# HEALTH AND STRESS

The Newsletter of

The American Institute of Stress

Number 5 2008


# STRESS FROM DECEPTIVE DRUG ADS & CORRUPTION


KEYWORDS: Direct-to-consumer drug advertising, ED, GERD, proton pump inhibitors and cancer, Dr. Robert Jarvik and Lipitor, Dr. John Kastelein, Senator Chuck Grassley, Senator Bob Kohl, the "49 Plan", Ortho Evra estrogen patch, torcetrapib and HDL, ILLUMINATE, Avandia, Exubera, AHA "Healthy Heart" logo revenues


"Ask Your Doctor", "Ask Your Doctor", "Ask Your Doctor". It's impossible to watch prime time TV without seeing an advertisement urging you to ask your doctor if some medication is "right for you". TV direct-to-consumer drug advertising was originally approved for educational rather than promotional purposes and this repeated request apparently helps to satisfy that requirement. It also implies he or she will agree, as in "If you don't believe me, ask (some authority)". Most of the message usually consists of supportive testimonials and other anecdotal hype. All drug ads must also list contraindications and side effects. However, this is often limited to warnings about avoidance if you are pregnant, nursing, have liver disease or some other unlikely condition. Several significant and even serious adverse complications may be ignored or are included at the end in mice type for five seconds, hardly enough time to read the list, much less remember them.



It's also highly unlikely that you can just call your doctor and get a quick answer over the phone, which necessitates making an appointment for an office visit. More and more patients are doing exactly that in droves, often armed with supportive literature obtained from the company's web site. And studies show that most of them are quite successful in getting a script for what they requested.

**Why Prescription Drug Advertising Is Dangerous And Banned Elsewhere.**
That's great for pharmaceutical manufacturers, which helps to explain why **TV drug advertising jumped to $1.6 billion for the first six months of 2007.** This progressive escalation in expensive TV promotions would obviously not have occurred unless it was cost effective. Confirmation comes from a Kaiser Foundation study reporting that **every extra dollar drug companies spent on ads boosted their revenue by $4.20.** Many doctors don't object to TV ads since they increase office visits that are usually uncomplicated and result in satisfied patients. After all, few physicians know whether Viagra, Levitra, or Cialis would be best for erectile dysfunction. Some Levitra ads specify that the drug is "indicated for patients with high cholesterol or diabetes", which suggests that it could also benefit these disorders. However, since there is little difference between any of these drugs, the easiest thing to do is to write a prescription for the patient's preference and possibly provide some samples. The same holds true for Nexium (the healing purple pill), Protonic, Prevacid and other proton pump inhibitors that block the production of gastric acid. These have been aggressively advertised to treat what is apparently a growing epidemic of GERD (gastroesophageal reflux disease), a diagnosis that sounds much more serious than heartburn or "agita". This is especially true for ads warning that erosive reflux esophagitis can lead to cancer, since there is the tacit implication that the drug prevents this. Consequently, people who complain of frequent heartburn are more apt to take these prescription drugs rather than less expensive over-the-counter products that are just as effective, such as Nexium's predecessor, Prilosec (the original purple pill).

Acid reflux is associated with Barrett's esophagus, an asymptomatic but precancerous lesion detected during endoscopy. As a result, even patients with no complaints of heartburn are often placed on a proton pump inhibitor for a year or more as a prophylactic measure. Unfortunately, none of these drugs has been shown to reduce the risk of esophageal cancer, and this complication is uncommon, if not rare. One report indicated **"a physician would have to follow almost 50 patients with Barrett's esophagus for 10 years to have a chance of finding a single cancer."** Esophageal cancer actually appears to be increasing since the advent of proton pump inhibitors. There are concerns that these drugs could be a contributing factor because they decrease the production of stomach acid that is needed to inactivate pancreatic enzymes. Pancreatic enzymes are very irritating to normal tissue, and if not inactivated by stomach acid, could produce precancerous changes in the esophagus that might explain this increase. Nexium and similar drugs also decrease the release of vitamin B12 from foods because they lower levels of stomach acid. Low vitamin B12 is associated with gastric atrophy and carcinoma of the stomach, especially in the elderly, and B12 deficiency is one of the main causes of increased levels

of homocysteine. Many authorities believe that homocysteine is a much more important contributor to accelerated atherosclerosis, heart attacks and coronary heart disease than cholesterol. High homocysteine has also been implicated in the recent increased incidence of hip fractures in older people.

