



WHEN

Drugs Collide

By Jim Oldfield

SOMETIMES, drugs meant to help cause harm.

While most medications are safe, dozens of regulatory withdrawals—and lawsuits—stretching back to thalidomide show that even when used alone and as directed, drugs can be unsafe. A much larger number, however, produce unwanted effects when they interact with dietary supplements, food, medical conditions—and other drugs.

Drug-drug interactions, in which one drug magnifies or reduces the effect of another, are particularly vexing for physicians, patients and researchers.

Although researchers screen new drugs for interactions via laboratory testing and clinical trials, they can't check for all interactions. Hundreds of prescription and over-the-counter medications are on the market. Potential two-drug combinations number in the tens of thousands, and figures for three-drug mixes are immense.

Moreover, studies that test for specific interactions don't replicate the diversity of patients who ultimately take them. This means drugs that appear not to interact with other drugs in the lab, or in healthy young volunteers, can produce different effects in the real world—where patients are typically older, have a higher burden of illness and take multiple medications.

While the process of drug testing is complex, the knot that binds drug-drug interactions to patient safety is Gordian in its difficulty to untangle.

Researchers have a weapon for that challenge: observational epidemiology. By applying statistical methods to databases of medications, patient care and outcomes—data that were not available just two decades ago—epidemiologists can identify and measure drug-induced harm in large populations. When premarketing drug testing fails to flag a safety problem, epidemiology offers a last line of defense.

Dr. David Juurlink is a scientist in clinical epidemiology at Sunnybrook Research Institute (SRI) and physician in internal medicine and pharmacology at Sunnybrook Health Sciences Centre. Through observational epidemiology, Juurlink, who is also an associate professor of medicine, pediatrics and health policy at the University of Toronto, has helped bring the scope of drug-drug interactions into focus, and has parsed the effects of specific drug combinations in patients with breast cancer, heart disease and other conditions. His findings have implications for millions

of patients and—critically—offer alternatives so that physicians can provide safer, more effective care.

The scale of the drug-drug interactions problem is difficult to gauge because such interactions are hard to detect; most, therefore, go unreported. But in 2003, in the *Journal of the American Medical Association (JAMA)*, Juurlink and colleagues published a study examining the clinical consequences of three dangerous and underappreciated, yet avoidable, drug interactions. They showed that over a six-year period in Ontario, hundreds of patients admitted to hospital with drug toxicity had been prescribed a drug known to interact with one they were already taking. Physicians had seen many of these patients shortly before the patients sought treatment for toxicity, suggesting they missed opportunities to avoid harm. This was the first study to characterize real-world consequences of drug-drug interactions.

In 2008, *JAMA* published a report noting that almost one in three American adults aged 57 to 85 years—about 18 million people—take five or more prescription medications. The same report found that 2.2 million may be at risk for drug-drug interactions. Other studies have found that adverse drug events, many of which are drug-drug interactions, account for up to 5% of hospital admissions, and that these hospitalizations cost, on average, \$16,000 (US). While these numbers



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outline the scope of the problem, researchers agree that the actual number of interactions dwarfs those recorded.

Whatever the real number, it will continue to grow, primarily because aging populations are taking more medicines in combination. Addressing the problem at the level of practice is difficult, because physicians cannot keep pace with the growing list of interactions and often rely on pharmacists to flag dangerous combinations. Pharmacists watch for interactions, but they are prone to human error and their computer warning systems, though helpful, are imperfect. Biotech companies are developing laboratory tests that screen for drug-drug interactions, but those tests cover a limited range of drugs, and new medications bring new mechanisms. For these reasons, epidemiologists are essential for catching drug-drug interactions and highlighting alternatives.

In 2010, Juurlink and his colleagues in SRI's Odette Cancer Research Program did just that in a study that showed women taking tamoxifen for breast cancer faced a higher risk of dying of the disease

if they received a widely used antidepressant, as opposed to many other antidepressants from the same class.

