Medicine's secret: Some drugs won't help most of those who take them

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In an era when a lack of interest in sex is considered a treatable medical disorder, these are the pros and cons for patients seeking a pharmaceutical fix:

If you give the new female sexual desire drug Addyi to 12 women, one will experience a modest improvement in her sex life, after factoring out the placebo effect. On average, a user can expect one additional satisfying sexual event each month - or less.

But one of out of seven will experience drowsiness. And, if they drink, some may pass out due to a dramatic drop in blood pressure.

Give nine men with low libido the testosterone supplement Androgel and one will report increased sexual activity.

But one of 14 will develop acne and one of 33 will experience troubling emotional swings, such as impatience or anger. And all who use it will be at higher risk for life-threatening blood clots.

In short, the drugs won't help most of the people who take them. In some cases, they are almost as likely to produce a negative side effect as a benefit.

"It's the biggest secret in medicine," said F. Perry Wilson, a researcher and physician at Yale University School of Medicine. "For the vast

majority of the drugs out there, the chance that you, as an individual, are going to see a benefit is quite small."

There is another secret: Even these numbers are exaggerated because the dangers and benefits are determined in clinical trials set up by drug manufacturers. The trials often are highly controlled tests that exclude the kinds of real-world patients who will be put on a drug once it gets on the market.

And a push by drug companies to turn a series of everyday conditions into medical disorders means more people are taking - and being harmed by - the suspect drugs.

A Milwaukee Journal Sentinel/MedPage Today investigation examined eight conditions that became part of mainstream medicine over the past 20 years, ranging from pre-diabetes to overactive bladder.

Those eight conditions alone are purported to affect more than 180 million Americans, or the equivalent of 77 percent of the adult population.

The conditions are not life-threatening. The treatment results are not impressive. In some cases, the treatments can be dangerous.

Consider just one measure of harm: Reports of negative side effects filed with the U.S. Food and Drug Administration.

Since 2013, nearly 65,000 reports of serious side effects involving drugs used to treat five of the conditions have been reported to the FDA, according to a Journal Sentinel/MedPage Today analysis. That includes more than 1,600 deaths.

Vinay Prasad, a health policy and ethics expert, said many patients

would be surprised by the lack of benefit and likely would turn down treatment with drugs that were part of the Journal Sentinel/MedPage analysis.

"Even when people take these drugs for weeks or months, the benefits are modest or small, and the harms are nearly of the same size," said Prasad, an assistant professor of medicine at Oregon Health & Science University.

To examine benefits and harms, Wilson, the Yale researcher, did a biostatistical analysis for the Journal Sentinel and MedPage Today focusing on drugs used to treat lack of interest in sex among women, low testosterone in men, overactive bladder, adult ADHD and binge-eating disorder.

Wilson started with something called the number-needed-to-treat. That's how many patients have to take a drug before one will get the desired benefit. The lower that number, the better.

Vyvanse is an amphetamine approved to treat two of the conditions: binge-eating disorder and adult ADHD.

The drug's treatment number for an improvement in adult ADHD symptoms is 2.9, meaning nearly three people have to take the drug before one sees any improvement. Its treatment number for a reduction in the number of binge-eating days per week is 2.3.

The measure for how many people have to take a drug before one will have an undesirable side effect is the number-needed-to-harm. The higher that number, the better.

In the case of Vyvanse, its harm number for the side effect of insomnia is 5, meaning for every five people who take it, one will get insomnia,

after factoring out the placebo effect.

At the same time, Vyvanse and other stimulants carry a high risk of dependence and abuse. They can increase blood pressure and heart rate, as well as the risk of a heart attack or stroke.

Vyvanse carries a retail price of $310 for a 30-day supply.

Clotilde Houze, a spokeswoman for Shire, which markets Vyvanse, said the company stands behind the safety and effectiveness of the drug, which has been on the market since 2007. She said Vyvanse is not right for every patient with ADHD or binge-eating disorder and that it is critical they stay under the care of a doctor.

Another drug in the analysis was Toviaz, which is used to treat overactive bladder.

An often more troubling condition once was known as incontinence, or leakage. But in the late 1990s, doctors with drug company financial ties gave it a new name and helped expand the definition to cover more people.

For every 3.6 people who use Toviaz, only one will have any reduction in incontinence. For every 5.7 people who use it, one will have reduced urgency, or the feeling of having to go.