Few TV ads really address the question of what is causing the problem, such as why you have erectile dysfunction (ED) or acid reflux (GERD). Difficulty in achieving or maintaining an erection as men grow older is not a disease. It is a normal consequence of aging, although it can occur earlier and more frequently in diabetics. Ads warn patients with coronary disease not to take ED drugs if they use nitroglycerin or long acting nitrates and to "ask you doctor if they are right for you", or if their heart is healthy enough for sex. Patients who are fearful of cardiac complications may also decide to take one of the numerous "all natural" nutritional supplements for erectile dysfunction in the mistaken belief that they are harmless. Nutritional supplements do not require a prescription or FDA approval for claims of efficacy or safety and regulatory restriction is rare unless there is proof they are dangerous. Although most are safe, some can react with other drugs. A very recent FDA press release warned consumers about Blue Steel and Hero, two of the top sellers, which also contain chemicals similar to the active ingredient in Viagra that react with nitrates to cause a precipitous drop in blood pressure.

Further proof of the efficacy of fraudulent TV drug advertising is illustrated by the Dr. Robert Jarvik fiasco, currently being investigated by Congress. A copy of Jarvik's contract reveals that Pfizer agreed to pay him a minimum of $1,350,000 over two years for promoting Lipitor. It is not clear what other family members were paid for their participation. Jarvik is portrayed in these ads as an authoritative and caring cardiologist who takes Lipitor because it is superior to other prescription and generic statins. He is also shown jogging with his son and skillfully sculling on a sunny and serene mountain lake. **The facts are that Dr. Jarvik does not treat patients since he is not licensed to practice medicine, does not know how to scull and doesn't take Lipitor.** The shots demonstrating his sculling expertise were of an athletic, late middle-aged accomplished rower who resembled him. The close up frames that actually showed Dr. Jarvik were taken while he was in a rowing apparatus on a platform to conceal that it was on dry land. Wearing a white coat, Jarvik tells viewers that **Lipitor can lower "bad" cholesterol by up to 60% to achieve a "36% reduction in heart attacks*".** "I'm glad I take Lipitor, as a doctor and as a dad," he says, before a final shot shows his double rowing in a vigorous and muscular fashion in the distance.

Much of the $258 million Pfizer spent for Lipitor advertising from January 2006 to September 2007 was for the Jarvik campaign, but it was a wise

investment. The 36% reduction in heart attacks was impressive and thousands of patients taking other brand name statins asked to be switched to Lipitor, **which brought in $12.6 billion last year.** Five months ago, Consumer Reports showed the Jarvik ad to almost 1,000 patients who had been advised by their physicians to lower their cholesterol and received the following reactions:

- Sixty-five percent said the ad conveyed that leading doctors prefer Lipitor.
- Forty-eight percent said Dr. Jarvik's endorsement made them more confident about Lipitor.
- Twenty-nine percent had the definite impression from the ad that Dr. Jarvik sees patients regularly.
- Thirty-three percent of those taking another prescription statin said they were likely to speak to their physician about switching to Lipitor.
- Forty-one percent said the ad conveyed that Lipitor is better than generic alternatives. (In fact, the vast majority of people taking statins can get the same results from a generic for less than half the cost.)

**Over 90 percent believed that the ad was credible and accurate. The message for many was that Lipitor could reduce heart attacks in more than one out of three healthy people, regardless of their cholesterol.** Few paid any attention to the asterisk after the claim that Lipitor resulted in a "36% reduction in heart attacks*". It pointed to a statement in mice type at the bottom of the screen explaining that there were 2 heart attacks out of 100 patients on Lipitor, compared to 3 heart attacks for controls taking a placebo. **However, this 1% difference was only for those with "multiple risk factors for heart disease" who took Lipitor daily for over a decade.** How many people would take Lipitor if they knew that its likelihood of preventing a heart attack was one in 100 if they took it for over ten years? And this is only for those at high risk. **Lipitor and other statins have never been shown to prevent heart attacks or heart disease.** This statement appears on some U.S. ads but is mandated in Canada and other countries. Nor is the public aware that Lipitor has not been proven to provide benefits in senior citizens or women of any age. Serious side effects, including the potential for cancer and more recently, amyotrophic lateral sclerosis, have also been skillfully suppressed.

