Interaction Decisions: Is the Outcome Important?

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In 1877, the English mathematician William K. Clifford wrote a remarkable essay that outlived all of his mathematical work—it is called *The Ethics of Belief*. In the essay, he proposes a hypothetical story of a ship owner whose old and rickety ship was about to carry a group of emigrants to the New World. At first, the ship owner thought perhaps he should have the ship overhauled, but he knew that the repairs would be expensive. The more he thought about it, the more he convinced himself that the ship would probably survive the trip. After all, it had safely made many trips before, and Providence would certainly watch over these unhappy people seeking a better life. So he stifled his doubts, and as Clifford says, the ship owner "got his insurance money when she went down in mid-ocean and told no tales."

Most people would have no difficulty condemning the ship owner for callous disregard of the lives of the emigrants who went down with his ship. Then, however, Clifford proposes a much more difficult question: What if the ship made that voyage, and many others as well, safely? Does that remove the guilt of the ship owner? "Not one jot," says Clifford, because a decision is right or wrong *forever* based on the evidence available at the time the decision was made.

At first, this may sound preposterous—that the outcome is irrelevant to the soundness of a decision. Upon reflection, however, Clifford appears to have a point. Clifford's argument can also be applied to drug interactions. Suppose a patient is stabilized on simvastatin, and the prescriber decides to give the patient 10 days of clarithromycin for an infection. Because clarithromycin inhibits CYP3A4 (and P-glycoprotein), simvastatin plasma concentrations are likely to substantially increase, leading to life-threatening myopathy in some patients.

Let us assume, however, that the patient in question has only a few minor muscle aches from the interaction, and they subside quickly after the course of clarithromycin. By Clifford's reasoning, the lack of a severe reaction is irrelevant because the prescriber had "no right to believe" the combination was safe, and the patient was unnecessarily put at risk. (Azithromycin does not interact with simvastatin and in most cases could be used as an alternative, or the simvastatin could simply have been discontinued during the clarithromycin therapy.)

The fact that most patients who concurrently receive simvastatin and clarithromycin do not have severe reactions also is irrelevant, because it is not possible to determine ahead of time which patients will develop serious adverse outcomes from the interaction. Therefore, even if severe myopathy only occurred in 1 in 100 patients on the combination, it would be unwise to subject patients to this risk.

One could argue, therefore, that placing patients at increased risk of an adverse drug interaction—when the risk is clearly avoidable—is ethically and professionally indefensible no matter what the outcome in a particular patient. The fact that patients are regularly placed at such risk, however, is more an indictment of our alerting systems for drug interactions, rather than representing lack of concern by prescribers and pharmacists. Hence, current efforts under way to improve drug interaction alerting systems are a much needed step toward the goal of reducing adverse drug interactions.

Clifford concludes his essay with some strong words: "To sum up: it is wrong always, everywhere, and for anyone, to believe anything upon insufficient evidence." To believe, for example, that it is safe to give simvastatin with CYP3A4 inhibitors—just because we have not personally observed any adverse effects from such combinations—is not good practice. The published clinical evidence exists, but it is not reliably reaching the health professionals who are making the decisions. We need to improve both the drug interaction detection systems and the information provided to pharmacists and prescribers if we are to reduce the risk of adverse drug interactions. ■