The drug's side effects include dry mouth (one out of every 3.6 people) and constipation (one out of 25).

It also has a retail price of $365 a month, or $4,300 a year.

Steven Danehy, a spokesman for Pfizer, the drug's maker, said Toviaz's safety and effectiveness have been well-established in clinical trials

conducted before and after it got on the market.

"Each product label details accurate information approved by regulatory authorities on the benefits and risks to ensure that both prescribers and patients are fully informed," he said.

There are now more than a dozen drugs and other treatments on the market aimed at overactive bladder.

But experts in the field say the condition is best managed using non-drug approaches known as behavioral therapy, which includes bladder training and pelvic muscle exercises.

The benefit-harm numbers are revealing.

James Simon, a clinical professor of obstetrics and gynecology at George Washington University School of Medicine, said such an analysis can be misleading when it comes to conditions that rely on patients' opinions to say whether they worked or not.

Simon has worked as a consultant for Valeant Pharmaceuticals, the company that markets Addyi.

With Addyi, he said, analyzing monthly satisfying sexual events is "a very strange metric," since a husband or partner could be out of town, angry, or uninterested. Yet, that was a primary measure the company itself used to obtain FDA approval.

Even harmful side effects can be over-represented, Simon said, as many come in the first few weeks of treatment and may disappear.

"I think we accept that flibanserin (generic Addyi) has some warts, because all drugs have some warts," he said. "At the moment, it's the

best thing we've got."

Indeed, Addyi is the only FDA-approved drug for the condition.

Its monthly retail cost is $830 - nearly $10,000 a year for a drug that will modestly help 1 in 12 women, according to the company's own clinical trials.

Tracy Valorie, a spokeswoman for Valeant, said trials showed using Addyi led to a statistically significant increase in sexually satisfying events.

"The trials also consistently demonstrated an improvement in sexual desire and a reduction in associated distress," she said.

Experts say clinical trials, by their nature, present a problem that most patients do not understand, and that doctors do not always consider.

Think of the trials as highly controlled tests, in which only certain types of people are allowed to participate. This is necessary to get clear, valid results. But it leaves out many of the very people who wind up taking the medicine.

What's more, the trials usually are of much shorter duration than how long a person actually may be on a drug. And patients in the trials may be checked more closely by a doctor or nurse than they would in everyday life.

"It's Disney World vs. the real world," said David Juurlink, a professor of medicine at the University of Toronto who studies drug safety. "The point is that, by design, industry-sponsored (trials) tend to make drugs appear more effective and safer than they are eventually found to be in practice."

Indeed, some clinical trials of the examined drugs left out vast numbers of people later likely to receive them:

The trial that tested the effects of Androgel on sexual function in older men excluded those who were at higher risk for prostate cancer and cardiovascular problems and those with severe depression. The minimum age was 65.

In the Addyi trial, many groups of women were excluded and those who participated had to be in "a stable, monogamous, heterosexual relationship that is secure and communicative."

The trial of Vyvanse for adults with ADHD excluded those who were significantly underweight or severely obese; those with other significant mental disorders; those with certain heart conditions; those who abused drugs in the previous six months; women who were pregnant or breast-feeding; and those with high blood pressure.

The Journal Sentinel/MedPage Today review of the FDA data found that since 2013 at least 20 people had serious medical complications attributed to Vyvanse while also being treated for high blood pressure.

A 52-year-old woman, for example, saw an increase in blood pressure and cholesterol after taking Vyvanse and Vasotec, a blood pressure medicine.

In its trials, Androgel excluded those with depression.

At least 180 people being treated for depression reported problems attributed to the drug after it hit the market, including a 52-year-old man who, after what was described as a "cerebrovascular accident," couldn't speak and had limited use of half his body, the Journal Sentinel/MedPage Today review found.

The monthly retail cost for Androgel is $550, more than $6,000 a year.

All told, there were nearly 12,000 cases where people had to be hospitalized because of side effects from the drugs used to treat ADHD, binge-eating disorder, premenstrual dysphoric disorder, low testosterone and overactive bladder.

An additional 1,000 cases were considered life-threatening. Among them was a 19-year-old woman, taking Yaz for premenstrual dysphoric disorder, who reported vaginal bleeding and was treated for a blood clot.