## The ENHANCE Study - Or How To Suppress And Manipulate Trial Results

The recent Vytorin ENHANCE study is an even more egregious example of fraudulent advertising. Vytorin is a combination of two drugs, Schering-Plough's Zetia (ezetimibe), which blocks the absorption of cholesterol, and Merck's Zocor (simvastatin), a statin that is also available as a generic. The FDA approved Vytorin in 2004, based on a study showing that it lowered LDL cholesterol 52% and was therefore presumably more effective in preventing

heart disease than Lipitor. The Vytorin ENHANCE study, which was designed to prove this started in 2002 and was completed April 2006. The results were scheduled to be reported November 2006 but was postponed until a cardiology conference in March 2007 so that an outside consultant could review the data. In January 2007, the independent consultant hired by the companies told them that the problems were no different than those usually seen in similar studies. Schering-Plough and Merck were apparently not satisfied, so the March date was not met and was again rescheduled for an American Heart Association meeting in early November 2007. When this third target date was missed, the media started to suspect that the companies might be suppressing negative data. These suspicions grew when the sponsors announced on November 19 that they were changing the study's criteria for efficacy based on recommendations from a panel of medical advisors at a meeting held three days earlier.

This unprecedented decision drew so much criticism, that on December 11, 2007 it was rescinded. Congress announced it would launch an investigational probe to determine why the study results were postponed for almost two years and if there was any evidence that company executives were aware of the negative findings during the period Vytorin was being vigorously promoted on TV. Because of the probe, the companies admitted on January 14, 2008, that the study showed Vytorin did not reduce the degree of carotid atherosclerosis any more than simvastatin (Zocor) alone. When the results were presented at the March 30, 2008 annual meeting of The American College of Cardiology, the data suggested that Vytorin might have almost doubled the amount of atherosclerosis, although the findings were not statistically significant. The *New England Journal of Medicine* web site published the study on the same day, with not one, but two critical editorials, both of which recommended that doctors should only prescribe Vytorin and Zetia as a last resort. This created a media frenzy and stock in both companies plummeted. A few days later, Schering-Plough announced that it would be closing plants and cutting 10 percent of its workforce of 55,000 in order to save up to $1.5 billion and that most of this would be in the U.S., "where intense new pressures on our industry and our company are centered." Vytorin and Zetia were the company's most important products and had more than $5 billion in sales last year.

Some of the damaging details uncovered by the Congressional investigators were concerns, as early as 2005, that some of the results were not favorable. Several pharmaceutical sales reps posted comments on an Internet site in March 2007 indicating they knew "the study is a bust." A July 6 email to a Schering-Plough executive from Dr. John Kaseltein, leader of the ENHANCE study, reflects his frustration over the unnecessary delay in allowing him to report the results at the November 2007 meeting of the

American Heart Association. "Is it correct that SP has decided not to present at AHA? If this is true, they must have taken this decision without even the semblance of decency to consult me," adding, "I can tell you if this is the case, our collaboration is over. This starts smelling like extending the publication for no other than political reasons, and I cannot live with that." An e-mail the following day stated, "I have been traveling half the globe in the past six months to a number of large and important meetings at the strong wish of Merck to chair them or to present ezetimibe data. At every single one of them I was cleared to say that ENHANCE would be presented at AHA." He further warned that, "you will be seen as a company that tries to hide something and I will be perceived as being in bed with you!"

Dr. Kastelein was not at the meeting of experts that resulted in the November 19, 2007 announcement changing the criteria for measuring the efficacy of Vytorin, allegedly based on their recommendations. Documents obtained by Congressional investigators released only a few weeks ago, reveal that the panel consisted of five outside experts and 11 company employees. All were told that no minutes would be kept so their remarks would not get back to Kastelein and they could speak freely. A memo from one of the medical experts objected to the change in criteria, noting, "This really overstates our recommendation. We did not vote on this. You asked each of us our opinions, the strength of which varied from complete comfort to a lukewarm feeling that it was 'reasonable.' The tone here implies that we strongly recommended this when in reality, we just advised you on what the scientifically valid approaches would be. **It was the decision of the company to change the endpoint."** When he received "minutes" that were sent to all panel members a month after the meeting, he wrote in the margins that they were an after-the-fact, "incomplete summary", that some statements "do not fit my recollection" and that he could not approve them. Investigators want to know whether the alleged "minutes" of this meeting of experts were created a month later because of the Congressional probe.

