Of White Swans, Bigfoot, and Drug Interactions

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"Well, I've observed many patients receive that drug combination, and I've never seen any problems with it. Therefore, this is not a clinically important drug interaction."

Have you ever heard that response after you informed a prescriber about a potential drug–drug interaction involving one of his or her patients? Several possibilities may account for this response, of course. It could be that the drug interaction truly is not clinically important, and the prescriber is correct to ignore it. Or, it could be that the prescriber is trying to "save face" by minimizing the importance of the drug interaction. More likely, however, the prescriber is coming to an erroneous conclusion due to inappropriate use of inductive reasoning.

What Is Inductive Reasoning?

Induction—in the philosophical, not the metabolic sense—is the process of coming to general conclusions from repeated observations of a particular event or thing. Human beings use inductive reasoning on a regular basis. For example, if a person drives down a particular road at rush hour several times and finds the traffic terrible each time, the person concludes that this is a good road to avoid at rush hour. Reaching that conclusion is inductive reasoning, and it is a useful tool for making many decisions.

Likewise, the majority of the "truths" in medicine and pharmacy are derived from inductive reasoning. If we as pharmacists observe that 90% of the patients with hyperthyroidism have a particular symptom, we say that the presence of this symptom constitutes evidence that supports a diagnosis of hyperthyroidism. That line of thinking is inductive reasoning as well.

What Are the Pitfalls of Inductive Reasoning?

Inductive reasoning is useful, but it also can be abused, especially when people use it to come to firm conclusions based on a limited number of observations. More than 250 years after 18th-century Scottish philosopher David Hume eloquently and convincingly exposed the limitations of inductive reasoning, abuse of this method remains alive and well.

The classic example used to show the poverty of this approach in achieving certainty is the experience of Europeans who—for thousands of years—had never seen a swan that was not white. They assumed that all swans were white, and they were disabused of this truism only when black swans were discovered in Australia. Hume used this example to show that no number of observations of white swans would be large enough to allow one to conclude with absolute certainty that all swans are white.

Nevertheless, inductive reasoning can be useful as a guide to making decisions (as opposed to divining "the truth") if the number of observations is high enough. For example, tens of thousands of people have hiked in the woods of the Pacific Northwest without a single confirmed Bigfoot sighting. With this number of observations, it is safe to conclude that the risk of encountering Bigfoot is vanishingly small—the inductive nature of the conclusion notwithstanding.

Accordingly, it is quite reasonable to behave as though Bigfoot does not exist. This belief, however, is nothing close to proof of Bigfoot's nonexistence. Absence of proof is not proof of absence.

Using Induction for Drug Interactions

So, what do all of these examples have to do with drug interactions? Most health professionals apply inductive reasoning naturally and effortlessly when assessing the potential danger of particular combinations of drugs. For most clinically important drug interactions, however, the number of observations made by individual practitioners is simply not sufficient to make accurate risk assessments.

A good example of this principle involves the concurrent use of angiotensin-converting enzyme inhibitors and potassium-sparing diuretics (Hyperkalemia Due to Drug Interactions, *Pharmacy Times*, January 2004). The combination can contribute to severe or fatal hyperkalemia in certain predisposed patients, but most people obtain benefit without significant adverse outcomes. Most prescribers, therefore, do not see severe hyperkalemia, and thus they conclude that it is of minimal concern. As a result, patients continue to be harmed by a preventable adverse drug interaction.

Another way to look at this problem is from a statistical standpoint. For an interaction that caused a serious adverse outcome in 1 of 1000 patients exposed to the combination, one would have to study 3000 patients in order to have a 95% chance of observing the event. Thus, for serious drug interactions that occur rarely, few practitioners would observe enough patients to see the adverse outcome.

Conclusion

Inductive reasoning based on personal clinical experience has serious limitations as a guide to the clinical importance of most drug–drug interactions. It is important, therefore, to consider the results of published literature in addition to personal clinical experience when making decisions about drug interactions in individual patients. PT