A KNIGHT RIDDER SPECIAL REPORT

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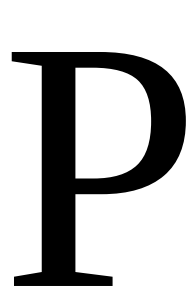
Tammie Snyder holds Presley, one of her twin daughters, in New Baltimore, Mich. Snyder was prescribed an asthma drug to prevent premature labor.

PRESCRIPTION FOR DANGER

Patients injured and killed as doctors prescribe drugs for unapproved uses

By Alison Young and Chris Adams
Knight Ridder Newspapers



NEW BALTIMORE, Mich. — For the last three and a half months she was pregnant, Tammie Snyder had a small medical device strapped to her thigh. It pumped a drug called terbutaline through her body to prevent her from going into labor too soon.

On Sept. 17, 2002, Snyder gave birth to two healthy girls. Within days, however, her lungs filled with fluid, her heart began to fail and she was told she might need a heart transplant. She recovered, but she's been told she can never have a baby again. Her heart wouldn't stand the strain.

Terbutaline is an asthma drug, and the Food and Drug Administration hasn't approved its use to prevent premature labor. The FDA has warned doctors that the treatment is "potentially dangerous" and may not be effective. Snyder said her doctor never told her about the warning or that the FDA had approved terbutaline only to treat asthma.

A six-month Knight Ridder investigation has found that patients nationwide are being injured and killed as doctors routinely prescribe drugs in ways the FDA never certified as safe and effective.

Moreover, these unapproved prescriptions are soaring. Over the last year, 115 million such prescriptions were written, nearly double the number of five years ago, an exclusive Knight Ridder analysis of prescriptions for the country's top-selling drugs found.

The practice, called off-label prescribing, often is driven by questionable research, aggressive drug-company marketing and cavalier doctors, and condoned by tepid regulators.

Doctors are giving their patients epilepsy drugs for depression and hot flashes and to help them lose weight. They use antidepressants to treat premature ejaculation and pain, and powerful antipsychotics for insomnia and attention deficit disorder. High blood-pressure pills are prescribed for headaches and anxiety; antibiotics are used to treat viruses.

Some drugs, in fact, are sold mostly for unapproved purposes. Eight out of 10 prescriptions for the epilepsy drug Topamax aren't for epilepsy. Thalidomide, the notorious morning-sickness drug that caused horrible birth defects and ushered in today's FDA drug-safety rules, today is on the market, and 99 percent of its prescriptions are off-label.

Knight Ridder reviewed 15 top-selling classes of drugs and found that some, such as cholesterol medicines, rarely are given as unapproved treatments. But three-quarters of anti-seizure medications are prescribed off-label, as are nearly two-thirds of antipsychotics and about one-quarter of antidepressants, the analysis found.

For patients with rare, intractable or fatal illnesses, off-label prescribing is sometimes appropriate. In other cases, there may be gold-standard studies backing an off-label use. But doctors routinely are choosing unapproved therapies that are questionable at best.

The practice is perfectly legal, widely accepted and defended by doctors and the American Medical Association — and it's taking a toll.

Victims of off-label prescribing whom Knight Ridder interviewed have suffered heart attacks and strokes, had permanent nerve damage or lost their eyesight. Most said they never were told that the FDA hadn't approved their treatments.

Based on the FDA's own data, Knight Ridder estimates that at least 8,000 people became seriously ill last year after taking some of the nation's most popular drugs off-label. The true number is likely to be many times higher.

"Sometimes it may help, sometimes it may do more harm than good and sometimes it may kill people," said Arnold Relman, a former editor of the prestigious New England Journal of Medicine.

Despite the rise in off-label drug use, the FDA has done little to discourage it, and is considering whether to allow drug companies greater leeway in pushing unapproved therapies.

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George Murphy's hands, made strong by years of climbing utility poles for Houston Lighting & Power, shake with tremors. His legs, now rigid, shuffle as he pushes his walker through his studio apartment in Deer Park, Texas.

"I wish I didn't have to use this thing," he said as the walker snagged on his recliner while he was showing off his Army dog tags from World War II, a plaque for 40 years of service as a Mason, his Shriner fez and the oil paintings his wife did a few years before she died.

Murphy, now 85, began having the tremors last year after he had a series of stroke-like attacks while taking Risperdal, a powerful antipsychotic drug that the FDA has approved only for treating schizophrenia.

Murphy's family practitioner in Pasadena, Texas, Dr. Dennis Yaworski, prescribed Risperdal for an off-label purpose: "cancer phobia," according to case notes from an office visit on Sept. 9, 2002.

The drug's maker, Johnson & Johnson, has marketed Risperdal heavily to doctors who treat elderly patients.

In 1999 the FDA cited Johnson & Johnson for downplaying the drug's risks to the elderly and making false and misleading claims that it could be used not just to treat schizophrenia, but also "for psychotic symptoms associated with a broad range of disorders."

While doctors are free to prescribe as they wish, the FDA prohibits drug-makers from marketing unapproved treatments.

Despite the FDA's action, Risperdal has become a popular off-label treatment for Alzheimer's disease and dementia. About 670,000 such prescriptions were written last year, up more than 350 percent from 1998, the Knight Ridder analysis found. Sixty-five percent of Risperdal's prescriptions last year were for unapproved treatments, generating $929 million in retail sales.

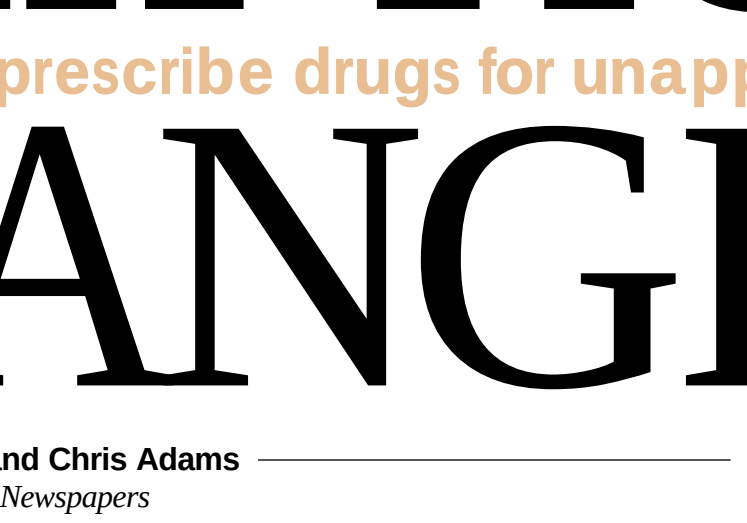
Murphy had been a familiar figure at his doctor's office, complaining of stomach pains, arthritis and the like, often convinced that any pain was a sign that he was dying of cancer. But he was otherwise fit, his daughters said, enjoying family dinners, a recent trip to an alligator festival and an active social life at his independent living center.

The FDA hasn't approved Risperdal for the treatment of hypochondria. But Murphy's family members said they weren't told this. Yaworski declined to be interviewed.

Within a month of starting the drug, Murphy had the first in a series of stroke-like events, called transient ischemic attacks, according to his family and hospital records. During the worst of them, on Nov. 14, 2002, Murphy suddenly couldn't walk, his speech became slurred and his face drooped. He became easily confused, and doctors at the hospital added dementia to his diagnoses.

Attack followed attack, but Murphy kept taking his Risperdal. He was still afraid of getting cancer, his family said.

Then in April 2003, Johnson & Johnson sent a letter to U.S. doc-



RISKY Rx

MICHAEL STRAVATO/KRT

"Our father has been taken away from us. Basically the last enjoyable times he could have with us are gone," said Robbie Murphy. George Murphy's family physician prescribed Risperdal, a schizophrenia drug to help with the 85-year-old's fear of getting cancer. Within weeks of taking the drug Murphy had a series of stroke-like attacks.

What does 'off-label' mean?

When the FDA okays a new drug, it also approves the instructions, or label, for using the drug based on data submitted by the drug company.

Off-label, or unapproved, uses can include prescribing for:

- **Different diagnosis**
  Drug approved to treat one condition, used for a different one
- **Less severe disease**
  Drugs with risky side effects used to treat relatively minor conditions
- **Different length of treatment**
  Some drugs are safe when used for only a short time, but risky when used long-term
- **A patient of a different age**
  Clinical trials often use middle-aged people, making many drugs off-label for children

Source: Knight Ridder Washington Bureau
Graphic: Todd Lindeman, Judy Treible

tors warning that Risperdal may be associated with an increase in strokes when prescribed off-label to elderly dementia patients.

The public warning came nearly two years after the drug maker privately alerted the FDA that there was a problem with Risperdal, agency officials said in response to questions from Knight Ridder. It came six months after drug regulators in Canada issued a similar warning and urged doctors in that country to reassess their use of Risperdal to treat dementia.

FDA officials, in a written statement, said it took several rounds of questions to the drug maker before they had enough evidence to have the drug company issue the warning. Johnson & Johnson, based in New Brunswick, N.J., had no comment.

Murphy and his family have sued the drug company, which in court filings denies any wrongdoing. His daughter, Robbie Murphy, said: "Our father has been taken away from us. Basically the last enjoyable times he could have with us are gone."

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Dr. Raymond Woosley, the vice president of health sciences at the University of Arizona, said off-label prescribing puts patients at greater risk than when doctors follow a drug's FDA-approved directions.

"I have no doubt about it," said Woosley, who also is the director of one of the national centers for drug research established by the federal government. "The caveat is we can't quantify it."

Few have even tried. One study that did was published in 1999 in Great Britain.

Examining about 1,000 children, researchers found that the number of side effects among those who were taking off-label prescriptions was small, but more frequent than for those taking drugs for approved uses.

"If you give a medicine in the right dose, and with good information on how a patient with that illness will handle it, you are less likely to get an adverse drug reaction than if you are prescribing outside of those boundaries," said one of the study's authors, Imti Choonara, a professor in child health at the University of Nottingham. "Otherwise, there's no point to anybody studying medicine. You might as well say, 'Here's a medicine, take it as you like and come tell me if there is a problem.'"

Doctors don't have to go very far off-label before they can put patients in danger. Sometimes, simply prescribing a drug for longer than it's approved for can cause problems.

