ON THE BRAIN

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Symposium Examines Pain Management Issues

Among man's many maladies, pain is perhaps the most perplexing. It can be fleeting and minor. Or it can be chronic, debilitating and crippling. It is also intensely personal. What one can tolerate in pain, another cannot. On March 2, the Harvard Mahoney Neuroscience Institute symposium on "Successful Pain Management" in Palm Beach examined broad aspects of pain, featuring four luminaries from Harvard Medical School (HMS).

The symposium, hosted by Joseph B. Martin, M.D., Ph.D., Dean of the Faculty of Medicine at HMS, and moderated by Arnaud de Borchgrave, editor-at-large of *United Press International* and the *Washington Times* and director of transnational threats at the Center for Strategic & International Studies, featured Anne Louise Oaklander, M.D., Ph.D., assistant professor of anesthesiology and neurology; Rami Burstein, Ph.D., associate professor of neurobiology; Richard Frank, Ph.D., the Margaret T. Morris professor of health care policy; and Ted Kaptchuk, O.M.D., assistant professor of medicine at HMS's Osher Institute.

(L–R) Dr. Joseph B. Martin with Mrs. David Mahoney and Mr. Arnaud de Borchgrave

The Link to the Nervous System

Dr. Oaklander, nationally recognized for her expertise in the management of chronic pain, especially neuropathic pain, is considered a leading authority on shingles, a painful nerve inflammation.

"Neurology is not the first thing you would think of when you think of pain," she told the audience. "I think of, say, orthopedic injuries or pain from cancer. But, in fact, neuroscience is really at the heart of pain, the medical problem of pain. And the reason for that is that all pain sensations are received, transmitted and perceived by the nervous system. So without the nervous system, we would have no pain sensation. We really need that sensation of pain to keep us out of harm's way."

An estimated three million Americans – about one percent of the population – suffer from neuropathic pain, which results from a nervous system malfunction set off by nerves damaged from diabetes, HIV, cancer, trauma, toxic doses of drugs or other causes. With this type of pain, said Dr. Oaklander, "the pain system doesn't work as it's designed to; there's an illness or injury that affects pain-sensing neurons." The pain system is designed to work in "short-term bursts and then go away," she explained. Patients who suffer from neuropathic pain, however, often experience severe pain for months, years and sometimes indefinitely.

Four classes of drugs have been shown in clinical trials to be effective for treating neuropathic pain. The first class of drugs includes tricyclic antidepressants, such as amitriptyline, nortriptyline and despiramine. Low doses of these drugs boost levels

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Audience listens attentively to the Symposium on Successful Pain Management in Palm Beach

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of the brain chemical serotonin, which has been shown to be low in people in pain.

Medications originally marketed to treat epilepsy are also successful in managing neuropathic pain. Both epilepsy and neuropathic pain are caused by uncontrolled neuronal firing. The most common anticonvulsant prescribed for pain is Neurontin (gabapentin), and Tegretol (carbamazepine) is also "very effective against brief shock-like neuropathic pain," Dr. Oaklander said.

Opioids, or morphine-like drugs, help some but not all patients with neuropathic pain. Many patients find these drugs effective, despite potentially unpleasant side effects. Another class includes local anesthetics, either in the form of a patch or various creams or ointments, that can be applied to skin that is painful.

At Massachusetts General Hospital, where she is an anesthesiologist, Dr. Oaklander is investigating the use of small skin biopsies to evaluate the pain-sensing neurons within them. She said that doctors are using this approach to help diagnose small, painful neuropathies associated with diabetes and HIV.

The Pathophysiology of Migraine Headache

For the past six years, Dr. Rami Burstein "has provided answers to a great number of questions. Why does a migraine throb? Why is migraine pain constantly around the eyes? Why does it hurt to brush your hair?" said Mr. de Borchgrave in his introduction.

