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Viagra: as good the morning after?

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The Washington Post

AMERICA is infatuated, the national mind giddy with the possibility of perfection. The object of desire is Viagra, the new pill for impotence. Like many crushes, however, this one may well rest on false hopes and unrealistic expectations.

You don't get much sense of that these days, though. In the five weeks since Viagra was approved by the Food and Drug Administration, the compound (whose generic name is sildenafil) is rapidly becoming one of the best-known pharmaceuticals in history.

In news stories, on talk shows and in Internet chat rooms, Viagra is being hailed as a holy grail of medicine — a highly effective treatment for a serious problem that, amazingly enough, also has potential for recreational use. All without serious side effects, and at a reasonable cost. What could be better?

It may well turn out that nothing could be better. It certainly seems, based on the experience of about 5,000 users in 21 clinical trials, that Viagra is remarkably effective. About 70 percent of men reported improved erections, and the side effects were minimal — headache in about 10 percent, upset stomach and flushing in up to 8 percent and occasional rare reports of altered color vision. All in all, the drug is clearly off to a good start.

Nevertheless, if Viagra proves to remedy a medical condition arising from numerous, hard-to-treat causes, while simultaneously being entirely benign and risk-free, it will be one of the few prescription drugs on the market fitting that description.

The truth is, the Yellow Brick Road leading to the Emerald City of the future, where every physical problem has a pharmacological solution, is littered with the bones of drugs like Viagra.

In some cases, the casualties were medications for problems (such as impotence) for which no good treatments existed. Others were touted as replacements for therapies that were inconvenient, marginally effective or unpleasant. For all of them, the risks appeared to be minimal and the payoffs great. They were what people were waiting for: perfect treatments to common problems such as pain, anxiety and obesity, and common diseases such as diabetes, arthritis and allergy.

A few of these drugs survived and are still with us today, huge successes and money makers. Many, however, turned out to be just as they seemed — too good to be true. The reasons for this are fairly obvious, although a person reading Viagra's recent press notices can be forgiven for not noticing them. For starters, drugs are blunt instruments.

"By definition, all drugs are poisons. They are given to interfere with normal bodily functions," said Brian Storm, a professor of medicine at the University of Pennsylvania's medical school. "I cannot tell you how many times, when I start (to prescribe) a drug, the patient asks: 'Does this drug have side effects?' And the answer is, 'Of course it does. All drugs have side effects.' The real question is, what are its side effects?"

This problem is not likely to go away even in the bio-tech age, when drugs are "designed" to tweak only a single type of cellular receptor, or block a single member of a family of enzymes.

An astonishing (and seemingly never-ending) revelation of modern biology is how a single molecule can have a half-dozen or more functions, often not clearly related to one another, in widely scattered organs of the body. For example, the biochemical dopamine affects mood, permits the smooth movement of muscles, raises blood pressure and suppresses lactation. A substance called "vasocactive intestinal peptide" is as active in the brain as it is in the intestine. Prostaglandins, first isolated from fluid in the prostate, turn out to be made by virtually every type of cell in the body, and have many dozens of effects.

For these reasons, drugs that target one organ are likely to have effects in lots of organs. Sometimes that's not a problem. Sometimes it's a big problem. In any case, it's not a problem that's likely to go away, no matter how fancy drug design gets.

Viagra blocks an enzyme called "phosphodiesterase type 5," which exists in blood cells called platelets, in the muscle cells of blood vessels, and in the penis. As such things go, it's a short list (though maybe not a complete one). Viagra doesn't seem to have hazardous effects on the other sites, but whether that's true when millions of men are taking the drug remains to be seen.

As a rule, the amount of pre-market testing on drugs permits pharmaceutical companies to identify severe adverse effects that occur more frequently than one-in-a-thousand uses. Rarer complications (or complications that masquerade as minor health problems from other causes) don't predictably show up. To catch them, you have to see what happens when the drug goes into the bodies of tens of thousands or millions of people.

However, the uncertainty about new drugs isn't just a numbers game. Without exception, once a drug is on the market, it's used by an older, less healthy, more diverse and less well-monitored group of people than the ones it was tested on. That's when a "benign" drug's bad interaction with other drugs or other diseases shows up.

For these reasons, the media hype of a new drug or medical device is itself risky. It's not just that newspapers and TV networks aren't competent to evaluate medications and predict their usefulness, it's that