In 2001, Glenna Baker, a loan officer from Burke, Va., came down with a debilitating stomach disorder that was suspected to be diabetic gastroparesis. She vomited repeatedly, prompting a specialist to prescribe Reglan.

The FDA has approved the drug to be used for less than three months at a time, but studies have found that it's frequently prescribed improperly and that long-term use exposes patients to unnecessary side effects.

One of the worst is tardive dyskinesia, a condition that causes relentless body tremors and facial tics. Baker, now 55, said she was never told about this, so when she moved into her fourth month on the drug she didn't realize what was happening when she began to twitch every now and then.

In her fifth month on Reglan, her symptoms worsened. Her primary care doctor quickly saw the connection.

"It's the Reglan," she said he told her. "We have to get you off it immediately." Her specialist, hearing the news, called Baker at home, angry with her for not alerting him to the oncoming symptoms.

"Don't scream at me," she recalled saying during the June 2001 phone call. "You didn't even warn me. You didn't tell me."

Today, Baker is out of work; the tremors make holding a job impossible. She can sit only for short spells; her right leg constantly bounces, and she endlessly wrings her hands.

She sued the specialist, Dr. Gabriel Herman of Fairfax, Va., and drug maker Wyeth. Both declined comment. Wyeth, of Madison, N.J., has since sold its interest in the drug. In its court filings, Wyeth noted that the drug's label mentioned both the risk of tardive dyskinesia and that the drug is recommended for short-term therapy. In a court filing, Herman has disputed Baker's lawsuit.

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The national prescription data that Knight Ridder examined reveal the startling breadth of off-label prescribing. Virtually every drug has been prescribed that way at some point, and many are regularly.

Dr. Nancy Nielsen, an elected official of the American Medical Association, doesn't think doctors have been "cavalier" about it. "They have been in meetings," she said. "They know it works."

But individual doctors and patients aren't in a good position to gauge the safety or effectiveness of off-label treatments, experts say. Even in the busiest of practices, doctors see too few patients to assess the drugs' range of side effects. They also have no way of knowing whether the drugs are working, if it's a placebo effect or whether the patients simply got better on their own.

Medical history is filled with examples of doctors who were convinced that an off-label therapy was safe and effective, only to be proven disastrously wrong.

Often, they based their certainty on secondhand anecdotes, small published studies or observations from their own practices. Off-label prescribing can continue for years before a thorough clinical trial finds it's ineffective or even dangerous. Often such trials are never done.

In the 1990s, there was Fen-Phen, an unapproved cocktail of two prescription appetite suppressants that was widely prescribed until 1997, when the Mayo Clinic noticed that some Fen-Phen patients were suffering from a rare heart-valve disease.

More recently, there was the rampant off-label prescribing of hormone replacements. Though they were approved for treating specific menopause symptoms, such as hot flashes, doctors put millions of women on the drugs for life. They believed hormones would prevent heart disease, breast cancer and Alzheimer's disease, uses the FDA hadn't approved. They even started women on the drugs years after they had gone through menopause.

A massive government-run study, the Women's Health Initiative, found that hormone replacement therapy actually increases a woman's risk of getting these diseases.

Many doctors don't believe the findings, theorizing that the study's outcome would have been different if the women in it had started hormone therapy ear-

Steps to off-Label

How a prescription drug approved for one illness becomes popular with doctors for treating others:

STEP 1
Drug is born

- Drug company identifies potential uses for new drug.
- It conducts large-scale clinical trials.
- It submits application to the U.S. Food and Drug Administration for one or two uses most likely to get approval.

STEP 2
Protecting Other Uses

- Company applies for patents, saying drug is effective for many uses beyond those approved by the FDA

STEP 3
Fueling Interest

- Company funds research of unapproved uses.
- Small, scientifically inconclusive studies are published in medical journals.

STEP 4
Convincing doctors

- Medical conference speakers, sometimes paid by drug firms, teach doctors about potential off-label uses.
- Doctors discuss such uses, and outcomes with one another.
- Companies sometimes push off-label uses, even though FDA prohibits it.

SOURCE: KNIGHT RIDDER RESEARCH

A file family photo of George Murphy taken in June 2002 shows how fit he was shortly before taking Risperdal.

The scope of off-label prescribing

Prescriptions written each year for uses not approved by the FDA for the top three drugs in 15 of the top-selling drug classes and some of their off-label uses, Aug. 2002-July 2003:

Drug class	Percent off-label prescriptions	Number of off-label prescriptions, in millions	Examples of off-label uses
Anti-seizure medications	74%	18.6	*Migraines, depression, nerve pain, hot flashes, weight loss*
Antipsychotics	60%	12	*Alzheimer's disease, attention deficit disorder, insomnia, autism*
Antibiotics	41%	15.1	*Viral and unapproved bacterial infections*
Antidepressants	40%	12.4	*Chronic pain syndrome, attention deficit hyperactivity disorder*
Quinolone antibiotics	38%	10.1	*Viral and unapproved bacterial infections*
Proton pump inhibitors (stomach acid)	21%	10.5	*Difficulty swallowing, hernia, pancreatitis*
SSRI/SNRI antidepressants	20%	12.7	*Pain, premature ejaculation, alcoholism, menopause symptoms*
Antihistamines	19%	9.1	*Ear infections/disorders, upper respiratory infections, asthma*
Cox-2 arthritis drugs	17%	7.7	*Chronic back pain, gout*
Beta blockers (high blood pressure)	16%	13.1	*Overactive thyroid, migraines, heart rhythm disorders, anxiety*
Birth-control pills	11%	3.3	*Ovarian cysts, menstrual disorders, hormone replacement*
ACE inhibitors (high blood pressure)	11%	5.8	*Kidney disorders, leg cramps*
Calcium channel blockers (heart disease)	10%	4.5	*Unapproved heart conditions, migraine, cluster headache*
Cholesterol lowering drugs	4%	3.5	*Irregular heart rhythms, kidney disorders*
Diabetes medications	3%	0.4	*Kidney disorders, high blood pressure*

Source: Knight Ridder analysis of prescribing data from Verispan's Physician Drug and Diagnosis Audit and its Source Prescription Audit
Graphic: Lee Hulteng, Judy Treible

How to find out if you are taking a drug 'off-label'

To find out if you're taking a drug for an unapproved or "off-label" purpose, ask your doctor or pharmacist. Or you can read the drug's Food and Drug Administration-approved prescribing information, called its label. A copy is available from your pharmacist, or you can look it up on the Web or at the library in the Physicians' Desk Reference.

Be prepared to wade through tiny type and medical jargon. But you can learn a lot by focusing on a few sections:

Indications and usage: What the drug is approved to treat.

Contraindications: When the drug should not be used.

Warnings and precautions: Just what it sounds like — serious issues for people taking the drug. Warnings emphasized with a black box around them are the most serious of those the FDA issues.

Adverse reactions: Information about side effects, often with details about what percentage of patients experience them.

Drug interactions: Explains what other medicines may cause problems if taken with the drug.

RISKY Rx

CHUCK KENNEDY/KRT

Glenna Baker, with mother Joyce in the background, at her home in Burke, Virginia. Baker suffers from tardive dyskinesia. Today, she is out of work; the tremors make holding a job impossible.

lier and had taken it longer.

Despite decades of off-label prescribing, drug makers universally deny that they push these uses at doctors.

"We don't track what you're calling prescribing for unapproved uses," said Doug Petkus, a spokesman for Wyeth, which makes an antidepressant in the Knight Ridder analysis as well as hormone replacement therapy. "We don't recommend that our products be used off-label."

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Once it's on the market, a drug might be prescribed for a dozen or more unapproved conditions.

The FDA approved Topamax in 1996 as a supplemental treatment for epilepsy.

It has several potentially serious side effects. It often causes numbness and tingling in the hands and feet. It can cause depression and kidney stones. It can slow the thinking of many patients, impairing memory and making it difficult to choose words. It can cause vision problems, including a form of glaucoma that can result in blindness.

To stop epileptic seizures, the FDA deemed these risks acceptable.

Knight Ridder's analysis of the last year of prescription data for Topamax found that doctors are giving it to patients for migraine headaches, schizophrenia, bipolar disorder, depression, pain, nerve damage and to help them lose weight.

In 1998, Topamax was prescribed only for epileptic seizures, the data show. Now, 79 percent of Topamax prescriptions are for illnesses and conditions that the drug hasn't been approved to treat, Knight Ridder's analysis found. The firm has asked the FDA to approve its use for migraines.

Carolyn Bartley nearly went blind in June 2000, a week after she began taking Topamax, which her psychiatrist prescribed as a treatment for bipolar, a disorder characterized by bouts of depression and mania.

"Everywhere I looked, it was like a watercolor painting, and somebody had smeared it," said the 44-year-old Annapolis, Md., bookkeeper. Laser surgery reduced the pressure in both eyes and restored her sight. In 2001, the maker of Topamax sent a letter to doctors warning about the kind of sudden glaucoma Bartley experienced.

Bartley's psychiatrist, Dr. Parviz Sahandy, said he hadn't researched the medical literature on Topamax, but that he considered it effective for bipolar disorder about 50 percent of the time.

Those who've read the studies are less certain.

"Topamax is no better than a placebo," said Dr. Joseph Goldberg, a research scientist at Zucker Hillside Hospital on Long Island, N.Y., who published a review of epilepsy drugs as treatments for bipolar disorder earlier this year while at Cornell University. "It's giving an ineffective treatment for a potentially life-threatening illness. It would be like giving Tylenol for pneumonia."

Goldberg said that even studies by the drug's maker, Johnson & Johnson, found it didn't work to treat bipolar disorder. As a result, company spokeswoman Lesley Fishman said, the drug maker didn't seek FDA approval for treating that condition.

Over the last year, doctors wrote 586,000 Topamax prescriptions to treat bipolar disorder, Knight Ridder found.

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The terbutaline pump therapy prescribed for Tammie Snyder in suburban Detroit last year is one of many off-label drug treatments doctors use in an attempt to stop preterm labor.

Nearly 500,000 babies are born prematurely each year, but the causes and cures for preterm birth largely elude science. Most of the treatments are based on hope and a desperate desire to try something.

