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NOVEMBER 2003 | WWW.SMARTMONEY.COM

THE WALL STREET JOURNAL MAGAZINE OF PERSONAL BUSINESS

The Lipitor Dilemma

There's little doubt that the world's bestselling prescription medicine saves lives. But as more and more patients link the cholesterol pill to memory loss and crippling muscle pain, some doctors are starting to ask: Is America overdosing on Pfizer's wonder drug?



BY ELEANOR LAISE

THERE'S AN AWKWARD SILENCE WHEN YOU ASK Mike Hope his age. He doesn't change the subject, or stammer, or make a silly joke about how he stopped counting at 21. He simply doesn't remember. Ten seconds pass. Then 20. Finally, an answer comes to him. "I'm 56," he says. Close, but not quite. "I will be 56 this year." Later, if you happen to ask him about the book he's reading, you'll hit another roadblock. He can't recall the title, the author or the plot.

The burly, broad-shouldered former high school quarterback has become accustomed to these uncomfortable moments. Once the owner of a successful ophthalmologic supply company, he now has trouble completing a sentence. "You would grasp a word, and it's like on a marquee in front of you," he says one afternoon in his suburban Los Angeles home. "But you can't get the word out. And nothing you can do will get the word out, nor can you leave

the word just sitting there. It freezes you." The condition, called aphasia, kept him from making sales calls. He'd also forget to fill orders and bill clients. Mike and his wife, Sharon, first borrowed money to support the struggling company, then abandoned it altogether. To stay afloat, Sharon cleaned out half of her retirement account and Mike, declared legally disabled, went on Social Security 10 years early.

As his speech and memory faded, his world, bit by bit, became smaller. The neighborhood where he has lived for 26 years is unfamiliar. He has forgotten his family's trip to the Kennedy Space Center, his daughter's wedding plans and the location of his favorite Mexican restaurant. He avoids the supermarket because it was recently reorganized and he can't master the new floor plan. He also dodges his buddies in the neighborhood, guys who were once fixtures around his house. "When you're afraid to speak

up, or when you do and it doesn't come across, that's a pretty ugly feeling," Hope says.

Then there's the physical pain. For the past five years, Hope has been at war with his muscles. They form knots in his shoulders, keep him awake till dawn and cramp so severely that Sharon has to straighten his arms each afternoon.

Though Hope tries to laugh off his memory problem as "the village idiot syndrome," he knows it has tormented his family. Sharon, a software engineer, spends her morning commute on her cell phone, calling neuropsychologists, clinical researchers, anyone who will listen. She keeps records of all the doctor appointments—52 last year alone—the brain scans and the MRIs. The doctors don't detect dementia or Alzheimer's or anything else. So what's causing this misery?

Sharon keeps coming back to one fateful day in January 1998—the day Mike took his first dose of Lipitor.

THE FAST-FOOD NATION HAS met its match. Forty-two million Americans have high cholesterol, and 16 million of them already pop Lipitor or a similar cholesterol-fighting pill. Prescriptions for these drugs, called statins, have jumped 22 percent in the past two years, propelled in part by new federal cholesterol guidelines published in 2001. A recent *Newsweek* cover story proclaimed this "the age of statins." Though AstraZeneca's Crestor, a "super-statin" more powerful than any competitor, was launched in September, Lipitor is the most potent of the five established statins sold in the U.S. Last year U.S. pharmacies dispensed nearly 66 million Lipitor prescriptions, according to pharmaceutical market researcher IMS Health—which is more than rivals Zocor, Pravachol and Lescol combined.

For many doctors, prescribing Lipitor or another statin is easier than babysitting patients as they choke down another bowl of oat bran in hopes of lowering their LDL, or "bad cholesterol." The statins all work the same way, blocking the body's production of HMG-CoA reductase, an enzyme that's a key ingredient in cholesterol. But Lipitor's superior potency has made it the statin of choice. The smallest dose of Lipitor, 10mg, is about as powerful as

20mg of Zocor, 40mg of Pravachol or lovastatin and 80mg of Lescol—and it will reduce LDL up to 39 percent. That means your doctor's happy, your insurer's happy, and your arteries are tickled pink.

It gets even better. Lowering cholesterol reduces the risk of coronary heart disease, the chief cause of death in the Western World. Put simply, statins save lives.

Tell that to Mike and Sharon Hope. They say Lipitor ruined theirs.

