

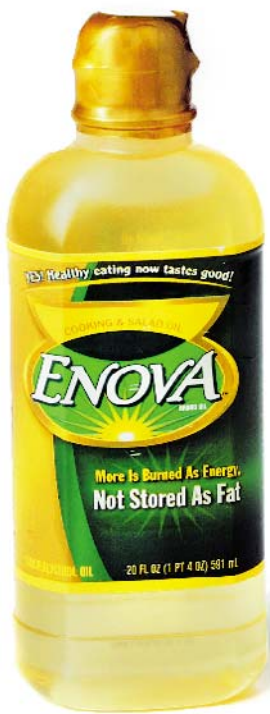
The Washington Post

HEALTH

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TUESDAY, FEBRUARY 1, 2005

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BY MELISSA CANNARAZZI FOR THE WASHINGTON POST

LEAN PLATE CLUB

Sally Squires

Enova's Claim:
Oil Slick

"I'm not asking you to change who you are," says the hip young woman on the television commercial. "I am asking you to change how you think . . . about pancakes, stir-fry, pasta, brownies, shish kebab, French fries, waffles, salad dressing, birthday cake, carrot cake. . . ."

The TV spot is for Enova, a new cooking and salad oil coming to a grocery store near you. A reformulated mixture of canola and soybean oils, Enova may soon also be an ingredient in commercially prepared foods from spreads to baked goods.

"Almost every major food company in the United States has expressed some interest in it," says Brann Lane, research manager of nutritional science for agricultural conglomerate Archer Daniels Midland, maker of Enova.

The oil is already making inroads in Japan, where it's been sold since 1999 as Econa. Consumers use it to stir-fry vegetables and to deep-fry tempura. Food manufacturers there have put it into mayonnaise and salad dressings.

"It does everything very well," says Lane, who notes "it's a nice, bland, light oil that has no inherent flavor that is passed on to food products. It can be used across the board so you don't have to have a [different] sautéing oil and a salad oil."

But Enova's most distinguishing feature may be its potential health benefits. Through a patented process, the oil has been altered to be rich in a naturally occurring kind of fat that is absorbed just like standard fat but is metabolized differently. Known as diglycerides, these fats aren't broken down easily by the body. So instead of being sent to fat cells for storage, diglycerides are more likely to be shuttled to the liver, where they are burned for energy.

In theory, that could result in less body fat and—possibly—weight loss, a selling point underscored on Enova's label, which says, "More is burned as energy. Not stored as fat."

"The key message that we are trying to drive home is the health benefit of Enova that less is stored in the body as fat compared to other vegetable oils," says Paul Tutt, director of the Enova Brand for ADM Kao, the Archer Daniels Midland joint venture that makes the oil. "We feel that Enova is a healthy alternative to cooking with

See ENOVA, Page F6

INSIDE

2 Problem Drinking
Some Recover

3 Flu Shot Available
Should You Bother?

3 Fitting in Fitness
Inspiring Examples

6 Office Stool Sample
Don't Rely on It

HEALTHY SKEPTICISM | First in an occasional series

Where the
Naproxen Story
Went Wrong

When NIH Halted a Major Study, Citing Risks From a Common Painkiller, the Media Played the News Big. That Was Just Part of the Problem

By STEVEN WOLOSHIN, LISA M. SCHWARTZ and H. GILBERT WELCH
Special to The Washington Post

Medical research often becomes news. But sometimes the news is made to appear more definitive and dramatic than the research warrants. This article dissects a recent health news story to highlight some common study interpretation problems we see as physician researchers and show how the research community, medical journals and the media can do better.

Raising doubts about the safety of a widely used drug like naproxen, also known as Aleve, is big health news. Add this to recently raised concerns about other drugs in the same broad category—nonsteroidal anti-inflammatory drugs (NSAIDs) such as Vioxx, pulled off the market this fall, and Celebrex—and the news is big indeed.