Migraines, characterized by a debilitating, pounding headache, affect nearly 25 million Americans. Patients can suffer migraines once a month or several times a week, and sometimes less frequently. They can last from a few hours to a day or two, during which time sufferers often find it difficult to function. For more than 100 years, said Dr. Burstein, clinicians thought that migraines were caused by dilation of the blood vessels in the head. As a result, efforts to develop migraine drugs were focused on medications that constrict those blood vessels.

"In recent years," Dr. Burstein said at the symposium, "it became apparent that migraines are caused by a sudden release of inflammatory chemicals, such as histamine and serotonin, following a brief abnormal activation of neurons in the outermost layer of the brain." This has led to a completely different direction in the approach to treating migraine.

Regardless of how they are triggered, the release of these inflammatory chemicals, said Dr. Burstein, irritates a network of neurons that sense pain signals as they originate in the dura (the outer membrane covering the spinal cord and brain). Researchers have found that this network of pain-sensing neurons in the dura changes rapidly during the course of a single migraine attack, making migraine treatment "a moving target."

Dr. Burstein and others found that if migraine pain is not stopped in the first 20 minutes, the first set of neurons – located above the mouth and outside the central nervous system – undergo molecular changes that make them hypersensitive to the changing pressure inside the head, which "explains why migraine headache throbs and is worsened by bending over and sneezing," he said.

If the pain is not stopped in the first hour or two, a second group of neurons, located at the back of the neck and within the central nervous system, undergo changes that convert them into an independent state in which they, in and of themselves, become the pain generator of the headache. "When this happens," said Dr. Burstein, "patients notice that brushing their hair, taking a shower, touching their skin around the eye, shaving, wearing earrings, et cetera, become painful."

Citing a recent study in the *New England Journal of Medicine,* he said that migraines could be "aborted" by currently available drugs only if they are taken when patients first become aware of increased sensitivity to pain.

"In spite of what the industry has told us for 12 years," he said, "migraine drugs act exclusively on the first set of neurons outside the central nervous system, rather than on the second group of neurons inside the central nervous system."

This has enormous clinical implications. Clinicians now instruct patients to take medication as soon as their pain starts, increasing the effectiveness of migraine drugs from 30 percent to 93 percent, "allowing patients to resume normal functioning faster and saving them money" on medication costs, Dr. Burstein said. "It allows us to predict with over 90 percent accuracy which migraine attack will be aborted by a given drug, moving the clinical management of migraine headache from a trial-and-error to a rational approach."

Promoting Pain Medications to Consumers

For the past several years, Dr. Richard Frank, the Margaret T. Morris professor of health care policy at HMS, has studied the issue of direct-to-consumer (DTC) advertising of prescription medications, especially pain-control drugs. Between 1995 and 2001, direct advertising of medications rose from $375 million to $2.5 billion. So-called "designer" pain medications such as Vioxx, Celebrex and Imitrex account for more than $300 million of this advertising.

Virtually nonexistent in the early 1990s, there has been a 4,000 percent increase in drug advertising since 1994. According to Dr. Frank, national spending on all prescription drugs increased by about 19 percent last year. But spending on large-selling pain drugs increased by about 30 percent, and 12 to 18 percent of that was attributable to direct-to-consumer advertising.

In his research, Dr. Frank has focused on assessing the impact of DTC advertising, using consumer surveys and economic models of sales and advertising data. He says he was amazed at the "reach" such advertising has. In one survey, he asked how many consumers had seen the Dorothy Hamill ad for Celebrex, the arthritis drug. More than 90 percent of respondents said they had seen the ad.

"About 33 percent of the people who talk to their doctor about pain ask for a drug they saw in an ad," said Dr. Frank. "Now, most of the time, the doctor either suggests a different line of action or a different drug. So it's not an automatic thing, but it engages, it creates a dialogue. The result is that the direct-to-consumer advertising clearly increases demand, not just for the advertised product, but also for the spread – so Celebrex ads will increase demand for Vioxx."

Dr. Frank sees a couple of major problems with DTC advertising. First, he says, only about 30 percent of people who ask their doctor for a drug they have seen advertised know what the drug is for. And, he says, "these advertising campaigns are very manipulative. American consumers have become extraordinarily sophisticated, and they all believe that the benefits [of the drugs] are overstated and the side effects are understated."