At first, when Mike's doctor prescribed 10mg of Lipitor in January 1998, the Hopes saw the statin as a necessity. Total cholesterol under 200 is considered desirable, but Mike's was a scary 350. Within a few months his cholesterol was under control. But he suffered some aches and

pains, and started misplacing things, like his keys. By 2001, his muscles were so weak that his legs would collapse under him. Just after the New Year in 2002, a bewildered Mike called Sharon from Home Depot. "Do you know why I'm here?" he asked.

"I freaked out," Sharon says. On the Internet she found message boards linking statins to memory loss. She took Mike for neuropsychological exams, and his scores on several tests were in the bottom 1 percent.

Mike also saw Beatrice Golomb, a neurobiologist conducting extensive statin research at the University

of California–San Diego. She believes it's likely that Lipitor caused Hope's problems. His symptoms, Golomb says, are "compatible with the spectrum and character of problems we see on statins." Hope's condition has improved since he came off Lipitor in January 2002. He'll no longer collapse on the floor. But he's far from a full recovery. He also has plenty of company.

Fifty-six-year-old John Mortin, a former California rancher, took 40mg of Lipitor a day for three years. Now, off the drug since 2002, he suffers severe cognitive problems, and he's on total disability. "He has trouble buckling his sandals," says his wife, Mari. "For a week and a half, we've been trying to teach him how to make a sandwich." Merline Maynard, also 56, has suffered crippling muscle pain since a two-week period in late 2001 when she took 10mg of Lipitor a day. "If I continued taking it for a

Mike and Sharon Hope

Since starting on Lipitor in 1998, Mike has significantly reduced his bad cholesterol. But in the process he has been hampered by extreme muscle pain, frustrating memory lapses—and the loss of his business.

When Kathleen Socha started taking Lipitor, she suffered such severe muscle pain that she barely left her home for weeks. The doctor ‘was thrilled with how much my cholesterol came down,’ she says, ‘but the drug was going to kill me.’

month,” says the New Plymouth, Ohio, homemaker, “it would have killed me.” Then there’s Kathleen Socha. The 60-year-old psychotherapist in Chandler, Ariz., experienced such extreme weakness in her hands after four months on Lipitor at 20mg a day that “I couldn’t hold a fork to eat a meal.” Socha’s condition has improved considerably since she stopped taking the drug in May.

Hundreds of patients have gathered online to share Lipitor horror stories. A message board devoted to Lipitor at *forum.ditonline.com* contains more than 800 posts, many detailing severe side effects and dismissive doctors. The Lipitor board at *www.rxlist.com* contains more than 2,600 posts. And a 1999 study at St. Thomas’ Hospital in London found that 36 percent of patients on Lipitor’s highest dose reported side effects, versus 10 percent of patients on the lowest dose. The researchers also concluded that Lipitor lowers cholesterol more effectively at the same milligram level than the next most potent statin, Merck’s Zocor, “but at the expense of a possible increase in side effects.” Golomb says that Lipitor’s potency appears to make patients more likely to develop severe side effects.

Gary Palmer, head of Pfizer’s cardiovascular medical group, downplays these charges. “When you choose to treat a disease, there’s always a balance of risk versus benefit,” he says. With Lipitor, “those benefits far outweigh the small risk.”

The Mortins and the Hopes would love to see Pfizer in court proving that. But lawyers tell them that the drug must be recalled before they’ll take the case. “Fighting Pfizer is like fighting God,” Mari Mortin fumes. “They can exhaust everything we have.”

New York City-based Pfizer, the world’s largest pharmaceutical company, derives a quarter of its \$32 billion in annual sales from Lipitor. Developed by Parke-Davis (since acquired by Pfizer) and launched in 1997, Lipitor produced \$8 billion in sales in 2002 and could become the first drug

to top \$10 billion in 2004. Patients pony up nearly \$900 a year for Lipitor’s lowest dose.

Of course, with their prescriptions, patients get the requisite warnings. All statins can cause side effects, including liver dysfunction, muscle pain and, in rare cases, muscle breakdown. But doctors who have studied these drugs say the stronger your statin, the greater your risk of side effects. “Seventy-five to 80 percent of all side effects are dose-related,” says Jay Cohen, an associate

professor of family and preventive medicine at the University of California–San Diego and author of *Over Dose: The Case Against the Drug Companies*. “When you double the dose, not only do you see an increase in muscle pain and memory problems and abdominal problems, but also liver toxicity doubles.”