So it is no surprise that the government's decision in December to halt the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) because of safety concerns about naproxen received intense

media coverage. In the three days following the announcement by the National Institutes of Health (NIH), the story appeared on the front pages of all 10 top-circulation U.S. newspapers and led numerous national TV and radio newscasts.

Front-page headlines included: "Heart Risk Seen in Naproxen" (Wall Street Journal), "Tough Choice: Pain or Risk?" (USA Today), "Patients, Doctors Agonize Over Risks of Painkiller" (Los Angeles Times), "Study Links a Fourth Painkiller to an Increase in Heart Problems" (New York Times) and "Warnings About Medications' Risks Add Worry to Pain" (The Washington Post).

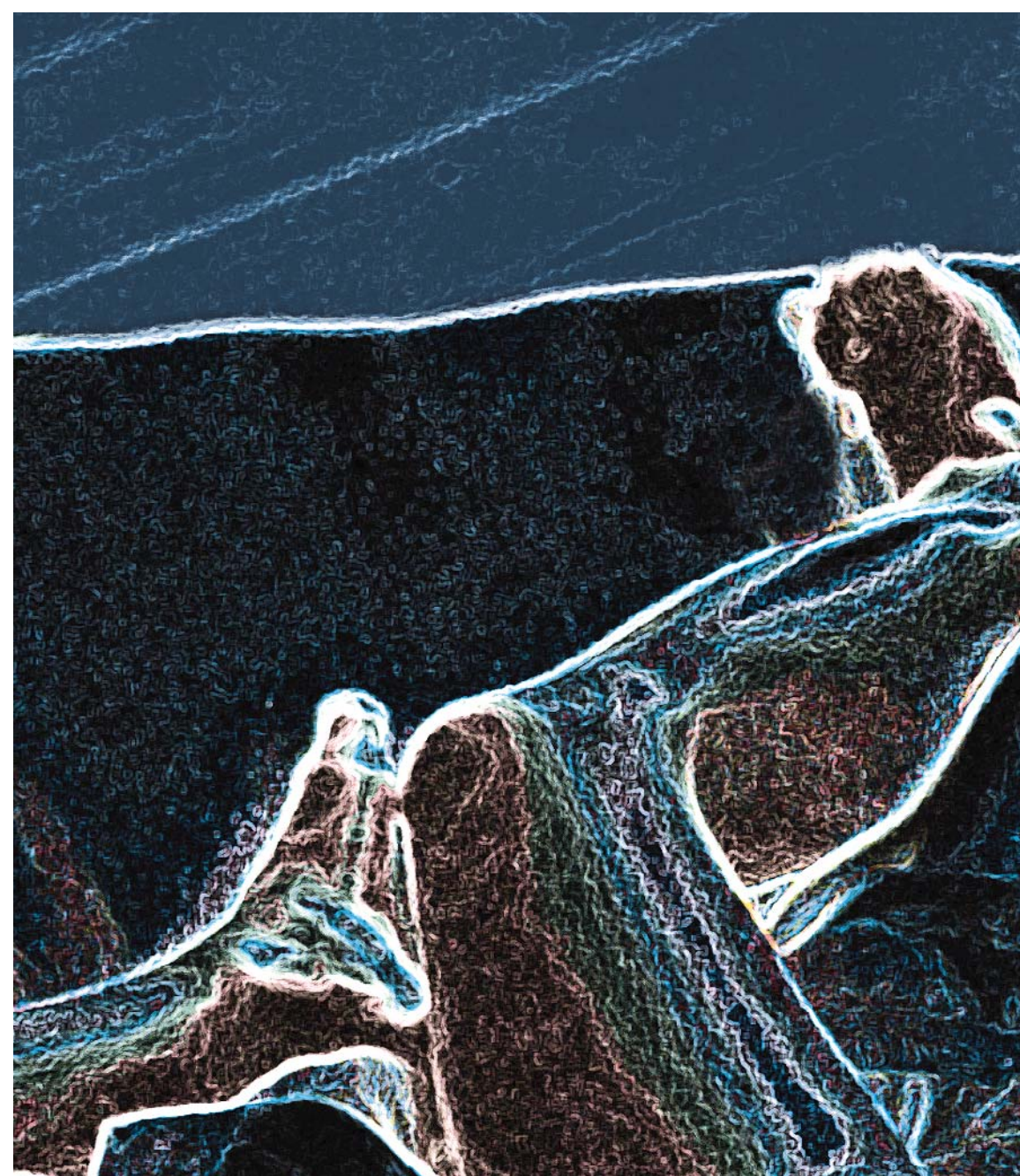
The headlines and the stories' prominent play overstated the nature of the evidence, inviting their audiences to believe that taking naproxen as directed for pain had been shown to be dangerous. As we explain, this may not be the case.

