

"Off-Label" Drug Use

When a doctor writes a prescription to treat your ailment, you probably assume that the drug has been approved for that use by the Food and Drug Administration (FDA). That's a reasonable assumption, but it is not always true. One in five prescriptions in the U.S. is for a use *not* approved by the FDA. And most of those (about 75 percent) are for a use that *lacks any evidence or rigorous studies to back it up*.

When a doctor prescribes a drug for an unapproved use, it's called an "off-label" prescription. The term refers to the fact that all drugs have "labeling" – detailed written descriptions of their intended use based on studies submitted to the FDA.

Importantly, off-label drug use is legal and often beneficial. But there is growing concern that (a) it's on the rise; (b) it's not always wise; (c) it's getting riskier; (d) drug companies skirt the rules restricting the promotion of off-label uses; (e) consumers aren't as informed as they should be when a doctor prescribes a drug off-label; and (f) inappropriate off-label use adds to wasteful health spending.

BRIEF BACKGROUND

All new prescription drugs must be approved by the FDA. The drug's manufacturer conducts studies (also called clinical trials) to prove that a medicine is safe and works. Those are submitted to the FDA.

Congressionally mandated rules govern the FDA drug approval process. Those rules strongly push drug companies to focus on proving their drug is beneficial and safe for a single main use. Put simply, this makes the testing of the drug manageable and affordable. With many drugs, this focus is quite logical because the drug may be effective against only one ailment or disease. But for other drugs, several or even many uses may be possible and the drug company will have to choose.

Cancer drugs are often cited as multiple-use. Many cancer drugs developed over the past two decades have gone through the FDA approval process with

testing against only one kind of cancer. But, even as they were being developed, researchers may have identified a drug's potential to treat another form of cancer. Today, over half of all uses of cancer drugs are off-label. (See sidebar on page 4.)

While cancer drugs are somewhat unique, other uses have been identified for many drugs that were first

approved for a single ailment. This is simply the nature of both drug development and clinical medicine.

Given these circumstances, Congress has long specified that the FDA can not "practice medicine," and that once a drug is approved and on the market for *any purpose*, doctors are the best arbiters of how it is used and for whom.

Once a drug is approved and on the market its maker can pursue approval of new uses from the FDA. But it must back up those requests with studies. Companies have a strong motivation to conduct such studies because they can't legally promote a drug to doctors (or consumers) for uses not approved by the FDA and stated in the drug's labeling.

In addition, insurers and government (Medicare and Medicaid) now scrutinize off-label uses much more closely, and don't pay for many off-label prescriptions.

One other important piece of background: there are really two kinds of



off-label drug use. One (let's call it Type I) involves using a drug approved for one disease to treat a completely different disorder. For example, using a drug approved to treat seizures to prevent depression or nerve pain instead.

A second kind (let's call it Type II) of off-label use involves prescribing a

drug to treat the condition or ailment it was approved for, but outside certain specifications. Perhaps the best recent example of Type II off-label use is Viagra and the other two erectile dysfunction (ED) drugs, Levitra and Cialis. All are approved to treat ED, which is a definite clinical symptom. But all three drugs are fairly commonly pre-

scribed off-label today to treat men who may not strictly meet the definition of having ED.

In the worst cases, such drugs – which carry risks – are prescribed to men who do not have erection or impotence problems but simply desire to be stronger sexual performers.

