

New Drugs Can Have Hidden Dangers

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By Dr. Gordon Guyatt

On March 18, 2000, 15-year-old Vanessa Young collapsed in her Oakville home and was rushed to the hospital. The following day, she died of complications related to her heart.

A medication that Vanessa was taking to relieve vomiting and a bloated feeling was responsible for her death. About 18 months before Vanessa died, American consumers received warnings about cisapride's dangerous effects on patients' hearts. In August, 2000, several months after Vanessa's death, the drug was pulled from Canadian shelves.

Cisapride was not a new drug. Health Canada approved the drug in 1990, and it was one of the pharmaceutical industry's big sellers. That proved to be plenty of time to do a lot of damage. Across North America, cisapride was responsible for the death of 24 infants who received the drug for harmless spitting up.

Unfortunately, the cisapride story is not unusual. Seven drugs approved since 1993 and later withdrawn from the market contributed to over 1000 deaths across North America.

Equally frightening are the number of people exposed to potential serious drug reactions. Nearly 20 million Americans took 1 or more of the 5 drugs withdrawn from the market between September 1997 and September 1998. That's more than 5% of the U.S. population exposed to drugs that had to be withdrawn.

Keep in mind that the drugs pulled off the market are the worst of the worst. If a drug has major benefits, and kills only a few people through toxic effects, it stays on the shelves. For instance, I was recently looking after a man dying of liver failure caused by a drug in common use. The benefits of the drug, amiodarone, in prolonging life in the patients with heart-beat abnormalities are worth the risks. But that is little consolation to the patient who develops major drug-related problems.

A research study published earlier this year in the prestigious Journal of

American Medical Association took a careful look at major problems with drugs that develop after marketing and distribution.

The authors examined the Physicians' Desk Reference (PDR), the source of drug information American physicians use most commonly. When a new serious drug reaction is reported, the Food and Drug Administration demands the addition of a warning highlighted by a black box – so-called "black box warnings". These warnings also appear in the PDR.

The researchers looked at 548 new drugs approved between 1975 and 1999, and examined the PDR up to the 2000 edition. Of these 548 drugs, 16, or 3%, were eventually withdrawn from the market because of serious bad reactions. Another 45, over 8%, had new black box warnings after they were marketed.

Because drugs introduced more recently had shorter follow-up, these figures underestimate the long-term risk of new serious reactions coming to light. For instance, a drug introduced in 1998 had only two years for doctors to discover major problems.

The researchers calculated that each of the 548 drugs they studied had a 20 per cent, or one in five, likelihood of withdrawal or new black box warnings over 25 years. Of these, half would occur more than seven years after being introduced.

What does this study tell us? First, unexpected serious reactions often turn up after a drug appears on the market. Second, it can take years of use before doctors discover serious drug toxicity.

Why does it take so long to uncover these serious, and sometimes fatal, reactions? Companies developing new drugs set out to prove their benefits. The studies they need to show that a drug works require only a few thousand, or at most tens of thousands, of patients. That is too small a sample to detect rare but serious adverse reactions.

In addition, once the drug gets on the market, physicians do a bad job of reporting adverse reactions. There are no rules requiring doctors to report the problems they see, and research suggests that more than 90% of the adverse drug reactions go unreported.

Put those facts together, and you see why it often takes a long time for the evidence to add up.

What is the bottom line of this story? New is not necessarily better. Doctors know the bad things that can happen with drugs that have been around for a long time, say over 20 years. The newer a drug, the more risk that we will find out in the near, or not so near future about some awful adverse reaction that drug has been causing.

Does that mean we should stay away from new drugs? That depends on how much they have to offer. If the new drug does provide a major advance over all existing drugs, holding back because of worries about long-term effects would be a mistake. Most new drugs, however, provide only minor, if any, improvements over older ones. Each year, only a handful of drugs represent an important step forward.

For instance, when the cholesterol-lowering cerivastatin appeared on the market, there were already three similar drugs with a long history that could lower cholesterol and reduce heart attacks. After about six years on the market, cervistatin was withdrawn when it caused 52 deaths from severe muscle damage.

Would doctors have been wise to stick with the older drugs? You bet.

If all this makes you slightly nervous about the medication you, or a loved one, are taking, you've got the message right. The lesson for doctors and patients is that if there is a tried-and-true drug that does the job, it is usually the one to use.