Company executives had previously claimed that the first inkling they had of the negative study results was in January 2008. However, internal documents indicate that key officials were aware of this at a much earlier date. Schering-Plough's president sold 900,000 shares of company stock worth an estimated $28 million in April and May 2007. The Senate Finance Committee is investigating the timing of sales of large blocks of shares by other executives who could also be prosecuted for possible insider trading. They also want to know why Vytorin was heavily advertised for at least nine months prior to releasing the negative results in response to the Congressional probe. Merck and Schering-Plough spent $102 million on Vytorin advertising from January 2007 to September 2007 and more than $80 million over the next four months. Almost everyone who watches TV has

seen the ads showing multi-racial relatives with their favorite fattening foods, emphasizing that Vytorin lowers bad LDL much more than Lipitor. These, as well as the false Jarvik promotions have now been pulled, but there are no plans to withdraw Vytorin ads in print media, since there is no obligation to do so. Red flags may have been raised but there will be no black box or other warnings, because there are no safety issues.

And, if anyone doubts that this is another triumph of marketing muscle over medical merit, one has only to compare sales in Canada and the U.S., where Vytorin is not available nor is direct-to-consumer advertising allowed. Zetia (ezetimibe) was approved in the U.S. in October, 2002 through a fast-track process called "surrogate markers" designed to speed up FDA approval. This allows manufacturers to use certain indicators or "endpoints" during clinical trials to substitute for other endpoints that would take much longer to demonstrate. The FDA allows cholesterol lowering to serve as a substitute for heart attack and stroke incidence because it is widely believed to be a valid surrogate. Vytorin was similarly approved in 2004 to lower cholesterol not only by reducing its production in the body, but also its absorption from food. Since Health Canada often works "in parallel" with the FDA, it approved ezetimibe (Ezetrol) in March 2003 based on the same standards and data used by the FDA, but Vytorin was never approved. Canada has also been stricter and more diligent about the need to report ezetimibe side effects, such as muscle and liver problems. In 2005, both Canada and Australia issued warnings regarding ezetimibe's potential to cause hepatitis, pancreatitis and depression, but the FDA has not followed suit.

With respect to the power of direct-to-consumer advertising, one study reported that the proportion of prescriptions for lipid lowering drugs written for ezetimibe in Canada increased from 0.2% in 2003 to 3.4% in 2006. In the US, ezetimibe also represented 0.2% of prescriptions for lipid-lowering agents in 2002, but this skyrocketed to 15.2% in 2006. The total monthly cost of prescriptions dispensed for either ezetimibe or Vytorin in the U.S. in 2006 was around $261.5 million, compared to only $6.6 million/month for ezetimibe in Canada. It is estimated that the ban on direct drug advertising to consumers probably saved Canadians with high cholesterol and their drug plans $150 million in 2006 alone. **It should be emphasized that the criteria that led to the approval of ezetimibe were established by drug companies rather than any independent agency and are now being questioned.** "Vytoringate" has led to at least a dozen class action lawsuits being filed in federal courts for "misleading" consumers into thinking that Vytorin was more effective than a generic statin costing less than half, and for not publishing two studies showing it increased risk of serious liver disease. Four states have joined in the suits and Senator Charles Schumer wants the companies to refund New York for the over $20 million Medicaid

spent on Vytorin. The U.S. government may seek restitution for "hundreds of millions of dollars' spent since the study ended in 2006. Numerous Internet ads from lawyers seek clients with claims about adverse effects.

## Why Preemption Will Permit Big Pharma To Prevail Over The Public

Most legal experts believe there is little likelihood that these lawsuits will be successful because of a recent FDA regulation stating that any FDA label, "whether it be in the old or new format, preempts decisions of a court of law for purposes of product liability litigation." **This essentially prevents lawsuits in state courts against drug companies for unanticipated injuries resulting from the use of their products even if the manufacturer failed to warn physicians or patients adequately about a known risk or had intentionally misled the FDA by hiding or fabricating clinical trial data.**