Dr. John Thorp Jr. was part of a research team for the federal government's Agency for Healthcare Research and Quality that reviewed the scientific evidence for terbutaline and a host of other drugs in preventing preterm labor.

Their report, published in June, found that the drugs weren't effective in prolonging pregnancy for a long term and can cause a wide range of harms, including heart-rhythm disorders and heart failure.

"There really is no evidence," Thorp said, noting that early contractions stop without any medical intervention 50 to 70 percent of the time.

Nonetheless, women across the country are taking these drugs that doctors know very little about.

"I think experiment is too good a word," said Thorp, a professor of obstetrics at the University of North Carolina at Chapel Hill. "It implies observation, measurement, alteration — that you're actually conducting science. Clinical crap-shoot would probably be better."

The best use of terbutaline is a series of three injections to calm contractions for about 48 hours or so, enough time to administer steroids to help the babies' underdeveloped lungs, said Dr. Washington C. Hill, the chairman of obstetrics and gynecology at Sarasota Memorial Hospital in Florida and a member of the board of directors of the national Society for Maternal-Fetal Medicine.

GRANT JEFFERIES/ BRADENTON HERALD

Dr. Washington C. Hill

But doctors still send women home with long-term prescriptions for terbutaline pills. If they were candid, Hill said, those doctors would admit: "I know it doesn't work, but it cuts down on the phone calls."

Last year, 63 percent of the more than 392,000 prescriptions for terbutaline pills were for pregnant women, despite pharmaceutical company labels that warn against the asthma drug being used this way.

While many doctors and mothers passionately believe in the treatments, especially in the terbutaline pump, the national company that is the largest provider of the therapy is ambivalent.

Dr. Gary Stanziano, the vice president for medical affairs at Matria Healthcare, based in Marietta, Ga., said he had no opinion about whether the therapy his company sold for about $10,000 a month worked. "There are studies out there that are positive and studies out there that are negative," Stanziano said.

Stanziano and Roberta McCaw, Matria general counsel, said their company is in the business of following doctors' orders, since physicians are the ones who write prescriptions for terbutaline pumps. Matria is a middleman, supplying the drug and pumps, then having its nurses hook up the women to the devices and monitor their progress. Stanziano wouldn't say how many women use Matria's pump therapy each year, but said he hadn't heard of any client who had been seriously harmed.

In 1997, however, the FDA warned U.S. doctors that the terbutaline pump "has not been demonstrated to be effective and is potentially dangerous." Four years earlier, the FDA had warned Tokos Medical Corp., one of the two companies that merged to become Matria, about promoting unapproved preterm-labor therapies despite promises to stop.

"This case could be viewed as a conspiracy to circumvent the FDA approval process," an FDA compliance officer wrote in a memo that year.

Matria officials said they had no information about this, because it happened before the merger. They said Matria doesn't promote the off-label use of terbutaline to doctors.

Snyder said she felt betrayed by her obstetrician, Dr. Federico Mariona, a clinical professor at Wayne State University in Detroit and a leader in the local medical societies. Mariona didn't respond to repeated requests for an interview.

Snyder's medical records from Matria include signed consent forms that say, among other things, that some of the treatments being prescribed by her doctor may involve the use of drugs "outside of their labeling." Only after having congestive heart failure, Snyder said, did she learn what those cryptic words meant.

Dr. Federico Mariona put Tammie Snyder on a terbutaline pump to prevent preterm labor. That use is not approved by the FDA.

While her heart has improved enough that she doesn't need a transplant, Snyder, 30, said her doctors had told her she couldn't have more children; pregnancy would be too dangerous for her heart.

Snyder and her husband, Chris, had wanted to have more children. Because they used in vitro fertilization to have their twins, they have other frozen embryos.

Now, those embryos remain in limbo.

"I hate terbutaline. I hate what they did," Chris Snyder said.

Knight Ridder Newspapers Researcher Tish Wells contributed to this report.

Epilepsy drug for bipolar disorder

After Topamax was approved by the FDA in 1996, doctors prescribed it only to treat epilepsy, its approved use. Now 79 percent of sales are for unapproved, or off-label, conditions.

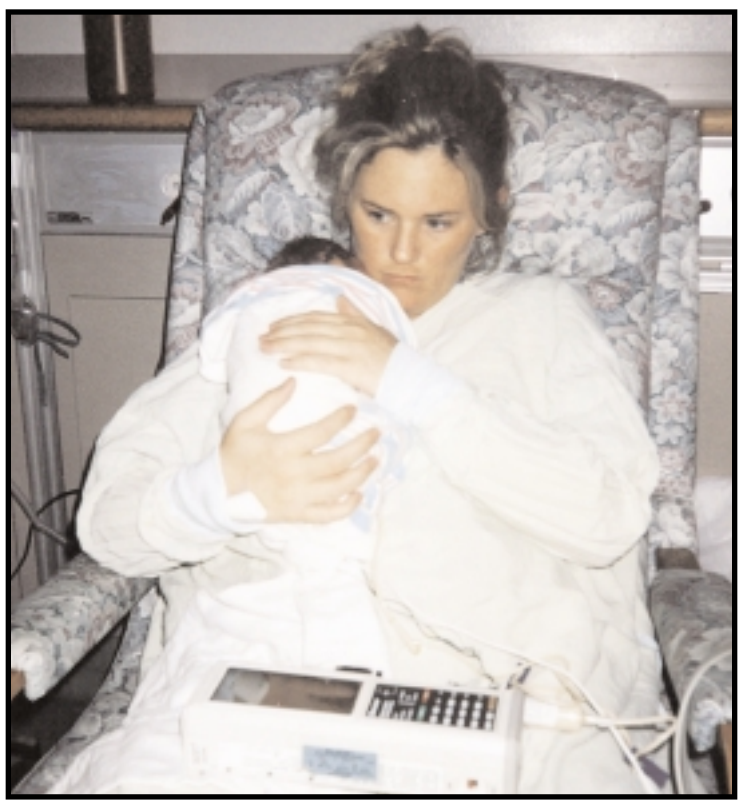
Topamax prescriptions for one year, Aug. 2002-July 2003*

Migraine/headache**	1.9 million	45%
Epilepsy/seizure	890,000	21%
Bipolar disorder	586,000	14%
Neuropathy (nerve disorder)	102,700	2%
Schizophrenia	89,900	2%
Depressive psychosis	85,600	2%
Tremors	85,600	2%
Post-traumatic stress	81,300	2%
Anxiety, weight loss, other	415,000	10%

*Estimates based on survey of doctors. National prescription estimates for diagnoses other than migraine/headache, epilepsy/seizure and bipolar disorder are subject to a higher level of sampling error.

**Johnson & Johnson has applied for FDA approval for migraine

Source: Knight Ridder analysis of prescribing data from Verispan's Physician Drug and Diagnosis Audit and its Source Prescription Audit
Graphic: Judy Treible, Lee Hulteng



In this family photograph Tammie Snyder holds one of her newborn daughters in the hospital and reacts to the news that she has congestive heart failure and may need a heart transplant because of the terbutaline she was prescribed.

How the Risky Rx drugs series was done

Knight Ridder's investigative series is based on dozens of interviews with patients, doctors, researchers and drug companies, and the review of thousands of records from lawsuits, government hearings and regulatory actions, medical records and scientific studies.

To calculate how often drugs are prescribed off-label, Knight Ridder purchased and reviewed prescribing data routinely used by the pharmaceutical industry. Verispan of Yardley, Pa., collects the data from a monthly survey of 3,400 doctors with office-based practices.

Knight Ridder analyzed the three top-selling drugs in 15 classes of medications, comparing what doctors said they prescribed them for with the FDA's approval for each. The analysis looked at 900 million prescriptions written in 1998 and 2003 for more than 1,000 different ailments. Its estimate of the prevalence of off-label prescribing excluded cancer treatments or pediatric off-label uses, because they already are known to have a large percentage of off-label use. When calculating whether off-label prescribing had grown over the last five years, the study considered only the 31 drugs that had been on the market the entire time.

Prescribing data are for the 12 months ending July 31; sales figures are for the 12 months ending Aug. 31.

The analysis is perhaps the most comprehensive ever done of off-label prescribing.

While various reports have quoted the American Medical Association as estimating that 50 percent of drugs are prescribed off-label, an association representative said that figure was a misinterpretation of a remark an official made years ago and that it has no good estimate. Knight Ridder's analysis found that 21 percent of the prescriptions examined were for off-label uses, and that some of the drugs had off-label uses as high as 90 percent.

To estimate how often patients are harmed by this practice, Knight Ridder reviewed the FDA's database of adverse drug reactions. The FDA estimates that only 1 to 10 percent of reactions are reported. Knight Ridder identified more than 800 reports filed during 2002 of serious reactions involving off-label prescriptions for its sample of 45 drugs. Experts say that means anywhere from 8,000 to 80,000 people probably were affected.

For detailed information about the drugs in the Knight Ridder analysis, go to www.krwashington.com.

Drug-makers' promotions boost off-label use by doctors

By Chris Adams and Alison Young
Knight Ridder Newspapers

SHAUN HEASLEY/KRT

Amby Cole, of Brighton, Tenn., gets emotional talking about husband Milton's death. Milton Cole killed himself in June 2001 after being prescribed the antidepressant Prozac for chest pain.

MEMPHIS, Tenn. — Dr. Gary Murray, a cardiologist, was faced with a common medical dilemma: He had no idea what was wrong with his patient.

Milton Cole, a 71-year-old man in generally good health, was complaining of chest pains. A battery of cardiac tests couldn't pinpoint the problem. To blunt the pain, Murray gave his patient a prescription and some free samples of the drug.

The drug Murray prescribed was Prozac, a popular antidepressant that isn't approved by the Food and Drug Administration for treating chest pain. Murray later said he had no idea that experts had debated for years whether Prozac caused suicide.

Thirteen days after that visit to the doctor, on June 28, 2001, Cole's wife, Amby, found him hanging from a beam in a back room of their shop.

"This was a patient of mine and I was trying to help him," Murray recalled. "I'm completely upset. ... I'll be that way forever."

That a heart specialist even had free supplies of a drug that's usually the province of psychiatrists says a lot about how drug marketing today encourages physicians to prescribe medications for unapproved, or off-label, uses.

