

CERTs Research: Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Agency for Healthcare Research and Quality

AHRQ's mission is to improve the quality, safety, efficiency, and effectiveness of health care by:

- Using evidence to improve health care.
- Improving health care outcomes through research.
- Transforming research into practice.

Background

The mission of the Centers for Education & Research on Therapeutics (CERTs) is to conduct research and provide education that will advance the best use of therapeutics (drugs, medical devices, and biological products). The program is administered as a cooperative agreement by the Agency for Healthcare Research and Quality (AHRQ), in consultation with the U.S. Food and Drug Administration (FDA). The CERTs receive funds from both public and private sources, with AHRQ providing core financial support.

The CERTs network currently comprises seven research centers, a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations. Each CERTs center focuses its educational and research efforts on therapies in a particular population or therapeutic area (see box).

CERTs Program Centers

Each center focuses its educational and research efforts on therapies in a particular population or therapeutic area:

- *Duke University Medical Center*—Therapies for disorders of the heart and blood vessels
- *HMO Research Network*—Drug use, safety, and effectiveness in health maintenance organization populations
- *University of Alabama at Birmingham*—Therapies for musculoskeletal disorders
- *University of Arizona Health Sciences Center*—Drug interactions that result in harm to women
- *University of North Carolina at Chapel Hill*—Therapies for children
- *University of Pennsylvania School of Medicine*—Therapies for infection; antibiotic drug resistance
- *Vanderbilt University Medical Center*—Prescription drug use in a Medicaid population





Collectively, the CERTs have more than 40 unique data sources and serve as a national resource of experienced researchers. The CERTs network seeks to increase awareness of the benefits and risks of new, existing, and combined uses of therapeutics, thereby improving the effectiveness and safety of their use.

CERTs Research on NSAIDs

The overarching goals of CERTs projects are to advance knowledge; inform health care providers, patients, and policymakers about that knowledge; and improve aspects of the health care system related to therapeutics. Since the inception of the CERTs program in September 1999, the centers have developed a portfolio of more than 200 completed and ongoing studies with results that have addressed important issues regarding the best use of medical therapies.

Nonsteroidal antiinflammatory drugs (NSAIDs) constitute one of the most commonly used drug classes in the United States. They are used for arthritis and muscular pain because of their analgesic (pain-killing), antiinflammatory, and antipyretic (fever-reducing) properties. NSAIDs—some available without a prescription and some available by prescription only—are used by a wide range of patients and for numerous medical conditions. Many older adults chronically use NSAIDs. This can be a problem since the risk of side effects increases with age. A number of CERTs studies of NSAIDs have been completed or are currently being conducted.

Advancing Knowledge

The CERTs study the beneficial and potentially harmful effects of drugs so that physicians, patients, and policymakers can make informed decisions about treatment options.

Current perspectives: NSAIDs and COX-2 inhibitors. Persistent, or chronic, use of NSAIDs can cause a range of gastrointestinal (GI) problems, from small ulcers to life-threatening perforations of the stomach lining. Although the exact mechanism for these effects is unknown, one theory suggests that NSAIDs affect the function of platelets, a type of blood cell important in blood clotting. In addition, NSAIDs block production of prostaglandins, which are a group of hormone-like substances that help prevent injury to the stomach and small intestine.

Cyclooxygenase-2 (COX-2) selective NSAIDs were developed as an alternative to traditional antiinflammatory drugs for people at risk for GI problems. While COX-2 inhibitors cause less bleeding and fewer ulcers, they are also more expensive than traditional NSAIDs. Three COX-2 inhibitors licensed for use in the United States are rofecoxib (Vioxx®), celecoxib (Celebrex®), and valdecoxib (Bextra®); others pending FDA approval include parecoxib, etoricoxib, and lumiracoxib.

In September 2004, rofecoxib (Vioxx®) was voluntarily withdrawn from the market by its manufacturer, Merck & Co. This action was taken in response to studies that suggested the popular drug increased the risk of cardiovascular events (including heart attack and stroke). In April 2005, the FDA requested that Pfizer suspend sales of valdecoxib (Bextra®) because studies indicated an excess of cardiovascular events with this drug. At the same time, the FDA asked manufacturers of all marketed prescription NSAIDs, including celecoxib, to revise the labeling in the package insert to include a boxed warning that highlights the potential for an increased risk of cardiovascular events and the well-

described, serious, potentially life-threatening GI bleeding associated with NSAID use.