For example, in 1996, Johnson and Johnson informed the FDA that it planned to develop the Ortho Evra contraceptive patch because its weekly use would expose women to less estrogen than daily birth control pills. In 1988, the FDA banned birth control pills with more than 50 mcg of estrogen to insure that less than 25 mcg would reach the blood stream, since over half the estrogen in pills is not absorbed. However, a 1999 study found that the patch actually delivered 30 to 38 mcg of estrogen into the blood stream, an amount that could be equivalent to a 76-mcg pill that would raise risk of heart attack and stroke due to increased blood clots. There were also complaints of breast soreness and nausea and an e-mail from one company scientist stated that these side effects seemed related to higher estrogen doses. Internal documents now reveal that the company arbitrarily applied a correction figure that reduced the amount of estrogen 40% to about 20 micrograms of estrogen daily. This was not revealed in the protocol submitted to the FDA, which approved the patch in 2001, nor was there any reference to this when the study was published in 2002. Another 2003 study showed that the patch actually delivered significantly more estrogen than previously found, but this was also withheld from the FDA. After approval, the company advertised that the patch only released 20 micrograms of estrogen daily, which it now admits was inaccurate, since it could be up to twice as much. Estrogen replacement therapy had also been shown to increase risk of cardiovascular disease and a new study confirms that higher doses produced more heart and kidney complications.

Prescriptions for the Ortho Evra patch soared but so did reports of side effects. There have been over 3,000 suits claiming that it caused heart attacks, strokes and deaths, and in some cases, in less than two weeks. There were at least 50 associated deaths from 2002 to 2006 but the true figure is probably many times higher since most such deaths are not

reported and many are not recognized. There was apparently little concern until the sudden death in 2004 of a healthy 18 year-old grade A college student, due to a pulmonary embolus, made national headlines. However, the FDA (sometimes called the Foot Dragging Administration) did not warn the public or doctors about any potential risk until November 2005, when the agency announced that it had placed a label warning that the patch "exposes women to higher levels of estrogen than most birth control pills". **That's six years after the company's own study showed this**. Patch prescriptions fell 80 percent, from 900,000 in March 2004, to 187,000 last February.

But because the FDA had approved the patch, the company is arguing that it cannot be sued by women who claim that they were injured, even though the old label inaccurately described the amount of estrogen it released. Many, including at least one plaintiff's attorney, suspect this legal argument known as pre-emption, will prove successful. The current administration has argued strongly in favor of pre-emption, which holds that the FDA is the only agency with enough expertise to regulate drug makers and that its decisions overrule those of other courts. The Supreme Court already ruled last February that similar suits against the makers of medical devices like pacemakers are pre-empted. Last month, a Federal Appeals Court in Philadelphia denied two suits brought by relatives of patients who had committed suicide shortly after taking antidepressant drugs. One of the drugs was Paxil, which is now under criminal investigation in the UK and New York State for failing to report clinical trial results showing an increase in suicides to regulatory authorities. The Appeals Court sided with the pharmaceutical industry's position that the FDA's decision not to provide adequate warning of suicidal risk preempts any state consumer protection laws. The Supreme Court will shortly decide on a case involving Wyeth's Phenergan that could result in banning citizens' product liability lawsuits involving drugs by making FDA pre-emption a legal standard in the U.S.

The above examples are hardly unique. Over the last decade, suits over Zyprexa, the withdrawn pain pill Vioxx, the withdrawn diabetes medicine Rezulin, the withdrawn heartburn medicine Propulsid, as well as several antidepressants, have revealed that companies failed to disclose negative clinical trial results and minimized the risks of their drugs while they continued to hype them with aggressive marketing. **(Six months ago, Merck agreed to put aside $4.5 billion to settle about 27,000 Vioxx lawsuits.)** As Dr. John Guerigian, who worked at the FDA for two decades, testified at the recent Zyprexa trial, the agency did not always ask for strong warnings, even if it believed a drug was risky. He explained that companies typically oppose warnings since the agency knows it must compromise on its requests or face years of delay, noting, "We at the FDA know what we can obtain and we cannot obtain." The FDA does not test new drugs but relies

on manufacturers to report the results of their own tests completely and honestly. But when companies fail to do this or to comply with other regulations, they are rarely penalized. Several independent assessments have concluded that the agency is poorly organized, scientifically deficient and short of funding. In February, FDA commissioner, Andrew C. von Eschenbach also acknowledged that the agency now faces a crisis and may not be "adequate to regulate the food and drugs of the 21st century."