DRUGS COMMONLY PRESCRIBED OFF-LABEL*

Class of Drug	Examples of Off-Label Use**
Anti-seizure drugs	Migraines, depression, nerve pain
Antipsychotics (<i>for Schizophrenia</i>)	Alzheimer's Disease, autism, dementia, Attention Deficit Hyperactivity Disorder (ADHD)
Antidepressants	Chronic pain, ADHD, bipolar disorder
Antihistamines (<i>for allergies</i>)	Colds, asthma, ear infection symptoms, as sleep aids
Antibiotics	Viral infections, such as common cold or flu, against which antibiotics are useless
Anxiety drugs	To ease "normal" life stresses, as sleep aids
Proton Pump Inhibitors (<i>for gastroesophageal reflux disease</i>)	Occasional heartburn, indigestion, irritable bowel
Beta-Blockers (<i>for high blood pressure and heart disease</i>)	Migraines, heart rhythm disorders, anxiety
Drugs to treat Attention Deficit Hyperactivity Disorder	For people not diagnosed with ADHD, to enhance alertness and concentration
Insomnia medicines/"Sleeping Pills"	For people with infrequent insomnia, insomnia associated with depression, anxiety
Narcotic pain relievers	For people with only mild, infrequent pain
Specific Drugs	Examples of Off-Label Use**
Aripiprazole (<i>Abilify, antipsychotic</i>)	Dementia, Alzheimer's Disease
Albuterol (<i>for asthma</i>)	Bad coughs
Lamictal (<i>antiepileptic, anti-seizure</i>)	Depression, bipolar disorder, mood stabilization
Tiagabine (<i>Gabitril, anti-seizure</i>)	Depression, mood stabilization
Gabapentin (<i>Neurontin, anti-seizure</i>)	Depression, nerve pain, migraines
Topiramate (<i>Topamax, anti-seizure</i>)	Migraines, bipolar disorder, depression, nerve pain
Risperidone (<i>Risperdal, antipsychotic</i>)	Alzheimer's Disease, dementia, eating disorders
Lidoderm (<i>skin patch for shingles</i>)	Lower back pain, sore muscles, tennis elbow,
Trazodone (<i>Desyrel, antidepressant</i>)	As a sleep aid and for insomnia
Propranolol (<i>Inderal, high blood pressure and heart disease</i>)	Performance anxiety
Modafinil (<i>Provigil for excessive sleepiness</i>)	To enhance wakefulness and alertness
Viagra (<i>erectile dysfunction</i>)	To enhance sexual performance in people not diagnosed with erectile dysfunction

*Examples, not meant to be a comprehensive list. **Does not imply whether use is clinically appropriate or inappropriate, beneficial or not.

Many doctors and consumers view Type I off-label use as more problematic and type II as more benign, or acceptable. But practically no research has quantified the actual harm from either, or determined whether the amount of harm differs between Type I and Type II off-label use.

THE GOOD, BAD AND UGLY

OK, so now you know that federal rules pretty much require companies to study and prove one use of a drug to get it approved. And you know that some drugs may have *multiple* beneficial uses. So the big plus for off-label prescribing is that if a new use emerges for a drug, and it looks pretty good, doctors and patients don't have to wait – potentially years – for the drug's maker (or anyone) to prove things.

Take plain old aspirin, for example. Preliminary evidence began to emerge in the 1960s and 1970s that aspirin could lower the risk of a second heart attack. Since aspirin is a cheap nonprescription generic drug made by dozens of companies, no company was going to spend millions of dollars to prove that aspirin really was a heart attack-



OUR ADVICE AND RECOMMENDATIONS

- When your doctor prescribes a drug – *any drug* – ask if it's an approved use or an "off-label" use.
- If your doctor does not know, that's not reassuring. Ask the pharmacist the same question if and when you fill the prescription.
- If the drug is being prescribed off-label, ask what the drug *has been* approved for?
- If you get an off-label prescription, ask your doctor whether the scientific evidence really supports this use.
- Go online and research the drug. Try to find the "label" – that is, the official printed information that specifies what the drug is approved to treat. The best place to start is the FDA's Web site search engine for drugs at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.
- Check other trusted Internet sites. If reassured, good. If further concerns are raised, talk with your doctor again.
- A drug that is often used off-label (such as some we list on page 2) is not necessarily a signal that the off-label use is OK or beneficial.
- Don't accept from a doctor or pharmacist the statement, "everyone prescribes this off-label. It's OK. Don't worry." What is his or her specific reason for prescribing the drug?

preventive. Instead, the government launched such studies.

That took years. But, meanwhile, doctors made the judgment that the benefit of trying aspirin in heart attack

victims was well worth the risk. They were right. The studies confirmed the positive affect and the FDA approved new labeling for aspirin, but not until 1998. Literally hundreds of thousands of lives were likely prolonged or saved during the aspirin-heart "off label" period.

Other heart disease drugs serve as additional examples of beneficial off-label use. A class of drugs called beta-blockers, for example, was initially approved in the 1980s to treat high blood pressure. But researchers and doctors quickly theorized – and evidence mounted from subsequent studies – that beta-blockers (such as propranolol and metoprolol) would be effective against angina and heart attack.

Again, the doctors were right. Large-scale studies have borne this out and

the labeling of all beta-blockers now reflects their significant benefit for heart disease generally.