What troubles Cohen and other scientists studying Lipitor is that many patients have no need for its added potency and the risks that come with it. In early clinical trials, Parke-Davis reported that doses of just 2.5mg of Lipitor produce a 25 percent reduction in LDL—more

than enough to bring at least 50 percent of U.S. adults to optimal LDL levels and 85 percent to “near optimal.” That should give patients pause, considering the American Heart Association and the American College of Cardiology have warned that, since muscle sickness is more likely to occur at higher doses, “doses should not exceed those required to attain the . . . goal of therapy.”

Pfizer doesn’t see a problem with Lipitor’s potency. “We’re very confident of the safety profile of Lipitor from 10mg to 80mg,” Palmer says. “We have over 50 million patient years of experience now to give us a lot of confidence.”

Makers of less powerful statins include low-dose information in their product labeling. Zocor’s starting dose is 20mg, yet Merck also makes 5mg and 10mg tablets. Pfizer doesn’t produce lower-dose Lipitor or make any mention of effective lower doses. Why not? The drugmaker ar-

Dr. Beatrice Golomb

In researching patients taking statins, Golomb has discovered that “people experience significant adverse effects from these drugs.” Among the most common: muscle pain and cognitive problems.

Pfizer denies a link between Lipitor and memory loss. ‘We think that lowering cholesterol may have some serious benefit in terms of cognition,’ says Dr. Gary Palmer, head of Pfizer’s cardiovascular medical group. ‘That’s not to say the odd case hasn’t been reported.’

gues that simplicity is key. Marketing lower doses, Palmer says, “doesn’t necessarily add anything. It makes it more complex and confusing. Physicians are busy. The more simple we can make treatment of a condition, the more likely they are to remember what needs to be done and put patients on the correct dose.”

Bob Ehrlich directed Lipitor’s consumer marketing campaign in the late 1990s. In the first full year of that campaign, Pfizer spent \$55 million—nearly 60 percent more than Merck did on Zocor, the closest competitor. Ehrlich acknowledges that Lipitor’s potent starting dose was a strong selling point for physicians. “The positioning to doctors was clearly that this is a much more efficacious drug at the same milligram level,” says Ehrlich, who left Pfizer in 2000 and is now an independent drug company consultant. Ten milligrams of Lipitor cut bad cholesterol by up to 39 percent; 10mg of Zocor had only a 30 percent reduction. “The goal was to have a starting dose better than other people’s starting dose,” Ehrlich says. If a patient doesn’t meet cholesterol targets at the initial dose, that means more office visits, tests and dosage adjustments. “Doctors don’t want to do that,” Ehrlich says. “If you ask most doctors, they’d say, ‘I want a drug that’s convenient, where I don’t have to do additional blood testing.’”

“I’m not saying it’s right for consumers,” Ehrlich adds, “but drug companies are marketing for doctor convenience.”

GOLOMB SITS IN THE FLUORESCENT GLARE OF HER deserted office at UC–San Diego. It’s after midnight, but her speech accelerates as she talks about her statin research. “There are people who experience significant quality-of-life-affecting adverse effects from these drugs,” she says. The potential for severe side effects “should be much, much, much more clear than it currently is.”

A RAND health consultant who studied Gulf War Syndrome for the Department of Defense, Golomb is currently conducting the first large-scale study of statins’ impact on cognition. She’s also running a series of observational studies on all statin side effects. Unlike many of her colleagues, she accepts no money from the pharmaceutical industry. Her cognitive study is funded by a \$4.5 million grant from the National Institutes of Health.

Golomb’s observational studies suggest that the danger of statins is indeed in the dose. In one study of 100 patients who reported muscular side effects, most of whom had taken multiple statins, she found that 98 percent of Lipitor usages were associated with muscle problems, versus just 33 percent of lovastatin usages. What’s more, patients who switched to the same or higher potency of the same or different statin had recurring problems 95 percent of the time, while those who switched to a lower potency had recurring problems only 55 percent of the time.