But the media were not the sole source of the problem. The Food and Drug Administration (FDA) and NIH played roles as well.

See TRIAL, Page F5



COLLAGE BY THE WASHINGTON POST



THE WASHINGTON POST

Night
Crawlers

Bedtime Gave Her the Creeps—Until Restless Legs Got Her Moving

By LIZ KELLY
Special to The Washington Post

I awoke at 2 a.m. to the distinct sensation of worms crawling through my flesh. Muscle was being squeezed out of place, twisted from within. I had to move immediately. I kicked to shake the creatures out.

As I slowly gained consciousness, reason returned. The problem wasn't worms; it was some kind of indistinct spasm in my legs—maybe the result of a day spent raking leaves, I figured. I flexed my toes, rubbed my calves and, eventually, fell back asleep.

Over the next few weeks, always when I was asleep, the writhing in my calves would return. Bedtime became a perverse nightscape where the more tired I was, the more likely I was to experience the wriggling sensations. I fought to ignore them, to keep my legs still, but the crawly feeling always won, not stopping until I stood up, massaged my legs and walked around a bit.

On the worst nights, which became more frequent, nothing helped. I'd end up reading at the dining room table, getting up every 15 minutes to walk, jealous of the sleeping dogs curled up on the couch. I'd doze off in a wooden chair at 4 or 5 a.m.

Whatever it was, it was starting to affect my waking hours, too. At work I felt like the undead—pale, mumbling and confused, unable to make even basic decisions, lashing out unpredictably at others. I tried using heating pads, elevating my legs, soaking in hot baths and, at a low point, tak-

See RESTLESS, Page F4

Naproxen: From Withheld Data to Exaggerated Risk

TRIAL, From F1

What Happened With the Study?

ADAPT was a large, federally funded study designed to investigate whether Celebrex or naproxen could prevent Alzheimer's disease. In January 2001 researchers began enrolling more than 2,400 healthy men and women age 70 and older who showed no signs of Alzheimer's but were considered at increased risk because of a family history of the disease.

Study participants were randomly assigned to one of three groups: One took Celebrex daily, another took naproxen, while the third took a placebo. The investigators planned to follow participants for about seven years to see how many people in each group developed Alzheimer's disease.

As in most major research studies, a committee was charged with periodically monitoring study results. It was the committee's responsibility to decide whether the study should be stopped early—either because of the occurrence of unforeseen risks or the appearance of a dramatic treatment benefit.

This data safety monitoring committee met early in December 2004 and, according to news reports, reviewed some data raising the possibility that naproxen increased cardiovascular or cerebrovascular risk—that is, risk of conditions involving the heart or brain and related blood vessels. But given the small size of the differences observed between the naproxen users and the placebo users and the possibility that they might be just a statistical fluke, the committee did not recommend stopping the study.

Later in December, spurred by growing concerns raised by other studies about risks associated with Celebrex, NIH also reviewed the ADAPT study data.

NIH reached a different conclusion: The study should be stopped. This dramatic step was taken, according to an NIH news release, to protect the safety of participants because the data "indicated an apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo."

How Risky Was Naproxen?