ENHANCE results are also unlikely to change anything because of the clout drug companies have on regulatory authorities and leading organizations that have been the recipients of their largesse. The American College of Cardiology and American Heart Association rapidly reassured physicians that Vytorin and Zetia were safe and discouraged patients from discontinuing them despite negative comments from leading authorities. A panel of four experts was assigned to discuss the study after it was presented at the meeting. One described Zetia as "a drug of last resort" and the panel's spokesperson called Vytorin "an expensive placebo". Nevertheless, in last month's impartial Sermo poll of several hundred physicians, 75% said the adverse portrayal of Vytorin and statins was "unwarranted" based on the ENHANCE study results, and 54% said it "would not at all" change their prescribing patterns. And although U.S. consumers and health plans could have saved several billion dollars had Canada's approach been adopted, the United Health Group, the largest U.S. health insurer, also recommends that patients continue taking Vytorin and does not plan to charge a higher co-payment than for other cholesterol lowering drugs because it sees no safety risk. Senator Chuck Grassley, head of the Senate Committee on Finance, was unhappy with the American College of Cardiology's support of Vytorin, and in a letter to the College's president, expressed concerns that "monies from Merck and Schering-Plough create the appearance of influence." Since 2003, the College has received nearly $5 million from Merck, $1 million from Schering-Plough, and more than $5 million from their Vytorin joint venture. The companies also paid $192,000 for 6400 square feet of exhibition booth space, $270,000 on a cholesterol education program, and $50,000 for hotel "Do Not Disturb" door hangers at the Chicago meeting.

Grassley also questioned the recently launched "49 Plan", a $3.5 million public relations campaign to "wine and dine" doctors in an attempt to offset the disappointing results of the Vytorin study. Noting that it was a "great deal of money for free lunches and dinners", he asked for all documents related to the seven week "schmoozefest", during which drug reps reminded physicians about the benefits of prescribing Zetia and Vytorin. Senator Herb Kohl, Chairman of the Senate Special Committee on Aging, was even more emphatic in his letter, stating, "I am troubled by any attempts to persuade physicians to prescribe a drug for any reason other than the patient’s

condition and the drug's effectiveness in treating it. Unfortunately, it appears that your '49 Plan' may do exactly that. Pharmaceutical reps often confuse educating with selling, and evidence shows that doctors' prescribing patterns can be heavily influenced by their sales pitches. Without academic detailing, physicians may not have access to information about the full array of pharmaceutical options, including low-cost generic alternatives. However, research has shown that when they do, doctors prescribe the best drug - not just the newest one - and healthcare spending is lowered." He asked Schering-Plough to provide a detailed description of the plan, including the number of reps involved and their compensation, as well as details on how the plan complies with industry guidelines and ethics.

What may have spurred Congressional investigators on were blogs on a web site from the company's own drug reps, such as "This instruction that we are to have a lunch or dinner EVERY DAY— come on!!... Hey Marketing Geniuses—this isn't 1990 anymore, ya know?? Throwing money at a problem is not the way to fix things—it will only make matters worse. Have the company come clean about the study, give us some good (or even not so good) evidenced based medicine—and let us earn back the business the right way." Another was even more outspoken, saying, "If Schering-Plough is hoping to get attention, they got it. Discussion of this plan is all over the Internet. However, this is definitely the wrong kind of attention. For a company that just created the ENHANCE fiasco, this is another stupid move. …. I seriously hope that the federal government raids Kenilworth and uncovers all the graft inside. It will be enough to put these people away for years. I've worked at a few Big Pharma companies and this one is the absolute most corrupt I've ever been exposed to, bar none!"

Such comments by disgruntled drug reps and other criticisms are not likely to derail a damage control campaign that has been carefully planned. It has already pointed out that executives with large amounts of stock options frequently exercise them for reasons other than any inside knowledge that will shortly fall in their value. The much anticipated reduction in atherosclerosis was not seen because almost all patients had previously taken statins for an elevated cholesterol. The National Lipid Association also downplayed the findings in a press release that emphasized the significant reduction in LDL, and that, "nothing in this study has changed our position about the necessity for lipid lowering or the need to treat patients to established National Cholesterol Education Program goals." That's not too surprising, since all of the nine doctors who drafted the release have financial ties to Merck and/or Schering-Plough. Other physicians on the payroll also chimed in, complaining that the media distorted the results. After all, LDL was reduced much more in the Vytorin group, as was CRP, a marker of inflammation, and therefore the drug must be beneficial. Perhaps

this would have been demonstrated if the study had lasted longer or if a different endpoint had been selected, as the expert panel recommended.