Typically, women with "estrogen-positive" breast cancer take tamoxifen for five years after initial treatment. The drug reduces the risk of recurrence by about 50%; the risk of death by about 30%. One-third of women who take tamoxifen also take antidepressants called selective serotonin reuptake inhibitors (SSRIs), either for anxiety or depression, or to limit the hot flashes caused by tamoxifen—or both. Physicians have suspected for years, on the basis of surrogate outcomes and basic pharmacology, that some SSRIs might limit the effectiveness of tamoxifen, but research on the issue had been inconclusive.

Juurlink and his colleagues confirmed that the use of the SSRI paroxetine (brand name Paxil) was associated with an increased risk of breast cancer death among women taking tamoxifen, and that the risk was related to the degree of overlap between the two drugs. Women in their study took Paxil, on average, for less than one-half of their time on tamoxifen. The researchers estimated that one additional breast cancer death would result for every 20 women so treated; however, many women took the two drugs together for a longer period. "A woman who took Paxil for the duration of her tamoxifen therapy was effectively not taking tamoxifen," says Juurlink. "Paxil abolishes the benefits of an extremely important anticancer drug."

The study was the largest and most rigorous to date on the interaction between tamoxifen and paroxetine. The *British Medical Journal* published the work with an editorial that recommended physicians avoid co-prescribing the drugs, and that regulators require more warnings about the interaction on drug labels. The journal also suggested physicians consider gradually moving women already on the combination to another SSRI—a call they could make with certainty because Juurlink's study also found that several alternative SSRIs do not interfere with tamoxifen.

In turn, Juurlink and his colleagues had confidence in those alternatives, not only because the study was carefully designed, but also because as a clinical pharmacologist and former pharmacist, he knew the results were supported by insights from pharmacology. Tamoxifen works only after it is converted to an active metabolite called endoxifen, a process that occurs in the liver and is controlled by an enzyme called CYP2D6. In lab tests, paroxetine turns off this conversion process, whereas many other SSRIs do not. "The study's results reflect what basic pharmacology suggests. Venlafaxine and other antidepressants



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don't cause this problem, but paroxetine and tamoxifen are simply a bad combination," says Juurlink.

Unexpectedly, the study found that another strong CYP2D6 inhibitor, fluoxetine (brand name Prozac), was not associated with an increased risk of death. That finding might have been due to the small number of those on fluoxetine, but it and other intricacies surrounding the biologic effect of tamoxifen suggest that some questions around this drug-drug interaction remain.

Without question, however, the study has changed care. Dr. Kathy Pritchard is a scientist at SRI, medical oncologist in the Odette Cancer Centre at Sunnybrook and co-chair of the National Cancer Institute of Canada's clinical trials breast cancer site group. In her practice, she avoids putting patients on paroxetine or other strong CYP2D6 inhibitors, and she has spoken with oncologists who have switched patients from paroxetine to antidepressants that aren't strong CYP2D6 inhibitors. She says Juurlink's

study, on which she and a fellow in her research group, Dr. Catherine Kelly, were co-authors, was a factor that has changed how she and other oncologists treat breast cancer patients.

The study's specificity was a particular strength, says Pritchard. It showed, for example, that another SSRI called venlafaxine does not interfere significantly with tamoxifen, and not simply because patients took it in lower doses—questions that, as Juurlink notes, would be impossible to examine through a clinical trial. "It's a nifty observational study," Pritchard says.

While Juurlink's breast cancer article tipped the balance on a question that researchers had already studied in patients, a paper he published in the *Canadian Medical Association Journal (CMAJ)* in 2009 alerted cardiologists to a drug-drug interaction that had only been shown in the lab—and of which many physicians were unaware.

Clopidogrel is an anti-platelet medication that reduces blood clotting in patients with heart disease or who have had a stroke.

Platelets help give blood an optimal consistency, but they can become sticky and block blood flow. This stickiness puts heart and stroke patients, in particular those who have had stents inserted (to prop open constricted vessels), at increased risk for cardiovascular problems.