To take a narrower example, you may know that drugs called statins (such as simvastatin, pravastatin, and brand-name Lipitor) lower “bad” cholesterol. Some statins have also now been proven to reduce heart attack and stroke deaths in certain groups of patients. The labeling now reflects that. But years ago

doctors started prescribing statins for people with diabetes even if they *didn't* have high cholesterol or other heart disease risk factors. This was an off-label use since the drugs were not proven yet to help people with diabetes.

Alas, studies have now clearly established that statins help prevent heart attacks and strokes in people with diabetes, and the labeling of some statins now reflects this.

The bad news is that for every such example of positive off-label use, there are two or three that tell the other side of the story – of unsupported or potentially harmful off-label prescriptions.

A study published in May 2006 in the *Archives of Internal Medicine* is the most recent and comprehensive to date to document the problem. It evaluated 725 million prescriptions writ-

CANCER DRUGS ARE A SPECIAL CASE

The National Comprehensive Cancer Network – an entity made up of cancer treatment centers – estimates that 50 to 75 percent of all use of cancer drugs in the U.S. is off-label.

As explained at the beginning of this brief, cancer drugs are somewhat unique in that cancer is, at the same time, both a uniform phenomenon and over 100 very different diseases. Breast cancer is not like leukemia, brain, colon, or kidney cancer, but all, of course, stem from the same kind of physiological problem (cell growth gone awry).

To put it very simply, some cancer drugs are quite broad-based and can be used to treat several (or many) different types of cancer (though they may be variously effective). Others are more specific, and target only one or two types of cancer. That was true 30 years ago and is still true today even with the newer drugs being developed.

As a result, off-label use of cancer drugs has been widely accepted by doctors, insurers, and patients. Medicare, for example, routinely covers off-label cancer drug use that has at least some evidence backing it up. It does not require a company to get FDA approval for that use. And many states require health insurers to pay for off-label use of cancer drugs.

Given the nature of cancer and cancer drugs, this approach sounds entirely reasonable. And for the most part it is.

But there is another – somewhat controversial – way of looking at the routine off-label use of cancer drugs. That perspective is that cancer patients are often guinea pigs for unproven chemotherapy treatments.

Despite the harsh-sounding nature of that statement, it's a useful perspective to keep in mind if you or someone close to you is ever diagnosed with cancer. The plain fact is that many of the drug regimens and combinations that cancer doctors use are not fully proved, and have never been vetted formally by the FDA. Indeed, cancer doctors can pretty much do what they want – picking and choosing among some 30 to 40 core cancer drugs.

In practice, of course, most cancer doctors watch the medical literature and follow new studies very closely – using those as a guide to what are the latest approaches being successfully tried.

But the history of cancer care is full of examples of once-hopeful drug regimens being used for years only to be proved at the end of the day to be no better (or worse) than previous treatments.

Our take-home advice for the off-label use of cancer drugs is this: it's unavoidable for many patients and you would never want to rule it out. But it still warrants asking the doctor what evidence exists to back-up the choice of a particular drug or combination of drugs.

Fortunately, today there is a lot more information available on the Internet that can help people navigate the difficult world of cancer treatment. That includes robust discussions of off-label use and the evidence supporting it.

OFF-LABEL DRUG USE AND KIDS

Most prescription drugs are approved with no or very limited testing in children or teens under age 18. As a result, the vast majority of drugs that are approved to treat diseases and conditions that primarily strike adults are prescribed off-label when a doctor chooses to use them to treat a child or teen.

Recognizing that this was a less-than-ideal situation, Congress in the 1990s passed a law that granted six months of additional patent life to any brand-name drug that was also tested in people under age 18. Drug companies can conduct such tests before a drug is submitted to the FDA for approval, or after.

If a company perceives a potential substantial use of the drug in young people (such as with an antibiotic), it may do the tests before submitting the drug for approval. But most of the time the companies go back to the FDA with tests in kids *after* a drug is approved, and often not until years later.

Thus, the situation, while better, remains less than ideal. And much prescription drug use in children and teens is off-label.

This includes use of drugs when kids are hospitalized. In a recent study at 31 children's hospitals across the country, researchers found that four in five patients received at least one off-label drug. The most widely prescribed were painkillers like morphine which are not specifically approved for use in children.

Pills kids get prescribed off-label to take at home – for allergies, asthma, and infections, for example – should not generally be a cause for worry, doctors say.

