PEDIATRIC PERSPECTIVE

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Doctors must prescribe without all the facts

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Headlines recently trumpeted serious concerns about two types of drugs: Merck's withdrawal of the pain medication, Vioxx, because of its link with strokes and heart attacks, and the recommendation by a US Food and Drug Administration advisory panel that certain antidepressants carry a stern "black box" warning that they may increase suicidal behaviors in some children. Many patients wondered: Why didn't physicians wait to use these drugs -- and why didn't the FDA delay approval -- until they knew all their potential dangers?

The answer is that physicians often act on the basis of limited or even faulty information, since patients might suffer if potentially helpful treatments are withheld. What's worthy of attention is how doctors grapple with this ambiguity, especially when prescribing new drugs or invasive therapies to children.

Last month, for example, I consulted on a premature infant whose immature, diseased lungs required a breathing machine for several weeks. The newborn's doctors wondered if a tiny, extra blood vessel might be harming the lungs by sending them too much blood, and asked if the vessel should be surgically closed. After extended discussion, we concluded there was no prior experience to guide us. I made an educated guess and recommended the operation, thinking the potential benefit of getting the infant off the respirator and breathing on his own outweighed the risks -- but the surgery didn't make the tiny baby any better.

One way doctors try to reduce uncertainty is by performing well-designed clinical trials to see if an intervention (like surgery on an extra blood vessel) improves patient outcomes (like newborn lung function). Though such studies are a great boon, the honest truth is they don't remove all confusion.

The goal of a clinical study is to tell whether therapies are likely to be effective, and to identify major common side effects. These are fundamentally untidy, complex questions.

Consider drug effectiveness. In a typical drug trial, patients are randomly assigned to receive the drug being tested or an inactive placebo, such as a sugar pill, and doctors then compare what happens to the two groups of patients.

But even when a drug seems effective in a clinical trial, it's not always likely to work in every patient. Drugs typically are approved based on studies of hundreds (rarely, thousands) of patients for a year or less. When the FDA allowed sales of the antidepressant, Paxil, in 1992, adults in a major clinical trial published that year in the Journal of Clinical Psychiatry were treated for only six weeks. Thirty-eight of 163 patients treated with Paxil (23 percent) recovered, but so did 24 of 162 (15 percent) of those getting only placebo. The drug was statistically likely to help -- but in a small percentage of adults in a research setting, and then only for a few weeks.

Such studies also are not intended to identify all side effects, which may not show up until thousands of patients take the drug over many years. The knowledge gap is even greater when treating children because most drugs have never been tested on them. But few parents would withhold a drug like albuterol, which has been shown safe and effective in adults but not in kids, from an asthmatic.

Also, drugs approved for one reason in adults may later turn out to have other uses, often in children. For example, sildenafil (popularly called Viagra) may help a potentially fatal condition called pulmonary hypertension in children. Abciximab, or ReoPro, is approved for adults having unstable angina--but it may also thwart a serious coronary condition called Kawasaki disease in children. The drugs' actual benefits and side effects are now unknown, however.

Desperate patients are often the first to try new drugs, and they don't want doctors to withhold them. When new drugs may be life-saving for kids, such as those with serious heart conditions or suicidal depression, most parents and pediatricians don't wait for long-term safety studies. Sometimes more mundane benefits, like more participation in gym class for an asthmatic child or reducing a preemie's chance of a severe infection, also justify trying a new treatment. As time passes, experience accumulates and physicians understand the side effects better. Gradually the learning curve proceeds, and doctors can offer more guidance about risks and benefits -- although rarely with total confidence.

For sure, some drugs get prescribed for no good reason except marketing; for example, the "purple pill" heartburn drug, Nexium, has minimal benefit over cheaper drugs, but it was prescribed so widely that a former FDA commissioner called it "purple crack." Once in a while, even therapies widely thought beneficial in initial studies, like the diarrhea vaccine, RotaShield, wilt under the scrutiny of larger, long term ones.

Though it's tempting to rail against doctors, most aren't incompetent or malevolent. Giving medications is messy. Unexpected postapproval side effects, as with antidepressants, will always occur. The FDA gets more than 1,000 reports a day of possible side effects, but it is hard to sort out problems caused by a drug from spurious correlations. Though various legislative remedies have been proposed, there's simply no way to prevent surprises entirely.

What's astounding is how few disasters occur. A vast protective machinery silently protects us. For example, epoetin, a synthetic hormone for anemia in children and adults, caused 175 people worldwide to suddenly stop making blood cells. Last month, the New England Journal of Medicine reported that, after the FDA was alerted to the problem a few years ago, authorities determined that certain production methods and forms of injection were responsible. With changes, the side effects dropped 80 percent.

Medicine is both a science and an art. Admitting this is the first step in understanding how good intentions can lead to bad outcomes -- and sometimes forgiving those responsible as we learn from their mistakes.

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