High frequency of NSAID use.¹ Prior to the regulatory changes with this class of drugs, the CERTs conducted a number of epidemiologic studies on NSAID and COX-2 inhibitor use, and the information continues to be useful for patients as they weigh the risks and benefits of using such medications. These studies were undertaken because the Merck-funded Vioxx Gastrointestinal Outcomes Research (VIGOR) clinical trial raised questions about dose-related adverse effects, such as high blood pressure and swelling, which are relatively common with high doses of rofecoxib. (Unlike other antiinflammatory drugs, rofecoxib's approved dose for acute pain [50 mg for a maximum of 5 days] was double the maximum dose recommended for chronic use.)

To ascertain the frequency of high-dose NSAID use, the Vanderbilt center analyzed NSAID use in patients age 50 and over in Tennessee's Medicaid program, TennCare. Of the nearly 300,000 patients enrolled, 14 percent had a current NSAID prescription for a supply of pills for longer than 5 days. Rofecoxib accounted for 25 percent of those prescriptions filled.

The researchers found that use of high doses of rofecoxib for longer than 5 days was relatively common, occurring in 17 percent of chronic users. The findings suggest that, in view of dose-related adverse effects, such use should be discouraged.

NSAIDs and the risk of serious coronary heart disease.²⁻⁴ Differential rates of cardiovascular events in the VIGOR trial prompted the Vanderbilt center to conduct a study on naproxen and other nonaspirin nonsteroidal

antiinflammatory drugs (NANSAIDs) to measure their effects on the risk of serious coronary heart disease in order to determine if, as hypothesized in VIGOR, the NANSAIDs had cardioprotective qualities. Researchers analyzed TennCare data obtained from 1987 to 1998 and identified a group of 181,441 new NANSAID users and an equal number of nonusers. The study reviewed records from a period prior to the development and eventual marketing of rofecoxib and celecoxib, so these two drugs were not included in the study. The most frequently used NANSAIDs were ibuprofen and naproxen, accounting for 38 and 27 percent of use, respectively. The study found no protective effect of naproxen or other NANSAIDs on the risk of heart attack or sudden cardiac death, which indicates that these drugs should not be used for cardioprotection without supporting evidence from additional studies.

A subsequent study by the same researchers using data from 1999 through 2001 found that a dose of 50 mg of rofecoxib increased the risk of serious coronary heart disease nearly twofold.

Another study, conducted in the same time period, compared the risk of coronary heart disease in patients taking rofecoxib and other NSAIDs, specifically celecoxib. Investigators from the Vanderbilt center, FDA, and Kaiser Permanente used data on about 1.4 million patients from 1999 to 2001. They concluded that patients taking rofecoxib had a 1.59 times increased risk of coronary heart disease over those taking celecoxib. For those taking high doses of rofecoxib, the risk was 3.58 times greater than for patients taking celecoxib. They also found no evidence that naproxen protected against coronary heart disease.

Gastroprotective measures for chronic NSAID users.⁵ A number of effective strategies have been developed to alleviate the risk of NSAID-induced complications. Such strategies include discontinuing NSAIDs entirely; substituting COX-2 inhibitors for traditional NSAIDs; or prescribing a gastroprotective therapeutic, such as an anti-ulcer agent, along with the NSAIDs. To characterize the extent to which NSAID users received protective therapy from GI complications, the Vanderbilt center reviewed TennCare records for 76,765 recurrent NSAID users.

Of these chronic NSAID users, only 16 percent received one of the recommended protective therapies: 10 percent took traditional NSAIDs in combination with an anti-ulcer agent and 6 percent took COX-2 inhibitors. Of chronic NSAID users with two or more risk factors for GI complications (75 years of age and over, history of GI bleeding, or taking multiple medications at the same time), only 30 percent were treated with gastroprotective therapy.

It was unclear to the researchers why so few regular NSAID users were treated with gastroprotective therapies. Further study will be necessary to determine why the recommended strategies were not used in at-risk populations.

