligible for enrolment — including other conditions they might have and which medicines they can take alongside the trial drug.

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A program predicts the potential side-effects of mixing different pills.

Once a drug hits the market, however, things can get messy as unknown side-effects pop up. And that’s where Altman’s algorithm comes in.

“Even if you show a drug is safe in a clinical trial, that doesn’t mean it’s going to be safe in the real world,” says Paul Watkins, director of the Hamner–University of North Carolina Institute for Drug Safety Sciences in Research Triangle Park, North Carolina, who was not involved in the work. “This approach is addressing a better way to rapidly assess a drug’s safety in the real world once it is approved.”

Bias cut

Altman and his colleagues have been studying drug–drug interactions as a way to understand how a person’s genes influence their response to pharmaceuticals. To do that, he says, you must first have a good picture of the molecular mechanisms that underlie drug responses.

“Adverse events are incredibly valuable clues to what these drugs are doing in the body,” Altman says. “They can tell you the other pathways in the cell that are being tickled by these drugs.”

But reports of adverse drug events are notoriously prone to bias. For example, cholesterol-lowering treatments are more often taken by older patients, and so conditions associated with ageing, such as heart attack, could be wrongly linked to a drug as a side effect.

Altman and his colleagues reduced this bias by adopting an approach sometimes used in observational clinical trials. They developed an algorithm that would match data from each drug-exposed patient to a nonexposed control patient with the same condition. The approach automatically corrected for several known sources of bias, including those linked to gender, age and disease[1].

The team then used this method to compile a database of 1,332 drugs and possible side effects that were not listed on the labels for those drugs. The algorithm came up with an average of 329 previously unknown adverse events for each drug — far surpassing the average of 69 side effects listed on most drug labels.

Double trouble

The team also compiled a similar database looking at interactions between pairs of drugs, which yielded many more possible side effects than could be attributed to either drug alone. When the data were broken down by drug class, the most striking effect was seen when diuretics called thiazides, often prescribed to treat high blood pressure and oedema, were used in combination with a class of

drugs called selective serotonin reuptake inhibitors, used to treat depression. Compared with people who used either drug alone, patients who used both drugs were significantly more likely to experience a heart condition known as prolonged QT, which is associated with an increased risk of irregular heartbeats and sudden death.

A search of electronic medical records from Stanford University Hospital confirmed the relationship between these two drug classes, revealing a roughly 1.5-fold increase in the likelihood of prolonged QT when the drugs were combined, compared to when either drug was taken alone. Altman says that the next step will be to test this finding further, possibly by conducting a clinical trial in which patients are given both drugs and then monitored for prolonged QT.

What should the drug regulators do with the thousands of possible side effects Altman and his team uncovered? That is a complex problem, says Watkins, who adds that regulators will have to factor in the availability of alternative treatments and the magnitude and seriousness of the side effect, among other considerations.

Altman, who serves as an adviser on the FDA's Science Board, says that he plans to present his results to the agency. He suggests that the algorithm could be used with the FDA's existing drug-surveillance programs to remove bias. However, he points out the enormity of the task: "We've just released a database with 10,000 or more adverse events," he says. "I do not expect the FDA to uncritically take these results and add them to every drug label."

Nature | doi:10.1038/nature.2012.10220

References

1. Tatonetti, N. P., Ye, P. P., Daneshjou, R. and Altman, R. B. *Sci. Transl. Med.* **4**, 125ra31 (2012).