But parents should be very alert if their children are prescribed drugs for psychiatric or mental health illnesses, such as depression or hyperactivity disorder. These medicines are frequently prescribed off-label for both adults and children, and studies have found them to have potent and unique side effects in children and teens that they do not have in adults.

As suggested in the box on page 3, any time your child is given a prescription, you should ask if it is for an approved use or an off-label use.

ten in 2001 and found that 21 percent of them were off-label. More importantly, 73 percent of those off-label prescriptions were for a use that lacked any firm scientific evidence.

The greatest disparity was for medicines to treat allergies and psychiatric illnesses. Off-label prescriptions for psychiatric drugs had scientific support *only four percent of the time*, while prescriptions for allergy medicines had scientific support 11 percent of the time.

See the list in the box on page 2 for other medicines that are often used off-label.

News stories also occasionally uncover or trumpet a potentially dangerous off-label use. In November 2006, *The Wall Street Journal* told the story of Actiq (fentanyl), a powerful narcotic painkiller available as an oral lozenge for quicker action. The drug was approved nine years ago for use in the treatment of severe cancer pain. But the article documented that in the first half of 2006 cancer doctors accounted for only *one percent* of the Actiq prescriptions filled at retail pharmacies.

In addition, a second source cited by the *Wall Street Journal* found that between June 2005 and October 2006, a representative sample of doctors prescribed Actiq off-label 80 percent of the time, primarily to treat migraine and back pain. A separate article in March 2007 in the trade publication *Med Ad News* cites yet another analysis of Actiq – a study of 95 people who got an Actiq prescription between April and June 2005 through a health plan in the Midwest. Only 21 had a diagnosis of cancer or AIDS.

Actiq's maker (Cephalon) is being investigated by the FDA's Office of Criminal Investigations, the U.S. Attorney's Office in Philadelphia, and the Connecticut Attorney General for



possible promotion and marketing of the off-label uses of the drug.

Media accounts have also revealed the potentially dangerous off-label use of three drugs approved to treat anemia in cancer patients undergoing chemotherapy (the chemo causes anemia); this use reduces the need for potentially dangerous blood transfusions. But many doctors were prescribing the drugs – Aranesp, Epogen, and Procrit – to treat anemia caused by cancer itself, and because they thought the drugs would improve patients’ energy levels.

Logical as that may sound, it was a scientifically unproven use in an already-sick population of patients. And, again, where might the doctors have gotten the idea the drugs were good for many cancer patients, whether or not they were undergoing chemotherapy? From the drugs’ makers, authorities allege. One Epogen ad in a medical journal in 2004, for example, told doctors to “elevate their [patients’] lives,” and cited improved energy and quality of life.

The marketing of these three drugs and the doses used for them are under intense scrutiny in the wake of important studies showing that the drugs may actually *make the cancer itself worse in some patients, and/or lead to a higher death rate.*



By the way, Aranesp, Epogen, and Procrit are very expensive drugs, costing \$8,000 or more a year.

WHAT YOUR DOCTOR KNOWS, OR SHOULD

As is hopefully clear by now, doctors are a major player in the off-label story. They wear white hats when they prescribe a drug off-label and it works well. They are also sometimes the unwitting victims of drug-company marketing or promotion of off-label uses – including informal office visits by drug company sales people.

But doctors can at times be the willful perpetrators of unsupported off-label use – when they should know better.

For example, the FDA has had rules, instituted in 1998, on precisely what sales representatives can say about the off-label use of a drug. They are per-

mitted to share studies that have been published in reputable medical journals and that are going to be used to support a future application to the FDA for approval.

But many critics, state Attorneys General, consumer organizations, and doctors themselves believe that the rules continue to be regularly violated, and that many doctors – during their busy days – don’t bother to hold drug sales people to the letter of the law.

In addition, studies over many years have shown that most doctors don’t always know about the detailed labeling of a drug, and what its “approved” use is. Rather, they rely on their colleagues and what is known as “community standards of practice” in their prescribing habits.

Even so, these days, largely because of recently increased publicity surrounding this issue, your doctor is likely to be more cautious about off-label use and more forthcoming with you about when a prescription is off-label than was the case just a few years ago.

Indeed, many experts are calling for the FDA and others to provide better information to both doctors and consumers that will help them differentiate between good off-label use and bad off-label use – without having to wade through hundreds of technical studies. We concur that such information would be highly valuable.

THE SHOPPER’S GUIDE TO PRESCRIPTION DRUGS SERIES

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