Statin users’ most common complaints are muscle pain and weakness. While that pain can be crippling, it may be just one manifestation of a still more frightening side effect. After three months on Lipitor at 10mg a day, Brenda Horton often felt her heart skipping beats, and she was afraid it would “just quit. It scared me enough to send me to the emergency room.” The 53-year-old Winona, Tex., receptionist consulted Peter Langsjoen, a cardiologist at East Texas Medical Center. Langsjoen found that her “ejection fraction,” the percentage of blood pumped out of the left ventricle per heart cycle, was just 52 percent, which is eight percentage points below normal. His diagnosis: “statin-induced diastolic dysfunction.”

Langsjoen had seen this sort of thing before. He recently studied 20 patients with completely normal heart function. His preliminary results showed that after six months on

Brenda Horton

After taking Lipitor for three months, Horton experienced such severe heart irregularities that she worried her heart would “just quit. It scared me enough to send me to the emergency room.”

20mg of Lipitor a day, two-thirds of the patients had abnormalities in the heart's "filling phase," when the muscle fills with blood. His explanation: Statins can cause a dose-related depletion in an essential nutrient known as Coenzyme Q10. Without CoQ10, the cell's mitochondria can't produce energy. The shortage may cause muscle pain and weakness, but the heart is especially susceptible because it uses so much energy.

Horton's tale is disturbing given the fact that patients with advanced heart failure are prescribed Lipitor every day. "We have not run a study specifically to look at the effects in heart failure," Pfizer's Palmer says. "It's not an area where we can give a definitive answer." As for CoQ10 depletion, Palmer says that it's just "one of the theories around muscle symptoms, and the mechanisms are not clear." In Lipitor trials, he adds, Pfizer was "unable to document any specific effect on CoQ10."

Canadian labeling for Lipitor and other statins clearly warns of CoQ10 depletion, and even notes that this nutrient deficiency "could lead to impaired cardiac function in patients with borderline congestive heart failure." Some regulatory agencies "insist on certain wording," Palmer says. "Sometimes an agency will want to insert words into the label that don't necessarily relate to our data."

There's some indication that statin makers have known about the nutrient depletion—and its dangers—for more than 14 years. In 1989 Merck filed for two patents for a combination statin/CoQ10 pill. The patent applications note that the compound can be a treatment for statin-associated myopathy, or muscle sickness, and elevated transaminase enzyme levels, which are released into the blood as a result of liver damage.

Michael S. Brown, the inventor listed on the first Merck patent, won a Nobel Prize for research that led to the development of cholesterol-lowering drugs. Currently a Pfizer board member, he declined to comment on the patent. Merck spokesperson Janet Skidmore would say only that the company never acted on the patent because "we thought we had more promising routes of research."

Since CoQ10 depletion can restrict cells' energy production, it has an impact on cognition that is "probably quite serious," says Salvatore DiMauro, a profes-

sor of neurology at Columbia University. He has found that patients with hereditary mitochondrial disease have a number of neurological problems, including dementia. Indeed, Golomb reports that cognitive problems are the second most common statin side effect.

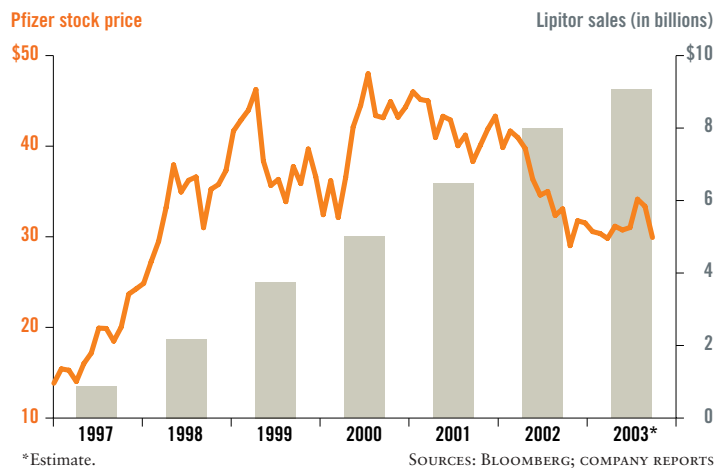
Pfizer denies a link between Lipitor and memory loss. "We think that lowering cholesterol may have some serious benefit in terms of cognition," Palmer says. "There may be some benefits in patients with Alzheimer's disease." As for aphasia, memory loss and total blackouts, "we have not seen any signals to indicate there's a causal relationship between taking [Lipitor] and any of those effects," Palmer says. "That's not to say the odd case hasn't been reported." Lipitor's label lists amnesia as a side effect occurring in under 2 percent of patients but makes no mention of other cognitive problems.