By offering specialty drugs to non-specialists, sending salesmen to doctors' offices and medical conventions, and touting their drugs' benefits on the slimmest of evidence, pharmaceutical companies have sent off-label retail sales soaring.

Off-label sales of the top-selling drugs Knight Ridder studied hit $12.9 billion in the last year, producing nearly a quarter of those drugs' retail sales.

With an aging population, a shift to drug-based health care and the prospect of a massive government prescription-insurance plan, prescriptions for unapproved uses are only likely to accelerate.

Promoting this growth is a symbiotic relationship between physician and drug makers in which sales representatives routinely target doctors untrained in the basics of drug therapy and with little time, inclination or independent information to assess a medication's usefulness or its risks.

Consider this courtroom conversation involving a lawyer representing Schering-Plough Corp., the mammoth U.S. drug maker.

A quizzical U.S. District Judge Lawrence McKenna of New York asked whether doctors "in any significant number" really based their opinions about drugs on pitches from sales reps.

"Yes, your honor," said Gregory Diskant, Schering-Plough's outside attorney.

"That's scary, isn't it?" the judge asked.

"It is scary. It is scary, but it is true," Diskant said. "You know what the truth is? ... (Sales calls) are the quickest, easiest way for the doctor to learn about the drug. ...It is a dangerous, largely unregulated phenomena in the wrong hands."

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The day Cole came in for his checkup, Murray had a drug closet stocked with dozens of medicines that cardiologists commonly prescribe, as well as some that general practitioners and other specialists use.

With little to go on beyond Cole's complaints of chest pain, Murray said, he had a choice between doing nothing and attempting to ease his patient's pain.

"I chose Prozac probably because I had samples of it," he said in an interview. "I thought it was a pretty harmless thing to do."

The FDA has approved Prozac to treat depression, panic, obsessive-compulsive disorder and an eating disorder, but not pain.

Murray didn't think Cole was depressed. The Brighton, Tenn., resident was upbeat, busy with friends and church, preparing for a new grandchild and a new house.

Doctors have prescribed antidepressants off-label for years to manage chronic pain, and as far as Murray knew, Prozac didn't have any serious side effects. He said he had never heard it might cause suicide. Articles debating the issue were published primarily in psychiatric journals throughout the 1990s.

A Knight Ridder analysis of government data found that over the last decade, 40 percent of Prozac prescriptions were written by nonpsychiatrists. Over the past year, 500,000 Prozac prescriptions were for off-label uses.

Prozac didn't help Cole's chest pain.

Soon, he complained of feeling jittery. His fingers tingled; he became easily aggravated. Days later, he hanged himself.

Amby Cole recounted the day she found him, describing how she rubbed her dead husband's neck where the rope had hurt him. "It was just horrible," she said, her hands trembling.

She blames drug maker Eli Lilly for not warning that Prozac can cause suicide, and her lawyer, Andy Vickery of Houston, has accused Lilly of overpromoting Prozac to nonpsychiatrists. Lilly settled the case earlier this year. The amount is confidential.

Vickery said it was his third settlement with Lilly over Prozac-suicide cases and off-label uses. Patients in the other two cases were given Prozac to treat migraines and for Tourette's syndrome, a neurological condition that produces uncontrollable tics.

Lilly officials said they had settled some lawsuits for economic reasons, but wouldn't comment on specifics. A spokeswoman, Tarra Ryker, said Lilly "does not condone or encourage off-label use of any of our medications, including Prozac."

The company long has contended that depression causes suicide, not Prozac. Even so, U.S. and British regulators warned last summer that Paxil, a drug in the same class as Prozac, may increase the suicide risk for children and adolescents, thus reviving the debate that has simmered for a decade. Ryker said this had no bearing on Prozac.

Murray still prescribes Prozac for pain, but now he warns patients of possible psychiatric side effects.

■ ■ ■

Federal law prohibits drug makers from advertising or promoting off-label drug uses, and since 1998 the FDA has cited companies nearly 70 times for improperly promoting their drugs that way, a review of its records shows.

Yet off-label promotions are commonplace, as was alleged in a recent whistleblower lawsuit against a company that's now part of Pfizer Inc. A former employee of the drug company said it employed a range of tactics to boost off-label sales of the epilepsy drug Neurontin. The widely reported case is pending.

Getting around FDA marketing rules isn't difficult. The agency acknowledges that it's impossible to police the millions of conversations between drug companies and doctors.

At the annual conference of the American Academy of Pain Management this summer at the Adam's Mark hotel in downtown Denver, 75 makers of drugs, medical devices and dietary supplements staffed sales booths, beckoning doctors with trinkets, slick promotional brochures, medical journal articles, even stopwatches.

At the Merck & Co. booth, Connie Mack said Vioxx, the blockbuster arthritis drug, was approved for certain types of pain. Then without prompting, Mack added: "They are using it pre-emptively, too," such as before surgery, she said. No, it's not approved that way, she said, but Merck could send some additional information. "They actually have a whole database now on pre-emptive use," she said.

At the Allergan Inc. booth, a representative described an approved use for Botox. She then volunteered, "There are physicians who have been using it off-label for lower back pain and migraine pain. That's all off-label." Asked about research to support such uses, she said, "there are no major gold-standard studies, but the physician community has been using it. ... They're telling us it is effective." She offered to send more information.

One of the biggest booths was for Cephalon Inc., based outside Philadelphia. Two big signs pitched Gabitril, a drug approved only to treat seizures. Four sales representatives in blue blazers answered questions.

Why, one was asked, was an epilepsy drug being hawked at a conference for pain doctors? "Most of the anti-epileptics have multiple other uses," replied Cephalon's Janeen Morgan.

Cephalon relies more on off-label sales than other companies. A Wall Street analyst touted "significant opportunities for off-label sales" as a reason to be bullish on the company, and Cephalon at times has aggressively marketed its drugs off-label; a 2002 letter from the FDA cited the company for making "misleading claims" about a "variety of unapproved uses" for another of its drugs, Provigil.

The company's messages apparently got through to doctors.

In Maine, for example, state Medicaid officials in 2002 noticed a growing amount of Provigil use.

Although approved at the time only for patients with narcolepsy, a disorder associated with feelings of pronounced sleepiness, Medicaid officials were receiving claims for its use to treat multiple sclerosis fatigue, attention deficit disorder, depression and "miscellaneous fatigue."

The Medicaid claims topped $1 million, with one doctor responsible for $370,000 of them, state records show.

From 2000 to 2003, 60 percent of Cephalon's sales were of Gabitril or Provigil, two drugs for which the majority of the written prescriptions are off-label. According to the prescription data that Knight Ridder analyzed, 88 percent of Gabitril's retail sales were off-label over the last year.

Cephalon has told the Securities and Exchange Commission that the "market for the approved indications of two of our three largest products is relatively small."

Even as the company begins to study whether Gabitril works for pain, tens of thousands of prescriptions for that use were filled in the last year, Knight Ridder's analysis showed.

Michael Fielder of Kansas City, Mo., said he'd taken Gabitril for the last 18 months to curb the pain of sickle cell anemia, a debilitating blood disorder. He got relief only after his doctor added morphine to the mix.

When asked for evidence that their drug may be useful for pain, Cephalon officials cited five studies — four of them with 10 or fewer patients.

Fielder is still taking Gabitril, because, he said, his doctor believes it helps. Over the years, doctors have given him Neurontin, another epilepsy drug, and Paxil, the antidepressant, for pain. None of them worked well, he said.

"When they try out something new, sometimes I don't think the doctors know if what they are using works," Fielder, 27, said recently.

■ ■ ■

Court records contain dozens of comments by some of the government's top health experts about doctors and prescription drugs. Many of them aren't flattering. The assessments about off-label prescribing are worse.

Robert J. Temple, a top official in the FDA's drug division, said in a court deposition in 1996: "I certainly believe in their good faith. I think they are trying. I don't believe that they necessarily have a capacity to get it right."

The FDA's lawyers said in a 1998 brief: "While physicians may believe that they are in a better position than FDA to evaluate off-label claims, both the evidence and the law say otherwise. ... Physicians tend to have confidence in their own ability to critically assess off-label information. The studies demonstrate, however, that such confidence is often unwarranted and incorrect."

Michael Wilkes, the vice dean of the medical school at the University of California, Davis, doesn't think that's surprising.

"I think it is embarrassing that so much of our practice is prescribing drugs and it's a joke how little our students and residents know about pharmacology," he said. "And once you graduate, how does a doctor learn about new medicines? It's from the pharmaceutical companies."

Wilkes, who studied the issue of off-label promotion for the FDA in the late 1990s, pointed to two rigorous studies that concluded that doctors — despite their protestations to the contrary — are swayed by pharmaceutical promotions.

"What gets marketed hard is what gets prescribed," said Jay Cohen, an adjunct associate professor of family and preventative medicine at the University of California-San Diego.

The marketing is massive.

Over the last decade, the number of drug company sales reps has more than doubled to 94,000, one for every seven doctors in the nation. In 2002, the value of the free drug samples passed out to physicians reached $11.9 billion, up more than 140 percent since 1996.

At the same time, pharmaceutical companies' spending for advertising in the traditional medical journals fell, according to IMS Health, a medical-data company.

In addition, there's evidence that when the FDA tries to get doctors' attention, they pay little heed.

Since 1990, 16 drugs have been pulled from the market for safety reasons. A review of FDA and other records shows that 11 of those were yanked, in part, because physicians didn't follow label instructions or disregarded the FDA's warnings.

Nonetheless, many physicians continue to think their practices are the best places to assess the worth and risks of prescription drugs.

Dr. Wasim Niazi, a neurologist from Rockledge, Fla., is a fan of Topamax, an epilepsy drug that's widely prescribed for conditions the FDA didn't approve it to treat. Niazi said Topamax had become the most-prescribed drug in his practice. He said he had hundreds of patients on it and wrote 10 new prescriptions a day.

While he also prescribes it for epilepsy, Niazi said, he mostly uses it to treat pain and migraines. He's also given it for tremors and to assist with weight loss. He considers it effective for all these uses, if his patient can tolerate the side effects.

Niazi said the basis for his prescribing of Topamax was his own clinical experience and what he'd learned from other doctors. What studies say about its usefulness means little to him. "Most of the literature is garbage driven by the economics," he said. And he's dismissive of clinical trials that are contrary to his own observations. "The real world is different than trials."