To make sense of the NIH announcement, readers need answers to two basic questions:

- What are the "events" that occurred more frequently among naproxen users?
- How much more often did these events occur?

Both the official NIH announcement and a related press release by the FDA were remarkably sparse in details and failed to provide answers to either of these questions. As of this writing, virtually no one outside NIH, the ADAPT study team and possibly the FDA knows which specific events prompted the announcement or how often these events occurred.

■ **Risk of what?** NIH halted the ADAPT study because more "cardiovascular and cerebrovascular events" occurred among patients taking naproxen than those taking placebo.

But what does that term mean? Unfortunately, the definition of the term was never released.

"Cardiovascular and cerebrovascular events" could refer to a slew of outcomes varying widely in importance. At one extreme, such "events" might refer to death from stroke or heart attack. But they could also refer to nonfatal heart attacks and strokes, some serious, some mild. Or episodes of chest pain. Or mini-strokes—known medically as transient ischemic attacks—which are generally mild and short-lived, and leave no permanent effects. Or even changes on an EKG test or a finding on an MRI scan that never produced symptoms.

All we know is that the events in question represent some combination of such incidents and perhaps others as well. The point is that not all events are equally important.

■ **How big was the risk?** Not only were the "cardiovascular and cerebrovascular events" not defined, the number of such events was not released. Assessing risk in the absence of such information is difficult. (See "Research Basics: Quantifying Medical Risk," at right.) The announcement did not even report the relative frequency of the events—that is, did the events occur twice or three times or four times as often in the naproxen group?

But thanks to the persistence of journalists, a few relevant numbers have emerged. Reporters have quoted study investigators as saying that there were 70 events altogether; and the occurrence of events among naproxen patients was 50 percent higher than among those taking placebo.

Based on these numbers and the number of patients in each study group—a figure available on an ADAPT study Web site (www.jhuccf.com/adapt/pdf%20documents/factsht.pdf)—it is possible to calculate the likely magnitude of the naproxen risk. Assuming that Celebrex posed no increased risk to patients (the NIH announcement stated that "no significant increase in risk for Celebrex was found in this trial"), we calculate that over about three years, cardiovascular and cerebrovascular events occurred in 3.7 percent of patients taking naproxen, compared with 2.5 percent of patients taking placebo. (See "What Was the Likely Risk of Naproxen in This Study?" below.) If the figures in the news reports are correct (that is: 70 events; 50 percent higher risk with naproxen; Celebrex and placebo have the same risk), no other mathematical solution is possible.

You don't have to take our word for it: You can do the math yourself, following the steps we outline at www.vaoutcomes.org/washpost.php. Be warned: If the word "algebra" triggers long-forgotten high school nightmares, you may want to enlist your son or daughter for the task. Although the math involves using algebraic equations to solve for three unknowns, it is actually straightforward.

Similarly, we can compute what the worst-case scenario would look like. Assuming (absurdly) that there were no cardiovascular and cerebrovascular events in the Celebrex group (that is, Celebrex reduced the risk to zero in the study), the events occurred in 5 percent of naproxen patients compared with 3.3 percent of those assigned to placebo. To test this or other scenarios, try the interactive calculator at www.vaoutcomes.org/washpost.php.

These calculations suggest that naproxen could pose a risk, but that risk would affect less than two people per hundred over about three years. And the risk must be considered in light of who the study participants were—patients age 70 and older. Because the chance that a person will experience a stroke or heart attack is strongly related to age, any added risk for younger people posed by naproxen—if it exists—would likely be considerably lower.

The Bottom Line

Although the precise risk of naproxen in the ADAPT study is hard to know—because we don't know what constitutes a "cardiovascular or cerebrovascular event"—it is possible to deduce from the information available that the size of the risk is, at most, modest.

In addition, the news from ADAPT conflicts with other credible studies that have found either no increased cardiovascular risk with naproxen or even some evidence that it actually protects the heart.