Clopidogrel, known by the brand name Plavix, reduces the risk of additional cardiovascular problems significantly; in 2007 it was the second-best-selling drug in the world, with sales of \$7.3 billion (US). Because clopidogrel can cause unwanted bleeding, however, especially in the stomach, physicians often prescribe it with a proton pump inhibitor (PPI), a drug that protects the stomach. In several laboratory studies, researchers have shown that one of the most commonly used PPIs, omeprazole, interferes with the liver's conversion of clopidogrel into its active metabolite, resulting in stickier platelets.

In an observational study of 13,000 patients who had been discharged from hospital after a heart attack, Juurlink and his colleagues found that those on omeprazole and most other PPIs while taking clopidogrel were at risk of having another heart attack. Patients taking a PPI called pantoprazole, in contrast, were not at increased risk. This study was the first large-scale clinical evidence of a drug-drug interaction that lab science had shown was possible.

Its publication sparked controversy. An editorial in *CMAJ* called for physicians to reevaluate whether their patients on clopidogrel needed a PPI, and recommended that those who needed both medications

be put on pantoprazole or a similar drug. Other editorials were more cautious, calling for more research. In late 2009, spurred by another study published in *JAMA* six weeks after the Sunnybrook study, the U.S. Food and Drug Administration issued a public health advisory on the issue, and in March 2010 required that clopidogrel labels warn of the possible interaction. Other studies followed, using different methods and yielding different conclusions about this interaction, which remains contentious. Researchers on both sides of the issue have cited Juurlink's paper 271 times.*

While noting that reasonable people can reach different conclusions when presented with the same information, Juurlink maintains that PPIs are, as a class, overprescribed, and that co-prescription of the two drugs should be limited to patients with a valid indication. He also acknowledges there is evidence these drugs prevent intestinal bleeding in patients taking clopidogrel with aspirin. "When this study came out, we were concerned that the results might be misinterpreted. Our primary message to physicians and patients was that if you want to combine a PPI with clopidogrel, it makes sense to choose pantoprazole, because it will not interact with clopidogrel," he says.

Physicians worldwide have heeded that advice. Dr. Jack Tu is a scientist at SRI and cardiologist in the Schulich Heart Program at Sunnybrook who holds the Canada Research Chair in Health Services Research. "This is a very important study in the field of cardiology, and as a result of it many physicians—myself included—either stopped giving proton pump inhibitors to all patients or switched to pantoprazole," says Tu, who is also a professor at U of T. Calls from patients and pharmacists exposed to media coverage of the study helped drive that change, which Tu says was immediate and dramatic, the latter because millions of patients had been taking the two drugs together.

Some cardiologists have questioned whether the shift in practice was warranted. They point out that Juurlink's study was an observational study, not a clinical trial, and was therefore prone to "selection bias": patients who get Plavix and a PPI are often sicker than those who get only Plavix, so their poorer health could account for their worse outcomes.

Tu acknowledges that possibility, but notes Juurlink's study controlled for that bias. "Even those who haven't switched their prescribing patterns have become more cautious about prescribing the two drugs together," he says. "It's an issue that every cardiologist in the world now knows about."

Juurlink recognizes that some physicians are more convinced by clinical trials than by observational studies, but says the two are complementary: "Each gives us

information the other can't. A trial tells us how good a drug can be under ideal circumstances, but in real-world practice the story is often different. My interest is the latter, because what actually happens is sometimes very different than what could or should happen."

Juurlink says he found the science behind drug-drug interactions fascinating from the earliest stages of his training, and as a clinician he is keenly interested in whether a drug he is considering for a patient might interfere with one he or she is taking. More exciting, though, he says, is expanding knowledge of drug interactions and disseminating the new knowledge to clinicians. "If you can show that two drugs in combination can be dangerous, but also that another isn't, you give clinicians an alternative. That's gratifying, especially when doing so changes practice."

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