■ ■ ■

At first glance, the results of a clinical study of Evista, an Eli Lilly osteoporosis drug, looked promising. Among other things, researchers noticed slightly fewer breast cancers among women who took Evista versus those who were given sugar pills.

As baby boomers age, that could mean the makings of a blockbuster drug.

Unfortunately for Lilly, cancer experts didn't think the numbers meant much.

On May 18, 1998, Eli Lilly convened a focus group of doctors who were attending the American Society of Clinical Oncology annual meeting. Shown the Evista breast cancer data, they responded that the study was too small, the time frame too short and the risk of patients having strokes too great.

Promoting the drug to prevent breast cancer would be "an egregious stretch," one doctor said. It also was called an attempt to "cash in on a byproduct of the study." A proper study to measure breast cancer prevention "should last at least 10 years, preferably 20," doctors said, according to the company's meeting notes.

Even so, the cancer physicians feared that primary-care and women's-health doctors would prescribe Evista for breast cancer prevention anyway.

A month later, Lilly conducted a different survey, this one of 341 primary-care physicians and women's-health doctors. The company tested various advertising messages about Evista, finding that "PCPs are more promising . . . indicate they will put more patients on Evista . . . and think the breast cancer data is more compelling."

Although the FDA had told the company it found "critical problems" with the Evista study and didn't approve the drug for preventing breast cancer, according to FDA records, it allowed Lilly to make a minor change in the drug's label. The company inserted three sentences that detailed the precise numbers of breast cancer cases from the study as well as the following: "The effectiveness of (Evista) in reducing the risk of breast cancer has not been established."

That was all Lilly needed to do. Company officials got the word to 1,000 sales representatives. In its plan "Maximizing the Breast Cancer Label Change," it scripted answers to deal with expected concerns, including the "relatively small number of cases" in its study.

The new sales strategy irked one of Lilly's competitors, now known as AstraZeneca PLC, the maker of tamoxifen, which the FDA has approved to prevent breast cancer.

The British company did its own survey of primary-care and women's-health doctors and found that nearly 65 percent of them learned about Evista from sales reps, not the medical literature. Another survey showed that 22 percent thought Evista was FDA-approved for preventing breast cancer. Many already were prescribing it that way.

AstraZeneca took the case to court, demanding that Lilly stop such practices and divulge the "call notes" its sales representatives wrote after visits to doctors. The case was settled, and the details are confidential. Evista someday may prove to be good for preventing breast cancer, although Lilly said it was at least two years away from completing the study that may allow it to apply to the FDA for such a use.

As for those call notes, some were illuminating.

"Told MD about the new indication of EV to prevent breast cancer," one sales rep wrote in December 1998.

One physician told the sales rep he was "extremely excited about the breast data!! Said that if his wife were eligible, he would put her on Evista."

"Sit down detail w/MD," another note read. "Went through entire Evista message w/disclaimer at first to let him know I could not talk about stuff that was off label unless he asked questions first. It worked. He asked all about breast cancer."

Knight Ridder Newspapers Researcher Tish Wells contributed to this report.

Questions to ask your doctor about off-label prescriptions

If your doctor has prescribed a drug for a purpose that the Food and Drug Administration hasn't approved, find out why. Here are some questions to ask:

What is the doctor's reason for prescribing the off-label treatment? Has the doctor researched the medical literature and does it support this use with large, controlled clinical trials? If not, what is the evidence for this use?

Are there FDA-approved alternatives? Why aren't they being prescribed instead?

All drugs carry risks of side effects, some more than others. Ask your doctor: Do I really need this prescription? What are the alternatives to this therapy? What are the risks and benefits? What is the lowest dose and shortest period I can take this drug?

Educate yourself about all side effects. Don't rely on the leaflet your pharmacy provides; it may be incomplete. Detailed information about side effects is in the drug's FDA-approved label, available at pharmacies or on the Web.

SHAUN HEASLEY/KRT

Cardiologist Gary Murray poses in front of the drug closet, where drug samples are stored at his practice in Memphis, Tennessee. Among the available drugs is the antidepressant Prozac, which Milton Cole (left) was prescribed as an off-label treatment for chest pain. Cole killed himself after just weeks on the medication.

Big money from off-label drugs

Percent of prescriptions written for uses not approved by the FDA for some top-selling drugs and resulting retail sales:

Drug name (class)	Off-label prescriptions	Off-label sales
Neurontin (anti-seizure)	90%	$1.8 billion
Topamax (anti-seizure)	79%	$643 million
Seroquel (antipsychotic)	78%	$778 million
Risperdal (antipsychotic)	65%	$929 million
Bextra (arthritis)	62%	$502 million
Biaxin XL* (antibiotic)	58%	$173 million
Avelox (quinolone antibiotic)	56%	$128 million
Trazodone HCL (antidepressant)	56%	$120 million
Remeron (antidepressant)	46%	$93 million
Zithromax Suspn. (antibiotic)	45%	$149 million
Zyprexa (antipsychotic)	42%	$913 million
Levaquin (quinolone antibiotic)	42%	$446 million
Zithromax Z-Pak (antibiotic)	37%	$409 million
Cipro (quinolone antibiotic)	30%	$291 million
Wellbutrin SR (antidepressant)	27%	$464 million
Depakote (anti-seizure)	25%	$162 million
Yasmin 28 (birth control)	25%	$46 million

*Abbott Laboratories attributes some of these off-label figures to possible coding errors; Biaxin is approved for acute sinusitis, but 22 percent of the drug's prescriptions were for chronic sinusitis. If all of the chronic cases were miscoded, the off-label percentage would drop to 35 percent.

Source: Knight Ridder analysis of Verispan's Physician Drug and Diagnosis Audit and its Source Prescription Audit for the most recent 12 months available
Graphic: Todd Lindeman, Judy Treible

CHRISTIAN MURDOCH/COLORADO SPRINGS GAZETTE

Above, Scott Murray of Cephalon Inc. talks to a doctor during the annual meeting of the American Academy of Pain Management in Denver, Colorado. Right, Amy Jordheim, also of Cephalon talks to Kim Uptergrove, far right, a clinical nurse and pain management specialist at Memorial Hospital in Colorado Springs.

Regulating prescription drugs

How the U.S. government has tried to keep unsafe drugs off the market:

1906: Congress passes Pure Food and Drug Act after revelations of worthless, dangerous cure-alls; Bureau of Chemistry formed, later called Food and Drug Administration

1937: Elixir Sulfanilamide, drug with lethal solvent, kills 107; highlights need for stronger drug laws

1938: Food, Drug and Cosmetic Act passes; new drugs must be shown safe before marketing

1962: Thalidomide, a morning sickness drug not yet approved in U.S., causes many birth defects in Europe; Congress says new drugs also must be proven effective

1970s: FDA checks effectiveness of more than 3,000 drugs on the market before 1962 law; one-third found to be useless

1989: National Institutes of Health study shows off-label prescribing of two heart drugs increases deaths; 1990 survey shows many doctors still prescribing these drugs off-label

1990s: FDA Commissioner David Kessler cracks down on off-label drug marketing; doctors, drug makers object; effort bogs down in court

1993: Effort by FDA to get American Medical Association, other medical societies to report well-researched off-label uses for inclusion on drug labels yields few results

1997: Amid reports of heart damage, FDA pulls half of off-label diet drug combo Fen-Phen off market due to "unacceptable risk"

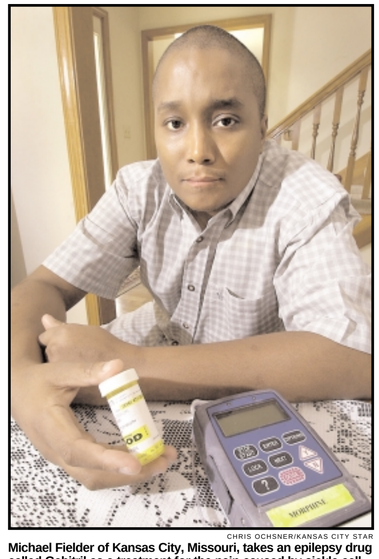
2002: NIH's Women's Health Initiative study finds off-label use of hormone replacement therapy potentially harmful; millions of women taking HRT at risk

2002: After court challenges, FDA considers relaxing rules against promoting off-label drug uses

SOURCE: U.S. FOOD AND DRUG ADMINISTRATION, KNIGHT RIDDER WASHINGTON BUREAU

CHUCK KENNEDY/KRT

David Kessler



CHRIS OCHSNER/KANSAS CITY STAR

Michael Fielder of Kansas City, Missouri, takes an epilepsy drug called Gabitril as a treatment for the pain caused by sickle cell anemia even though this use of the drug lacks FDA approval.

RISKY Rx

Off-label drugs slip through FDA safety net

By Chris Adams and Alison Young
Knight Ridder Newspapers

WASHINGTON — In 1962, a Congress horrified that thousands of European babies had been deformed by the medication thalidomide ordered the Food and Drug Administration to make sure the same thing never happened in America.

Congress gave the FDA the power to assess the safety and effectiveness of all drugs before they could be sold on the U.S. market.

Forty years later, however, an ever-growing segment of the American pharmaceutical business is eluding that rigorous scrutiny. Millions of patients are being given drugs by their doctors that the FDA hasn't approved for treating their particular illnesses. Off-label prescribing, as it's called, puts patients at risk while offering no assurance the drugs will work.

And while the FDA has argued in court that the "risk to the public from unproven uses of drugs and devices is both real and substantial," the agency rarely has tried to curb it. When it attempted to do so in the 1990s, its efforts fizzled.

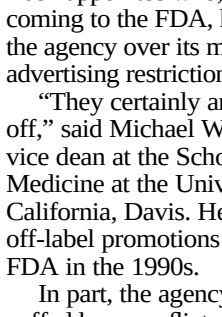
Now as the phenomenon soars — Knight Ridder found that off-label prescribing for a sample of top-selling drugs has nearly doubled in the last five years — the Bush administration has opened the door to doing even less to stop it.

Saying recent court rulings have eroded its power, the FDA has sought public comment on whether drug makers should have more leeway to market the unapproved uses of their profitable drugs. Overseeing the effort is a Bush appointee who, before coming to the FDA, helped sue the agency over its marketing and advertising restrictions.