Statins may cause cognitive problems simply *because* they lower cholesterol. "Cholesterol is the main organic molecule in the brain and constitutes over half the dry weight of the brain," Golomb says.

A study conducted by Matthew Muldoon of the University of Pittsburgh showed that patients treated with statins for six months compared poorly with patients on a placebo in solving complex mazes, psychomotor skills and memory tests. "Given the wide use of these drugs, any adverse cognitive effect might be interpreted as important," Muldoon says.

Hearty Returns

Lipitor's sales have grown more than sevenfold since it was launched in 1997. Shares of Pfizer, meanwhile, have returned more than 130 percent, 83 percentage points more than the Standard & Poor's 500.



Families like the Mortins and the Hopes would love to see Pfizer in court. But lawyers tell them the drug must be recalled before they'll take the case. 'Fighting Pfizer is like fighting God,' Mari Mortin fumes. 'They can exhaust everything we have.'

It's certainly important to John McGuire, a 53-year-old supervisor at a restaurant equipment company in Crownsville, Md. In 1999 he began taking Lipitor at 20mg a day. After a couple months he started experiencing blackouts. McGuire took himself off the drug, though his doctor said his problems couldn't possibly be related to Lipitor. The blackouts disappeared. Now McGuire spends much of his time on Lipitor message boards, urging his fellow sufferers to broadcast the bad news.

DOCTORS DON'T HAVE TO LOOK FAR FOR REASONS to prescribe Lipitor. Some health plans even give them financial incentives to lower patients' cholesterol. Lipitor is a quick and easy way to do that. It's being tested to treat conditions beyond high cholesterol, such as osteoporosis and Alzheimer's. And—they believe—it's safe.

In the past year Pfizer presented results of two major trials showing that Lipitor reduces the risk of heart attack in patients with high blood pressure and diabetes. In 2002 the Food and Drug Administration expanded the Lipitor starting-dose range from the original 10mg to include 20mg and 40mg. Last year Lipitor was approved for use in teenagers with severely elevated cholesterol. The 2001 recall of Bayer's statin Baycol, which was found to cause rhabdomyolysis, or muscle breakdown, did nothing to dampen the enthusiasm.

Dr. David Orloff, head of the FDA's division of metabolic and endocrine drug products, acknowledges that significant statin side effects are dose related, but notes that the vast majority of statin users take relatively low doses. "Even though the drug is approved," he adds, "we have not stopped our ongoing evaluation of risk and benefit."

The good news about statins can be so deafening that doctors often dismiss patients' complaints of side effects. "My doctor was furious that I stopped taking Lipitor,"

Kathleen Socha recalls. "He said, 'Start taking it again.'" Socha took a few more pills, "and it mushroomed into one of the worst experiences of my life." The pain was so severe that she barely left her home for several weeks. The doctor "was thrilled with how much my cholesterol came down," Socha says. "That's all well and good, but the drug was going to kill me." Socha's doctor, Robert Bell, says he was upset only because Socha stopped taking the drug without consulting him. He notes that he advised her to restart the Lipitor simply to confirm that the statin was the cause of her pain.

Doctors may also turn a deaf ear to suffering patients because they believe a simple test can detect statin-related muscle damage. Statin labels warn doctors to look for high levels of creatine kinase (CK), an enzyme released by damaged muscle. But that test won't always do the trick. Statin-related muscle damage can occur in patients with normal CK levels.

"Doctors need to be educated," Golomb says. If there's any good news about these drugs, "you can be sure that the \$18 billion-a-year statin industry is going to ensure that people hear those good things. There's no corresponding interest group to ensure that people hear the other side." She hopes her studies will provide part of the solution by identifying patients at risk of developing severe side effects and by uncovering possible treatments.

Such research could have made all the difference for Mike and Sharon Hope. As Mike tools down Pasadena's Foothill Boulevard in his '66 Pontiac GTO, Neil Sedaka crooning on the eight-track, you get a glimpse of how things used to be. At the classic car show where he typically spends Saturday nights, he'll laugh a bit and show a few boys the gleaming engine of his GTO. But many old friends there are strangers, and he can't sustain the conversation. Soon he'll break away and come to stand quietly by Sharon's side. **SM**