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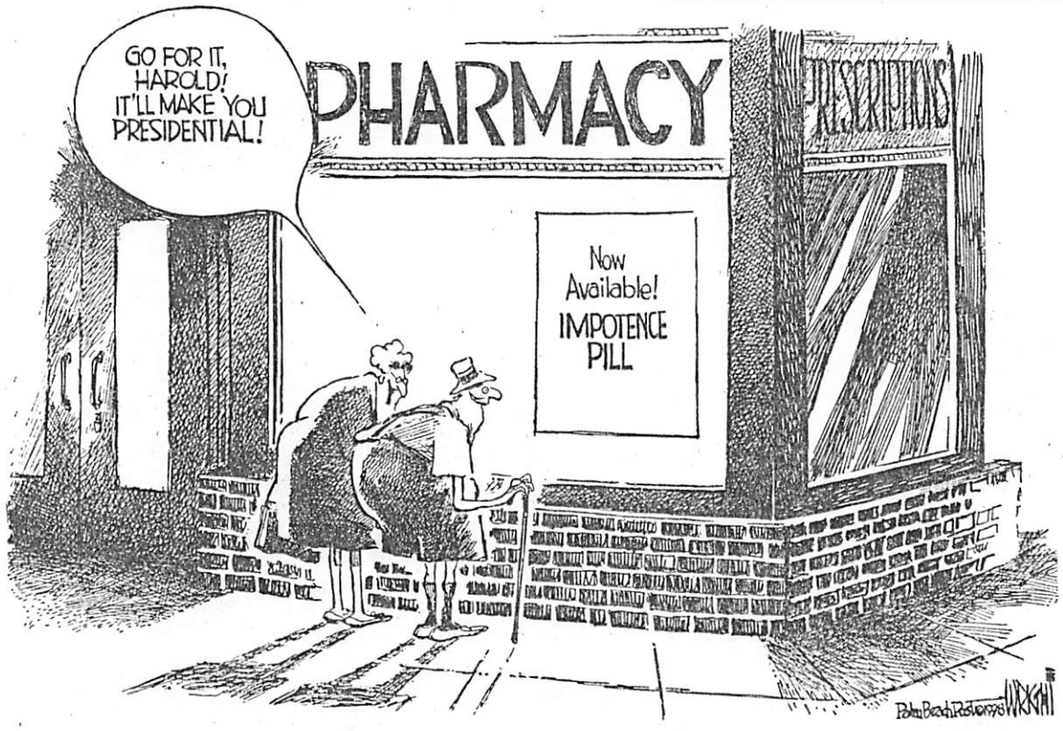

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nobody knows the full story until well after a drug has been around for a while.

This is not to say that drug disasters are common in the United States. In fact, they're extremely rare. Nevertheless, there are more than a few examples of surprise and disappointment in "breakthrough" pharmaceuticals in recent decades.

A diuretic called Selacryn was greeted with great enthusiasm in 1979 because, unlike similar drugs, it didn't raise blood levels of uric acid — a condition that can lead to the painful condition called gout. Unfortunately, it *did* cause fatal liver disease in a handful of patients, and was gone in a few months.

Zomax, a "non-steroidal anti-inflammatory" pain-killer marketed in the 1980s, was one of medicine's other holy grails — a drug as potent as morphine, with none of morphine's risks. It had an unacceptably high level of allergic reactions, some fatal, and was withdrawn.

EARLIER THIS decade, Seldane and Hismanal, the first allergy pills free of the sedation and dry mouth associated with older antihistamines, ran into trouble when some patients taking them with some other drugs developed abnormal, life-threatening heart rhythms. Seldane is now off the market, and Hismanal carries many warnings.

Just last year, the FDA yanked fenfluramine and phentermine ("fen-phen"), the most popular — and seemingly, the safest — anti-obesity drugs on the market. A physician in North Dakota had noticed a troubling cluster of heart valve problems in high-dose fen-phen users. When doctors in other places went looking for the rare complication, they found it, too.

The fact that early reports tend to be overly optimistic isn't just true of drug treatments. It's often true of other kinds of medical therapy, also.

For example, early this decade two large clinical trials of a surgical procedure known as carotid endarterectomy were done at hospitals that were chosen for their excellent surgical track records. Both studies found the operation, intended to prevent strokes, worth the risk in a highly selected class of patients.

The second of these studies made big news three years ago. Officials of the National Institutes of Health held a news conference, and the results favoring the operation made every major newspaper and network.

But in a recent article in the *Journal of the American Medical Association*, David E. Wennberg, a physician and epidemiologist, looked at the experience of Medicare patients having carotid endarterectomy at the very same hospitals where the studies were done. For them, the surgical mortality was more than twice as high as it had been in the clinical trial patients.

The reason was no mystery. The Medicare patients were sicker, older, more complicated — precisely the patients at the greatest risk for strokes. The risks were even higher at other hospitals, which of course is where most Americans would get the operation.

In real life, then, it turns out the odds aren't quite as good as they looked when the stop-the-presses, "Carotid Endarterectomy Is Safe and Effective" stories appeared.

Of course, there are treatments, and drugs, that almost never bite back, no matter how much you provoke them. The "statin" family of cholesterol-lowering drugs (Mevacor, Pravachol and many others) are proving beneficial to an ever-expanding fraction of the population, with virtually no side effects. Similarly, the "H2-blockers," such as Zantac, used to treat ulcer and heartburn are among the most widely consumed drugs in the world. They are also among the safest.

The chance that a drug may cause dangerous, even fatal, reactions doesn't mean it's a bad drug. In fact, it may be a great drug. An antibiotic that causes Stevens-Johnson syndrome (an allergic reaction equivalent to a total body burn) once in a million uses may be worth taking — assuming, of course, you actually have a bacterial infection, and therefore stand to get some benefit in exchange for the risk. Obviously, the worse a disease is, the bigger the risk people are willing to take. What makes some doctors worried about wildly popular pills is that while the risk-benefit calculus differs greatly between patients, the actual risks tend not to change much.

"The trade-off in someone who weighs 400 pounds and is at great medical risk from obesity might be such that one plausibly considers the (one in 20,000) chance of pulmonary hypertension (an often-fatal complication associated with the recently withdrawn diet drug Redux) worth it," said Jerry Avorn, a physician at Brigham and Women's Hospital in Boston who does research on how medications are used. "Unfortunately, the risk doesn't get any better if you're treating someone who wants to look better in a bikini."

WHEN IT comes to risks and benefits, Viagra may turn out to be as great as everyone says it is — a sure-fire success, with no downside. Let's hope so.

Meanwhile, it's good to remember that in pharmacology, as in most places, free lunches are hard to find.

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