"They certainly are backing off," said Michael Wilkes, the vice dean at the School of Medicine at the University of California, Davis. He studied off-label promotions for the FDA in the 1990s.

In part, the agency is handcuffed by a conflicted mandate from Congress. The FDA is trying to do many things: Get powerful drugs to market while protecting the public, respect the First Amendment while regulating drug advertising and let doctors practice as they see fit — except when they make dumb errors. Given the rapidly growing number of drugs in the marketplace, prescribing is far more complicated for doctors today.

"There's some limit to what the federal government should do, I think, because it's not going to be effective," said Dr. Janet Woodcock, the director of the FDA's drug division. "You can't just Band-Aid and patch something that has systemic, underlying problems."



Dr. Janet Woodcock

But it's also clear that the agency hasn't followed through on its limited efforts to reduce the risks of off-label drug sales:

■ Under FDA rules, if a drug maker knows a drug is being used for off-label purposes, it's required to come forward with evidence supporting those unapproved uses. FDA officials said in a court deposition that the rule had not been enforced.

■ After the FDA took a major drug company to court in 1993 and won a hefty payment for overt off-label sales pitches, its commissioner vowed to use such sanctions again to control illicit marketing. But FDA officials could point to no other case since then when they have.

■ Last year, the FDA issued 28 violation letters for improper drug marketing, down from 158 in 1998. The agency said it would need nearly twice as many people to adequately police the industry's 37,000 advertisements and other promotions each year.

■ Twenty-four years ago, the FDA said it wanted to ensure that patients got useful, easy-to-understand information about the drugs they took. Most still don't.

The bottom line for consumers: Beware.

JOYCE MARSHALL/FORT WORTH STAR-TELEGRAM

Martha Andreasen, of Bowie, Texas, lives with badly damaged lungs after taking the drug Pacerone. The drug, also called amiodarone, wasn't FDA-approved for her heart condition.

"We as patients have got to raise the questions ourselves and take care of our own selves," said Jere Goyan, who was FDA commissioner from 1979 to 1981.

■ ■ ■

The drug Kristen Pettijohn took was called Avelox. It's part of a family of antibiotics called fluoroquinolones.

Those powerful but risky drugs are intended for patients who are fighting particular bacterial bugs. But they're widely prescribed off-label for less serious illnesses, sometimes even to treat viruses, which can't be killed by antibiotics.

A study this year funded by the National Institutes of Health reviewed 100 emergency room prescriptions for fluoroquinolones and found that only 19 were written for appropriate conditions and only one was given in the correct dose and for the proper duration.

The FDA long has been aware of the possibility that Avelox could be misused.

Just before it approved Avelox in 1999, a member of the agency's expert review panel — Robert Danner, a critical care expert at the NIH — offered a warning: "This is exactly the kind of place that you get into trouble. ... I am absolutely convinced that the drug will be used differently once it's marketed frequently."

Avelox was approved, however, and marketed hard by Bayer Corp. In 1999 and 2001, the FDA admonished company officials for encouraging unapproved uses.

This past May, Pettijohn, a gregarious 23-year-old nursing student from Batesville, Ind., who recently had gotten engaged, picked up the persistent cold that had been running through her family. "Her version was a little worse than ours," said her father, Gary Pettijohn. "I would say it was moderate at best."

Early in the morning of May 15, Pettijohn's mother took her to an emergency room. Going there, Pettijohn told her mom, would be quicker than waiting for an appointment with their family physician.

Forty-two minutes later, Pettijohn was on her way to the drugstore. The doctor had diagnosed her with acute bronchitis and prescribed Avelox. The potent antibiotic's label says it's approved for cases of chronic, or long-term, bronchitis, and only after blood tests have been taken to identify the bacteria causing the problem. Her medical records show no blood work was done.

That was a Thursday. By Sunday, Pettijohn was nauseated and suffering abdominal pain. Her mother packed a plastic bag with the remaining Avelox pills and took her to the hospital.

Over the next five days, Pettijohn was incoherent. She had a burning rash and her skin began peeling off. She slipped into a coma, resting on an air bed, totally wrapped as though she were a severe burn patient.

By Wednesday, a doctor approached Gary and Ruth Pettijohn.

"Our problem just got twice as difficult," he said. "She has two life-threatening conditions simultaneously."

Pettijohn's liver was in full failure, and she was experiencing a form of Stevens-Johnson syndrome, a rare and extreme drug reaction mentioned on the Avelox label.

She had a liver transplant on Friday. The doctors reported that her old liver had turned to mush and fallen apart in their hands.

Soon after the operation, Pettijohn had a heart attack, then another. Her death certificate cited Avelox as the prime contributing factor in her death.

The hospital had no comment about her death. Bayer had no comment beyond saying the death "was promptly and accurately reported to the FDA," and that it thinks its antibiotic should be prescribed only for approved conditions.

■ ■ ■

As Congress reworked the nation's drug-safety laws after thalidomide, it sought to create a regulatory system that guaranteed that the drugs Americans used were safe and effective.

Lawmakers in 1962 worried that drug makers might be tempted to get a medication approved for one use and then promote it for others. "The initial claim would tend to be quite limited," said a group of senators led by the late Tennessee Democrat Estes Kefauver. "Thereafter, the sky would be the limit. ... Extreme claims of any kind could be made."

Congress told the FDA to require stringent tests before a drug could get to market. Once a drug passed, a company could advertise it only for the approved uses.

The FDA began reviewing all the drugs that had been on the market as of 1962, when the new approval rules kicked in. Of 3,443 drugs commonly prescribed, 1,124, or one-third, were deemed useless and taken off the market, FDA records show.

Even though that shows that doctors often can't judge drugs' effectiveness, the FDA largely has stayed out of the doctor's office.

The agency's rules say it can require a drug company to prove that an off-label use is safe and effective. The FDA has said that a drug's "actual use" by doctors can show a drug maker's "intent" in selling it.

However, asked in a lawsuit deposition in 1996 if the FDA had ever considered using the option of requiring proof of off-label effectiveness, the agency's Dr. Robert Temple replied: "We think about this all the time. ... We just don't know quite how to do it."

Knight Ridder found that the off-label use for some drugs is as high as 90 percent of all prescriptions sold for it.

Off-label uses became a concern in the 1990s, under the activist tenure of then-Commissioner David A. Kessler, who noted that "medical history is replete with examples of products and procedures that were based on medical anecdote, not evidence, and were thought for years by most clinicians to be effective, but later turned out to be useless and sometimes even dangerous."

In 1991, the FDA established a task force to examine off-label uses of drugs and medical devices.

The agency also found that drug companies often had no incentive to evaluate the merits of off-label prescribing because they might discover that their drugs didn't work when prescribed off-label and sales would suffer, according to a review of FDA records.

The drug makers, which are among the most profitable industries in the United States, know they can continue to get off-label

Do you have complete information on your prescription?

Sometimes FDA-approved labels are dramatically different from the information pharmacies give patients when they pick up prescriptions. Leaflet from Walgreens compared with the FDA-approved label for the heart drug Cordarone (amiodarone), which is often prescribed for off-label uses:

FDA-approved label

- **Uses:** "Because of its life-threatening side effects and the substantial management difficulties associated with its use ... Cordarone is indicated only for the treatment of the following documented, life-threatening recurrent ventricular arrhythmias" when other treatments have failed.
- **Warnings:** "Several potentially fatal toxicities, the most important of which is pulmonary toxicity ... at rates as high as 10 to 17 percent in some series of patients. ... Pulmonary toxicity has been fatal about 10 percent of the time ... every effort should be made to utilize alternative agents first."
- **Adverse reactions:** Are "very common" with the most serious being lung toxicity, a worsening of the arrhythmia and rare serious liver injury.

Walgreens leaflet

- **Uses:** "This medicine is an antiarrhythmic used to treat an irregular heartbeat. ... It may also be used to treat other conditions as determined by your doctor."
- **Cautions:** Chest X-rays and lung, liver, thyroid and eye tests "should be performed periodically to monitor your progress or check for side effects. Consult your doctor for more details." The section cautions about increased sun sensitivity, dizziness and possible harm to a fetus and that there have been rare reports of permanent blindness.
- **Possible side effects:** "constipation, loss of appetite, bitter taste in mouth, nausea, vomiting, dizziness, trouble sleeping, headache, flushing of the face, or decreased sexual interest." It says to contact a doctor if the person experiences a variety of things, including muscle pain, vision changes, tingling or irregular heartbeat.

There is no mention of watching for the pneumonia-like symptoms of pulmonary toxicity

There is no mention of fatal problems, such as pulmonary toxicity

Not listed as drug of last resort

Source: Knight Ridder Washington Bureau
Graphic: Lee Hulteng, Judy Treible

FDA responds

Beginning early next year, all patients taking amiodarone will receive FDA-approved information about the drug to ensure all risks are disclosed. For other drugs, ask your pharmacist for a copy of the FDA label or insert.

Walgreens responds

Walgreens spokeswoman Carol Hively said the patient information given consumers at the chain's 4,229 pharmacies is written by an outside contractor. The Cordarone information will be revised to reflect more of the drug's risks, she said. "We asked their editors to relook at their wording and to rewrite it to reflect the concerns that you brought up."

RISKY Rx

RANDY AMICK/KRT

Gary and Ruth Pettijohn, of Batesville, Indiana, hold a photo of their daughter, Kristen, who died after being prescribed a powerful antibiotic called Avelox for a condition that was less severe than what the drug is approved to treat.

sales without going through the expense of proving a drug's effectiveness for the off-label use to the FDA.

Also interfering is the patent protection process. Once a drug's patent lapses, there's little financial interest in taking on the added costs of new FDA application.

Based in part on the work of the off-label task force, the FDA attempted a host of fixes. But a decade later, those efforts largely have fallen short:

■ One push was to have companies apply for FDA approval for popular off-label treatments. While the effort initially produced more applications, the numbers have been dropping. From 1998 to 2002, the number of approvals for new uses of existing drugs went from 74 to 39, according to the FDA.

■ An attempt to revise the prescribing labels for doctors has dragged on for more than 10 years. The agency says its labels are confusing even for doctors, and that fixing them could reduce medication errors.