But more concerning is the nature of the NIH announcement. It failed to distinguish between naproxen users in the study—who were taking the medication only in hopes of preventing Alzheimer's disease—and naproxen users in the general public who take the medication because of its demonstrated effectiveness in treating

Research Basics

Quantifying Medical Risk

News stories about the findings of medical studies often contain statements like: "Treatment X reduced the risk of heart attacks," "treatment Y causes cancer" and "treatment Z saves lives." These statements are *qualitative*—they describe the effect without using numbers. But without numbers, it's hard to tell how big the effect is—and how meaningful it might be to you.

You apply this principle regularly in daily life. How you react to news that taxes are increasing, rents in your building are going up or salaries in your firm will rise depends entirely on the size of the increase. When it comes to money, it is hard to imagine anyone who would hear "going up" and not want to know what the real numbers were.

But surprisingly, many people don't demand the same kinds of numbers when judging medical findings. Yet the only way to assess the importance of medical research statements such as "treatment X reduced risk" or "saves lives" is to examine *quantitative* data—the frequency of events in those receiving and not receiving treatment.

Even then, knowing the numbers is just half the story. You also need to know to what extent the numbers might apply to you. The tax increase, for instance, might apply only to people without dependents; if you're a parent of young children, you wouldn't be affected. Likewise, in the case of medical research, it is important to consider the characteristics of patients in the study—particularly their age, sex and major risk factors or diseases.

Imagine a study designed to investigate a treatment to reduce heart attack risk. In considering how well the treatment works, you must also factor in patient characteristics that influence risk. Age, sex and whether or not a person smokes all matter a lot in determining how likely a person is to have heart problems. (See "What is the chance of having your first heart attack in the next 10 years?")

According to the table, the average 65-year-old man who smokes (10-year risk of heart attack = 16 percent) is 16 times more likely to have a heart attack in the next 10 years than is a 50-year-old woman who does not smoke (10-year risk of heart attack = 1 percent). A 65-year-old man's heart attack risk would be even higher if he had high blood pressure or if he had already had a heart attack.

Different people face very different risks of not only heart attack but also other health events. This is not only because their ages differ but also because they have different genetics and different environmental exposures. Consequently, the effectiveness of treatment will differ in different groups of people.

If you are a woman age 50 who doesn't smoke, a study showing a reduced risk of heart attack among 65-year-old men who smoke may not apply to you. Look for studies that involve patients that are similar to you. In other words, the more you resemble the patients being studied, the more likely the study findings will be relevant to you.

—Steven Woloshin, Lisa M. Schwartz and H. Gilbert Welch

What Is the Chance of Having Your First Heart Attack in the Next 10 Years? *

	Women		Men	
	Age 50	Age 65	Age 50	Age 65
Non-Smokers	1%	3%	5%	13%
Smokers	3%	5%	12%	16%

* Based on an average cholesterol level and normal blood pressure. SOURCE: National Heart Lung Blood Institute's risk assessment tool (<http://nlh.nih.gov/atpi/calculator.asp>)

What Was the Likely Risk of Naproxen in This Study? *

The chance of undefined "cardiovascular or cerebrovascular events" among relatively healthy people age 70 or older over about 3 years

	Naproxen	Placebo	Celebrex	TOTAL
Events	26	26	18	70
Number In Group	702	1,057	704	2,463
Risk	3.7% (3.7 in 100)	2.5% (2.5 in 100)	2.5% (2.5 in 100)	
Possible Effect of Drug	50% higher risk than placebo (1.2 more events per 100 people)	N/A	Same risk as placebo	

* Calculation assuming that Celebrex had no effect on risk. SOURCE: News reports, ADAPT study facts (www.jhuccf.com/adapt/pdf%20documents/factsht.pdf) and authors' calculation.



Aleve's Maker Tries to Reassure the Public

The setting: A comfortable living room in a family home. Two women are chatting, when the younger one spots a bottle of Aleve (naproxen) on a counter.