The analysis includes only cases that were reported to the FDA by manufacturers or health care professionals. Even then, it was limited to cases where the drugs were considered the primary cause. Cases where they were a contributing factor were not included.

Many of the treatments "don't strike me as a worthwhile trade-off," said Michael Hochman of the University of Southern California, who also practices as a primary care doctor.

"Too often, patients get started on medications and don't experience any benefit, yet the medications are continued," Hochman said.

"Or worse, they experience side effects that they do not realize are related to the medication and the net result is more harm than good."

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WAYS IN WHICH ILLNESSES ARE INFLATED

In 2016, the Milwaukee Journal Sentinel and MedPage Today examined eight conditions once considered part of everyday life that over the past two decades moved into the medical mainstream after a push from drug

companies.

Some of the conditions, such as overactive bladder and lack of interest in sex, occur more often as people age. For some of the others, such as pre-diabetes, binge-eating disorder, premenstrual dysphoric disorder and intermittent explosive disorder, there are doubts about whether they should be considered medical or psychiatric conditions at all.

Adult ADHD

Definition: Pattern of behavior that can include failure to pay attention to details and difficulty organizing tasks.

Background: For years, the legitimacy of the condition was based on it being the same condition that started in childhood and persisted into adulthood. But in a 2015 study that followed people into their 30s, researchers found little overlap between the groups. A 2010 study found that 22 percent of adults tested for ADHD exaggerated their symptoms.

Binge-eating disorder

Definition: Recurring episodes of eating significantly more in a short period than most people would eat, with a feeling of lack of control.

Background: Independent doctors say it is not a disease at all, but simply an unhealthy habit.

Female sexual interest/arousal disorder

Definition: The absence of or significantly reduced sexual interest/arousal for at least six months.

Background: To test whether the drug Addyi caused a dangerous blood

pressure drop for women when used with alcohol, a study looked at 25 people. Of those, 23 were men.

Intermittent explosive disorder

Definition: Uncontrolled bouts of anger or rage that are out of proportion to what triggered the outburst.

Background: The definition was relaxed in 2013 by a panel of experts of whom 78 percent had drug company financial conflicts. The new definition said the outbursts could be verbal, rather than just physical. No estimates have been done on how many more people might have the condition under the new definition.

Low testosterone

Definition: Levels of the hormone that are significantly below those of healthy younger men, marked by symptoms, including low energy, decreased libido and erectile dysfunction.

Background: A 2006 study funded by a company that sold a testosterone product deemed that 38 percent of men over the age of 45 had it.

Overactive bladder

Definition: A sudden urge to urinate that may include incontinence and having to get up at night.

Background: In the late 1990s, the drug company Pharmacia funded efforts to expand the market. A slide presentation used by a company executive included one headlined "Creating a disease."

Pre-diabetes

Definition: A blood sugar level at the higher end of normal, but not high enough to qualify as Type 2 diabetes.

Background: When the American Diabetes Association lowered its blood sugar threshold in 2003 and 2010, it increased the number of Americans with the condition from 17 million to 87 million. Nine of the 14 experts on the 2010 panel had worked as speakers, consultants or advisers to companies that make products to treat diabetes.

Premenstrual dysphoric disorder

Definition: A form of premenstrual syndrome, said to be more severe, with symptoms that may include depressed mood, anger and anxiety.

Background: The U.S. Food and Drug Administration approved four drugs to treat it starting 2000, 13 years before it was recognized as a psychiatric disorder.

More information: John Fauber is a reporter for the Milwaukee Journal Sentinel. Kristina Fiore and Matthew Wynn are reporters for MedPage Today.

This story was reported as a joint project of the Journal Sentinel and MedPage Today, which provides a clinical perspective for physicians on breaking medical news at medpagetoday.com.

The biostatistical analysis done by F. Perry Wilson of Yale University School of Medicine involved four drugs - Toviaz, Addyi, Vyvanse and Androgel - approved to treat five conditions: overactive bladder, female sexual interest/arousal disorder, adult ADHD, binge-eating disorder and low testosterone in men.

The other three conditions in the Journal Sentinel/MedPage Today

investigation (intermittent explosive disorder, pre-diabetes and premenstrual dysphoric disorder) were not included in the analysis because there were not approved drugs to treat them or due to a lack of reliable data. The analysis of the FDA's adverse events database was limited for similar reasons.