Informing Patients and Providers

Understanding the risks and benefits of medical therapies is a critical step to improving the safety and effectiveness of their use. It is also critical to ensure that patients and providers have the knowledge needed to use medical therapies appropriately.

Chronic use of NSAIDs among the elderly.^{6,7} As stated before, NSAIDs are among the medications most frequently prescribed to the elderly, primarily for musculoskeletal symptoms associated with osteoarthritis. The risk of GI bleeding and other complications increases in chronic NSAID users over age 65, but there are alternative therapies to NSAIDs that are safer and may be equally effective.

In order to lower NSAID use to more appropriate numbers, the Vanderbilt center developed a physician educational program to communicate the risks of chronic NSAID use and suggest alternatives. They measured the effectiveness of the educational program in a group of physicians who treated TennCare participants.

Through face-to-face visits, physicians learned from other physicians about substitutes for NSAIDs. Some of these alternatives were acetaminophen (Tylenol and other products) and nonsystemic treatments such as topical ointments. A packet of materials, including educational messages and reprinted journal articles, was distributed to each physician.

The results indicate that this educational program reduced NSAID use by 7 percent in elderly patients who were regularly taking these drugs to relieve musculoskeletal symptoms. While the reduction was relatively small, the researchers believed that this approach, if used with higher intensity and broader application, could reduce chronic NSAID use to those for whom no other option works. Followup research will be necessary to determine if the physician interventions were indeed successful in producing a sustained decrease in NSAID prescriptions in at-risk populations.

The Vanderbilt center also developed an educational program designed for nursing home physicians and staff to reduce the use of NSAIDs among nursing home residents. The results were similar to those of the prior study.

Importance of physician-patient communication about over-the-counter medications.⁸ Self-care with over-the-counter (OTC) medications, including NSAIDs, is very common among patients. But as the number of prescription products becoming available OTC increases, so does the risk of drug interactions and duplication of medications.

The University of North Carolina at Chapel Hill center used data collected from the University of New Mexico Health Sciences Center's general medicine and family practice clinics to study communications between patients and providers about the use of OTC medications. Fifty-seven percent of patients reported using one or more OTC medications in the past month. The most commonly used OTC drugs were analgesics such as aspirin; cold or allergy products; and antacids. Physicians asked questions about OTC medications in 37 percent of the encounters, but infrequently asked questions or informed patients about potential duplication of prescription and OTC drugs and drug interactions.

The study found that patients wanted their physicians to ask questions about OTC medication. Twenty-three percent of patients said they did not tell their physician about their OTC medications because the physician did not ask, and 13 percent of patients simply forgot to share the information. To better understand what people are doing for their health and to reduce the risk of adverse drug reactions, physicians need to routinely ask patients about OTC medications, and patients need to be



proactive about discussing with their physicians what medicines they are taking.

Intervention to promote safe prescribing and use of NSAIDs.

Recent studies have shown that serious adverse reactions may occur when OTC NSAIDs are used alone or in combination with other medications. However, patients may not report to their health care providers that they are using OTC NSAIDs as well as their prescription NSAIDs. The University of Alabama at Birmingham center has begun a 4-year project to test the effectiveness of an intervention promoting safe prescribing of NSAIDs in an outpatient setting. Their approach focuses on both patients and physicians.

Researchers are developing toolkits for patients and physicians to promote safe prescribing and use of NSAIDs. The Patient Activation Kit for NSAID Safety will include a self-assessment of NSAID risk and pointers for discussing personal safety risk factors with the physician. It will be given to patients in a routine appointment before their physician visit. The goal of the project is safer prescribing practices as reported by patients.

Looking to the Future

The CERTs continue to conduct research and develop educational projects, such as those described above, that study and report the efficacy, safety, and use of various medical therapies. The studies highlighted in this Program Brief demonstrate progress, but additional research is needed.

For More Information

The CERTs welcome input about the types of research and education needed to better address costs, effectiveness, and safety issues related to the use of

therapeutics. More information on the CERTs program is available from AHRQ's Center for Outcomes and Evidence:

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AHRQ Pub. No. 06-P001
October 2005