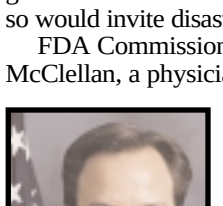
■ Proposals to give patients more meaningful drug information have been stalled even longer. The FDA repeatedly backed away from plans, dating to 1979, to ensure that all patients get basic information about the drugs they buy. Opposition has been fierce. Doctors have argued that the information would frighten patients unnecessarily. Today, most of the leaflets patients get about drugs are part of an industry-run voluntary program. The quality of the information they provide varies widely, with only about half of the leaflets studied meeting FDA goals for usefulness, according to an FDA-commissioned study announced last year.

■ Proposals to restrict drug makers' efforts to get around the ban on promoting off-label drug uses ran into a blizzard of legal challenges by the Washington Legal Foundation, a free-market advocacy group. On free-speech grounds, the courts turned away many of the FDA's arguments; U.S. District Judge Royce Lamberth said the "FDA exaggerates its overall place in the universe."

Helping the Washington Legal Foundation make its case was Daniel Troy, a prominent First Amendment and corporate lawyer. Today, Troy is chief counsel of the FDA, a Bush administration appointee who has started a process that could substantially rewrite the FDA's rules on commercial speech, including those regulating off-label drug promotions.

The pharmaceutical industry has jumped on the opportunity, pushing the agency to relax some of its restrictions on promoting off-label uses. Consumer groups, such as Public Citizen Health Research Group, and many congressional Democrats say to do so would invite disaster.

FDA Commissioner Mark B. McClellan, a physician, said the agency would like to see more evidence submitted about off-label uses, stressing that it was important for such treatments to meet the "gold standard" of FDA approval.



Mark McClellan

To help curb risky off-label prescribing, he wants to improve the FDA's system for reporting drugs' side effects, and he wants better information in the hands of doctors and consumers. The effort to rewrite the labels doctors read will be finished "in a matter of months," he said. "I think we can do much better than we have."

The FDA has had some success using its authority to get the pharmaceutical industry to study drugs' affects on children and put that information on the label. Those efforts, begun in the 1990s and involving congressional and agency action, have produced some results, although they recently have been set back in court.

■ ■ ■

In many ways, the FDA's 1962 mandate to determine whether drugs are safe and effective is irrelevant in today's market, in which some off-label treatments have become so widespread that they're now considered the standard of care.

Amiodarone — under the brand name Pacerone — was the drug taken by George Cox, a Buckner, Mo., man who lost nearly all his sight, and by Martha Andreasen of Bowie, Texas, who's struggling with lung damage.

Amiodarone can have a devastating effect on the lungs: As many as 17 percent of patients in some studies experienced lung damage, and about 10 percent of them died. Patients taking the drug have suffered thyroid, liver and eye problems, including blindness. The FDA approved it only as a drug of last resort for patients with a life-threatening heart condition called ventricular tachycardia.

In 1999, Cox, now 75, was given amiodarone for atrial flutter, a heart condition that isn't life-threatening. He got the prescription a full decade after the FDA began telling the drug's makers to stop promoting it as something other than a last-resort drug.

Andreasen also was given amiodarone off-label. She had atrial fibrillation, a common heart problem similar to atrial flutter. Like many patients, she said she was never warned of the drug's risks or that her prescription was off-label. Her pharmacy leaflet mentioned nausea and dizziness, but not death from lung problems.

Today, Andreasen is tethered to an oxygen tank each night, and at age 54 she's already made her funeral arrangements. She's homebound and doesn't have the strength to clean her house, a humiliating letdown for a woman who's been a member of her town's Young Homemakers club for 30 years. Since she was dropped by her husband's health insurance, the Andreasens now pay $800 a month for high-risk insurance and co-payments. Their dining room table sits atop plywood because they can't afford to finish a repair to the floor.

JOYCE MARSHALL/FORT WORTH STAR-TELEGRAM

Andreasen and her husband Terry in a family photo taken in 2000.

"The FDA is supposed to protect the general public from situations such as this — or so I thought," Andreasen said.

Since at least 1988, the FDA has warned two drug companies to stop false and misleading promotions that downplayed amiodarone's risks while suggesting it as a first-line therapy. The agency sent letters to amiodarone makers in 1989, 1992 and 1998. "Your firm has an intolerable record of compliance with the law," read the 1989 letter to Wyeth, one of the amiodarone makers.

Wyeth's promotions continued. From 1999 to 2002, a slick magazine-style brochure that Wyeth paid for proclaimed "Amiodarone From Last to First-Line Antiarrhythmic Therapy" on its glossy purple cover.

Wyeth spokesman Doug Petkus said the brochure was educational, not promotional. Regardless, Wyeth no longer is doing any promotion of its amiodarone drug, Cordarone, because its patent protection has expired.

After Cox lost most of his sight, his Missouri pharmacist gave him Wyeth's "First-Line" brochure, and he passed it on to the FDA in 2001.

The agency wrote back, saying it can "take action when unapproved (off-label) uses become widespread or endanger the public health," but until last month it had done little to try to curb the widespread off-label prescribing of amiodarone.

In the last year, doctors wrote nearly 2.3 million off-label amiodarone prescriptions, according to Knight Ridder's analysis. That's 82 percent of all the prescriptions for the drug.

In response to Knight Ridder's findings, the FDA's Woodcock said the agency would require that all amiodarone prescriptions be accompanied by an FDA-approved patient guide to ensure that consumers know exactly what the drug is approved for and what its dangers are. Patients will get the guides starting early next year.

"What you brought to the table was the extent of off-label use and some specific patient experiences of not getting all of the information about this drug," Woodcock said.

"Obviously this drug is a very risky drug," she said.

While many cardiologists defend amiodarone's off-label use for atrial fibrillation, a recent NIH study challenged their long-held beliefs.

Called AFFIRM, the study concluded that patients taking drugs such as amiodarone to control their hearts' rhythm experienced more side effects and hospitalizations than those given safer drugs to control how fast their hearts beat. For all its extra risks, amiodarone was no more effective.

Dr. Claude Lenfant, the recently retired director of NIH's National Heart, Lung and Blood Institute, said amiodarone didn't appear to be the best treatment for many patients with atrial fibrillation. But changing a doctor's practice "takes place very, very slowly."

"I personally feel there's a system failure," he said.

■ ■ ■

Even when it's aggressive, the FDA has been unable to stem off-label prescribing.

For more than a decade, the FDA has tried to corral the use of Accutane — a drug for severe forms of acne — which can cause birth defects.

As early as 1990, a frustrated FDA official wrote that "intensive regulation has not, cannot and will not achieve the Agency's goal of eliminating pregnancy exposure to Accutane." At the time, the official estimated that 90 percent of Accutane's use by women was off-label, typically for mild acne that can be treated with safer drugs.

Even tough new warnings on the drug's label about suicide, psychosis and depression didn't stop sales.

According to an internal company sales plan for 2001, drug maker Roche concluded that despite extensive media coverage about those new dangers, "prescribers were apparently unmoved by this information."

In 2002, the same FDA official made another estimate that 90 percent of Accutane use was off-label. The company disputes the FDA estimate.

■ ■ ■

Thalidomide's entry into the U.S. market shows how physicians and the drug industry consider the FDA irrelevant.

The drug was approved in 1998 for a leprosy-related skin condition that's virtually nonexistent in the United States.

After studies showed that the drug might be useful for treating multiple myeloma, a form of cancer, Celgene Corp. aggressively sold that idea to doctors.

One company sales representative went further, telling an oncologist that the drug, marketed as Thalomid, is "good for weight loss," could be used "as an appetite stimulant" and is a "great drug for feelings of general well-being," according to an FDA document describing the sales pitch.

When the doctor asked whether the FDA had approved Thalomid for those uses, the sales rep said, "No, but do you want some material anyway?"

In 2002, the FDA told Celgene that its existing data on multiple myeloma wouldn't be enough to win the agency's approval. The earliest the company says it might seek authorization as a treatment for that form of cancer is 2005.

Today, 70 percent of Thalomid uses are for multiple myeloma, while only 1 percent are for its approved leprosy condition. Celgene, in filings with the Securities and Exchange Commission, declared: "We may not be able to attain or maintain profitability" if physicians prescribe Thalomid only for patients who are diagnosed with leprosy.

Knight Ridder Newspapers Researcher Tish Wells contributed to this report.

KEITH MYERS/KANSAS CITY STAR

George Cox of Buckner, Missouri, displays promotional brochures for amiodarone. Cox was left blind in one eye and almost blind in the other after taking the heart drug, he now uses his mower for transportation around town.

What to do if you experience side effects

Report adverse reactions when you're taking any prescription drug. Doctors are supposed to report to the Food and Drug Administration when patients experience side effects.

If you have one, ask your doctor to report it, and follow up to make sure he or she does. If the doctor won't file the report, do it yourself on the Web at www.fda.gov/medwatch/how.htm or by calling 1-800-332-1088. You also can call the company that makes the drug.