"Hey Mom," she asks, sounding concerned. "Are you still taking Aleve for your arthritis pain. . . What about all the news lately?"

"Oh honey, I checked with my doctor," her mother answers; she says he told her it is "fine" for her to keep taking Aleve as long as she "follow[s] the directions on the label."

This is a scene from a television commercial intended to reassure the public that Aleve is safe. The ad is running more than a month after the National Institutes

of Health (NIH) halted a major drug trial, citing health risks tied to naproxen. A spokesman for Aleve maker Bayer HealthCare last week refused to say exactly when or why the company launched the ad campaign, or if more television or print spots are planned.

National sales for Aleve in 2003, the most recent year tallied, totaled \$151.2 million, excluding sales at Walmart and club stores, according to Brandweek magazine. Market research groups say it is too soon to tell if sales of the popular over-the-counter drug have dipped since NIH stopped the trial.

This is not the first time in recent months a drug manufacturer has sought

to control damage through advertising. In November, a few days after Food and Drug Administration (FDA) scientist David J. Graham publicly called into question the safety of cholesterol drug Crestor, manufacturer AstraZeneca placed print ads in major newspapers—including The Washington Post, the New York Times and USA Today—asserting that the FDA had "confidence in the safety and efficacy" of the product. In December, following a complaint from health advocacy group Public Citizen, the FDA ordered the drug company to stop running the ads, calling their claims "false or misleading."

Sidney Wolfe, director of Public Citizen's Health Research Group, said last week the Aleve ad did not misrepresent facts as the Crestor ad did. But he complained that the Aleve ad does not mention a heightened risk for gastrointestinal side effects associated with the use of nonsteroidal anti-inflammatory drugs—the drug class that contains Aleve. Aleve's label advises people ages 12 to 64 not to exceed two pills every eight to 12 hours or three pills a day; those over age 65 shouldn't exceed one pill every 12 hours without a doctor's okay. In addition to arthritis, the drug is commonly used for backaches, muscular aches, headaches and menstrual pain.

—January W. Payne

Attention High School Seniors

APPLY NOW FOR THE 2005 HIGH SCHOOL WRITING SEMINAR & SCHOLARSHIP PROGRAM

The Washington Post's Young Journalists Development Program has partnered with the National Association of Hispanic Journalists and the Asian American Journalists Association to help area high school seniors, who are interested in journalism careers, build their writing skills.

At the end of the seminar, each participant will produce a newspaper or magazine story. Professional journalists will judge the stories. Prizes will be awarded for the top two stories based on clarity of thought, organization, writing style, grammar, spelling, punctuation and evidence of research. (There is no fee to apply.)



When:

- March 5, 12, 19, and 26, 2005 9:00 a.m. – 1:00 p.m. Workshops will be held at The Washington Post on four consecutive Saturdays.

Eligibility:

- High school seniors attending Washington-area schools. The program is not limited to Latinos and Asian Americans, but special emphasis is placed on participation by minority students. All interested students are encouraged to apply.

Requirements:

- An interest in a print journalism career and a command of the English language. Students must attend all four Saturday sessions. Interested students must submit a written application, including a one-page writing sample, parental/guardian approval and a recommendation from a high school teacher or newspaper adviser.

Prizes:

- Two scholarships of \$2,500 – Prizes will be based on the stories produced in the seminar, financial need, class attendance and participation in all four seminars.

Deadline:

- Completed applications should be addressed to: The Young Journalists Development Program, The Washington Post, 1150 15th Street, N.W., Washington, D.C. 20071. Applications must be postmarked by Thursday, February 10, 2005. Students who are accepted will be notified by Friday, February 25, 2005.

How To Apply:

- Get applications from high school journalism advisers or download applications from www.washpost.com/yjdp (click on high school writing contest and download application.)
- For more information contact:**
Athelia Knight: 202-334-7132, knights@washpost.com
Nancy Tita: 202-662-7151, ntita@nahj.org
Or Tan Ly: lyt@washpost.com

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