The companies are also banking on support from another ongoing study comparing Vytorin with Zocor alone in patients who have had a heart attack or unstable angina. Although it started in 2005, before the ENHANCE results were known, the aptly called IMPROVE-IT study hopes to prove that Vytorin patients will have fewer coronary events and that this will show a clear correlation with the degree of LDL lowering. The original protocol called for approximately 10,000 patients, and the study was projected to end in 2011 so that there would be at least 2 1/2 years of follow-up after the last patient's data had been obtained. There are now over 11,000 patients in the study to allow for dropouts and other contingencies. All trial participants and leaders are blinded to which treatment the patients are receiving, save for a Data Monitoring Committee. Its purpose is to periodically evaluate the results to determine if IMPROVE-IT should be halted prematurely to protect the participants because of evidence suggesting either excess harm or benefit. Following their last evaluation, the Committee reported on February 18, 2008 that they found no indication of adverse safety signals that would warrant any changes in the protocol.

It therefore seemed strange that despite criticism over the repeated delays in reporting the disappointing ENHANCE results and just a few weeks after they were published, a press release announced that IMPROVE-IT would now also be delayed. This information was released at 4 PM on a Friday afternoon so it would not attract media attention and did not contain the usual Schering-Plough or Merck logos so the companies would not appear to be responsible. The plain release explained that the academic leadership of the study trial recommended increasing the size of the patient population up to 18,000, and the sponsors had agreed. Questions were raised since both were presumably blinded to the data and many believed it was designed to delay the report until the patents on Zetia and Vytorin expire in 2013 or shortly thereafter. These suspicions seemed to be supported by the statement, "With the increase in enrollment, the current estimate for the completion of the trial is 2012. However, the actual date of completion is highly dependent on the observed event rates during the follow-up phase of the trial and the rate of enrollment. **Therefore, it is not possible to determine with precision an exact date that the trial will end."**

## Will IMPROVE-IT Prove The Death Knell For The Lipid Hypothesis?

IMPROVE-IT seems unlikely to succeed since Zetia has never been shown to prevent heart disease. Vytorin also raises questions about the use of LDL levels as the basis for FDA approval of a drug with a novel mechanism. Pfizer's torcetrapib was touted as a breakthrough because it not only

lowered LDL but also increased HDL. The ILLUMINATE torcetrapib and Lipitor trial was terminated after it was found that the combination group had 60% more deaths compared to those just taking Lipitor. Improving laboratory results does not always guarantee clinical benefits, as evidenced by Avandia, a Type 2 diabetes drug approved in 1999. Avandia had never been shown to reduce any microvascular complications and a 2007 *New England Journal of Medicine* article found it was associated with a 43% increase in heart attacks. The FDA mandated a black box warning but critics feel it should be banned, and that the increasing number of lawsuits could make Avandia the next Vioxx. Pfizer's Exubera, an inhaled insulin approved by the FDA in 2006, now also has a black box warning and may be withdrawn because of a recent study that found it could cause lung cancer.

New drugs tend to be advertised the most because patients assume that they must be better, and adverse long-term side effects are not known. As Osler advised doctors 100 years ago, **"Use the new medicines as soon as they come out, before they lose their effectiveness."** Not infrequently, they are no better than much less costly medications, some of which may not require a prescription. Some have urged a ban on new drug advertising for two or three years until post marketing survey results are in. Many feel that all drug ads should include a toll free number and web site so consumers can report adverse side effects to the FDA. However, nothing is likely to change and the lipid hypothesis will probably continue to prevail because it is so profitable. In addition to drug and food companies, others are also raking it in. The American Heart Association quickly criticized the negative reports about Vytorin, but few people are aware that its sponsors pay them $2 million/year. **Subway has shelled out $10 million to use the Association's "Healthy Heart" logo for its sandwiches.** Over 175 other products from cereals to orange juice also carry this meaningless seal of approval so they can increase prices. But that's just the tip of the iceberg, since there are several similar scams, – so stay tuned!

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**Health and Stress**
*The Newsletter of*
*The American Institute of Stress*
124 Park Avenue Yonkers, NY 10703

**ANNUAL SUBSCRIPTION RATE:**

E-Mail……$25.00

**ISSN#108-148X**

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