About the series


WOW! LIONS WIN!
The Detroit Free Press
16 killed as missile hits U.S. chopper
PRESCRIPTION FOR TROUBLE

DETROIT FREE PRESS
Nov. 3, 2003


Sunday
TIMES·LEADER
A prescription for peril
Insurers plan little increase
Republican, Democratic hopefuls vow unique brands of change

WILKES BARRE (Pa.) TIMES LEADER
Nov. 2, 2003


East Manatee
SUNDAY HERALD
It's your birthday – get ready to run
Risky Rx
Parents can see plans to rezone
Foundation announces USF nursing scholarship

BRADENTON (Fla.) HERALD
Nov. 2, 2003


Jones County man races to division's top spot
Salaried B&W employees get severance news
The Telegraph
CAST YOUR BALLOT
Paperwork swamps counselors
Macon tells pet owners to pay fees
WR baseball talks yield optimism
FDA oversight of off-label drug use names as prescriptions rise

MACON (Ga.) TELEGRAPH
Nov. 4, 2003


The Miami Herald
SUNDAY
Drug perils: Wrong use makes thousands sick
INK AND BLOOD
Bombing kills 2 American soldiers
Citrus industry fears for survival

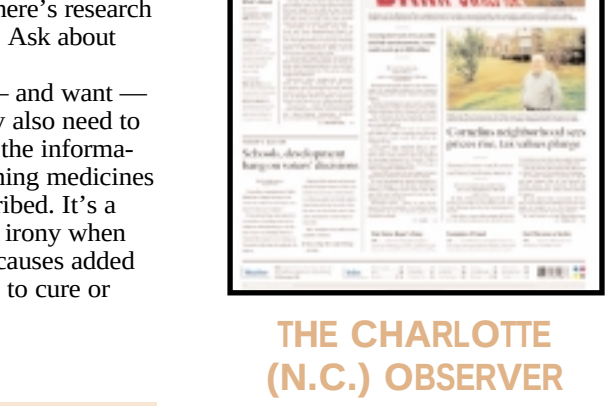
THE MIAMI HERALD
Nov. 2, 2003


Sunday
Star-Telegram
Motorist breaches Bush security
PRESCRIPTION FOR DANGER

FORT WORTH (Texas) STAR-TELEGRAM
Nov. 2, 2003


SUNDAY
PANTHERS ROAR INTO TEXAS
The Charlotte Observer
Mortgage fraud sweeps Charlotte
BANK BUSTED

THE CHARLOTTE (N.C.) OBSERVER
Nov. 2, 2003


Monterey County
The Herald
Copter attacked in Iraq; 16 killed
What the salesman pitches may be what doctor orders
Not much left for fire victims

MONTEREY COUNTY (Calif.) HERALD
Nov. 3, 2003

About the series

More than 30 newspapers published Knight Ridder's series about off-label drug use. Below are several editorials and front-page images that show how the series was played.

The off-label use of drugs has delievered relief to patients. It has also resulted in harm the FDA could easily prevent

Akron (Ohio) Beacon Journal, Nov. 10, 2003

Drugs have become a major part of the practice and business of health care. Many more effective products cover a wide variety of diseases and conditions. In a very competitive industry, drugs are also eagerly promoted to health-care professionals and the general public. The increasing role of drugs invites concerns about improper uses. The risk in routinely prescribing drugs for treatments other than those for which they were approved — off-label use — is one such concern.

A fair amount of off-label prescription is inevitable. For instance, there are numerous conditions for which precisely formulated medications are simply not available. Some diseases are rare and affect so few people that drug companies have little financial incentive to invest in drug development. Other illnesses, like AIDS and cancers, require treatment with multiple drugs in combinations.

Some off-label uses have proved generally beneficial as well, most notably the discovery that regular, small doses of aspirin protect against heart disease. Claims abound of other "happy discoveries," such as an AIDS drug effective in treating ovarian cancer.

All the same, the findings of a Knight Ridder Newspapers study of off-label prescription uses offer alarming indications of the risks. Drugs are improperly prescribed for the wrong diseases, in dosages and for durations unapproved by the Food and Drug Administration and to treat populations not tested for the particular usage. The consequences have proved fatal or severely injurious to some patients. The study noted off-label prescriptions accounted for $21.9 billion in sales in 2002, and free drug samples to doctors were valued at $11.9 billion.

The risks are sure to increase with the growth in drug therapies and the aggressive marketing of drugs, both their approved and off-label uses, to health-care professionals, most of whom have neither the time nor the resources to verify the therapeutic claims of drug representatives.

The FDA has established regulations and guidelines to recognize off-label uses. Its obligation is to protect the public health without infringing on manufacturers' freedom to tout their products to doctors.

One solution is to get the FDA to monitor and aggressively enforce requirements for drug manufacturers to provide scrupulous documentation about the safety and effectiveness of unapproved uses. Another is to curtail the pressure of sales promotions on doctors, who rely on sales representatives for up-to-date information on drugs and their side effects.

Patient safety is worth the cost of beefing up staffing at the Federal Drug Administration to do the job.

Pills' purpose: Off-label use is risky; Information is key to safety

The Detroit Free Press, Nov. 5, 2003

The Food and Drug Administration is charged with keeping the nation's drug supply safe, but it doesn't do enough to control how a drug is used once approved.

Over the past decade, so-called off-label use — prescribing a medication for a condition other than the one the FDA OK'd — has exploded unchecked. Such treatment is not necessarily wrong; it often gives people relief they otherwise do not find. But it isn't necessarily safe, either.

Clearly, the FDA should be more aggressive about going after companies that illegally market off-label uses. But if it hasn't done so yet, it's unlikely to under a White House that favors corporate freedom over regulation, nor a Congress swayed by pharmaceutical contributions.

The industry — which shuns regulation so it can be free to find cures — should exercise self-restraint. But as long as it's making money, that's not likely, either. Perhaps, if a more critical power structure lands in Washington, the industry might scale back so as not to invite tighter regulation or ramped-up enforcement.

Don't count on it.

So the responsibility falls to often-harried doctors and to consumers, who must ask more questions.

Doctors cannot take at face value the claims of pharmaceutical sales reps — nor should they ever prescribe a medication without reading about its potential risks. No time is no excuse.

The broader medical community, through med school and continuing seminars, should teach this issue. Disease and pain are managed at a rapidly increasing rate through pills, not procedures; doctors must know more about potential risks as well as benefits.

Reform Rx drug laws

Grand Folks (N.D.) Herald, Nov. 5, 2003

Doctors and regulators alike should call for tighter restrictions on off-label drug use.

The Knight Ridder series' startling conclusion: "A six-month Knight Ridder investigation has found that patients nationwide are being injured and killed as doctors routinely prescribe drugs in ways the Food and Drug Administration never certified as safe and effective."

"Injured and killed." Hard words — but the series backed up its conclusions with hard evidence.

Off-label prescribing, as the series explained, is the doctors' practice of prescribing a drug for uses that the FDA hasn't formally approved. The drug-approval process is famously long, complicated and expensive; the FDA demands drug companies submit lengthy studies that document side effects and prove the drug's effectiveness against a certain disease.

And that's the catch. Because once the drug comes on the market, all bets basically are off, the series reports. Doctors can prescribe the drug for any condition, not just the one the FDA approved.

What to do? Two points: Clearly, the federal government will have to regulate the practice more tightly. As a supermajority of Americans surely would agree, patients who enter our nation's health system should be confident they'll be treated in a way that's both based on good science and within a protective set of rules. Commercial air travel is handled in exactly that way. Health care should be, too.

Second, America's physicians should be the first to call for meaningful reforms. Following an accepted set of effective rules doesn't hurt the medical profession. It helps, by raising patients' confidence as well as giving doctors a stronger defense against malpractice suits. Those things will work to doctors and hospitals' benefit.

Vigilance the cure for off-label drug woes

Wilkes Barre (Pa.) Times Leader, Nov. 6, 2003

The unintended consequences of off-label prescribed medications can be a bitter pill.

The practice is legal, common and defended by doctors and the American Medical Association.

But the six-month study by Knight Ridder showed the practice surprisingly common, with 115 million such prescriptions written in the past year.

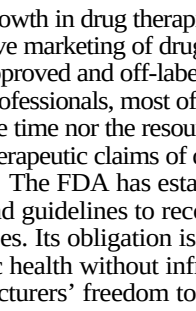
Occasionally, the consequences have been costly. Even deadly. While doctors are free to prescribe medications as they see fit, drug companies are restricted in their marketing. Such restrictions can be circumvented and may contribute to the misunderstanding about the risks of some drugs.

And those existing restrictions may be relaxed depending on the outcome of public comment being solicited by the FDA.

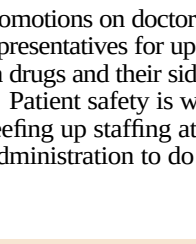
In the meantime, concerned patients should ask doctors or pharmacists the intended use of a drug or read the FDA's approved prescribing information. Look for indications and usage, contradictions, warning and precautions, drug interactions and adverse reactions. Ask your doctor the reasons for a prescription and if there's research to support using the drug. Ask about alternatives.

While patients need — and want — to trust their doctors, they also need to have some confidence in the information doctors have concerning medicines that are commonly prescribed. It's a terrible and unacceptable irony when the prescribed treatment causes added harm, rather than helping to cure or comfort.

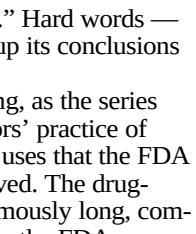
About the writers



Investigative reporter Alison Young came from the Detroit Free Press, where she was consumer affairs reporter, enterprise editor and deputy metro editor. Her reporting has won numerous awards, including the Roy W. Howard Award for Public Service for coverage of abuse and neglect in nursing homes and the Gerald Loeb Award for an investigation of a deadly national outbreak linked to Sara Lee deli meats. Prior to joining the Free Press in 1993, Young was a children's issues reporter at The Arizona Republic and covered environment issues for the Dallas Times Herald. She is a graduate of the University of Kansas.



Investigative reporter Chris Adams joined Knight Ridder in 2003 from The Wall Street Journal, where he covered health and steel from Washington and Pittsburgh. From 1989 to 1996, he reported for The (New Orleans) Times-Picayune. He has won the George Polk Award, the Robert F. Kennedy Award, the Worth Bingham Prize, an Investigative Reporters and Editors Award, three Education Writers Association awards, and the Livingston Award, and been on teams that won the National Headliner Award and the SPJ/SDX Award for Public Service. He was a finalist for the Pulitzer Prize in 1996 and 1999, and in 2000 was part of a six-person Journal team that won the Pulitzer for stories on Pentagon spending. He graduated from Iowa State University.



Tish Wells is the Knight Ridder Washington bureau's researcher and Web editor. A graduate of the Pratt Institute in New York, Wells also holds a master's degree in library science from the University of Maryland in College Park. She has worked in law firms, the National Library of Medicine in Bethesda, Md., and as a freelance book researcher. She is an expert in computer-assisted reporting and served as a senior librarian at USA Today and Gannett News Service for more than a dozen years before joining Knight Ridder in 1999. Working with Sumana Chatterjee and Sudarsan Raghavan, she also won a 2002 Overseas Press Club award for Best International Reporting on Human Rights for the bureau's chocolate slavery package, "A Taste of Slavery."

On the Internet

The series is available on the Knight Ridder Washington bureau's Web site at **www.krwashington.com**.

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