Alternative Approaches to Pain Management

Ted Kaptchuk, O.M.D., an internationally known expert on the phenomenon of the placebo effect, has spent considerable time examining the effectiveness of alternative medical therapies for the management of pain. "Despite the best efforts of many of my colleagues," Dr. Kaptchuk said at the symposium, "chronic pain is for many, many people a cause of despair, disappointment, and drugs that don't work as well as we'd like to see them work. And it is understandable that many people look for alternative therapies – therapies that, until very recently, were totally unrepresented in mainstream health care institutions in our country."

The most widely used alternative therapies for chronic pain in the United States, he said, are chi-

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Dr. Anne Louise Oaklander, responding to question from the audience, with Dr. Rami Burstein.

A Special Evening: HMNI-HMS Dinner in Palm Beach

Many friends and donors to the Harvard Mahoney Neuroscience Institute (HMNI) at Harvard Medical School gathered for a special evening at the home of Mrs. David Mahoney, following the symposium on *Successful Pain Management.* Established in 1990 by the late David Mahoney and his wife, Hillie, the HMNI seeks to make the public aware of both the pace and importance of scientific discoveries about the brain, and to increase the funding that makes this possible.

The Right Honorable Brian Mulroney, Mrs. David Mahoney and Mr. Winston Churchill.

(L–R) Mrs. Abe Rosenthal, Mrs. Guilford Dudley and Mrs. T. Suffern Tailer.

Mr. Stanley Rumbough with his wife, Janna.

(L–R) Mr. Arnaud de Borchgrave, moderator, Mr. Winston Churchill, Mrs. Arnaud de Borchgrave, Mr. Brian Mulroney and Mrs. Winston Churchill.

Mrs. Brian Mulroney chats with Mr. Tom Quick.

(L–R) Mrs. Henry Ford, Dr. Roy Duke and Mrs. Edward Cook.

Dr. Rami Burstein talks with Mrs. William Hamm over dinner.

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ropractic, massage and acupuncture. Chiropractic, which involves restoration of proper joint function of the spine and extremities, can help to relieve headache and low back pain. Acupuncture, an ancient Chinese practice of inserting needles at specific points of the body, has been shown to be useful in relieving low back pain, as well as pain caused by osteoarthritis, repetitive stress injuries, fibromyalgia and headache. Massage therapy involves restoration of proper joint function of the spine and extremities by strengthening supporting muscle and tissue. It has proven to provide effective pain relief for spinal injuries and headaches by reducing muscle tension.

Alternative medicine is a $32-billion-a-year business. By the late 1990s, more Americans paid office visits to alternative medicine providers (629 million) than they did to primary care practitioners (386 million), a phenomenon called "the hidden mainstream." About 50 percent of these visits were for massage therapy or chiropractic treatment.

In addition to acupuncture, chiropractic and massage, Dr. Kaptchuk said other alternative therapies increasingly are being used to treat pain, including hypnosis, the relaxation response, and meditation. Dr. Oaklander added to his comments, citing hypnosis research conducted by Henry Beecher at Harvard during World War II in which Beecher coined the term "distraction and amusement."

"What [distraction and amusement] basically means," said Dr. Oaklander, "is mind over matter. The brain is capable of being distracted to a point where it can ignore a very painful stimulus if it gets focused on something else – whether that occurs through hypnosis or something else. It's mind over matter."

Following on Dr. Kaptchuk's presentation, Dr. Joseph B. Martin, in his closing remarks, talked about the patient-physician relationship that is so much a part of Dr. Kaptchuck's research on placebo effect.

"One should never underestimate the power of the human-to-human interaction as it occurs in the physician-patient relationship," he said. "One can never overestimate the importance of the confidence, faith and trust that should exist between the physician – whatever kind of physician – and the patient."

Dr. Richard Frank listens as Dr. Ted Kaptchuk answers question from the audience

Clinical Connection: Shingles and PHN—A 'Neurological Emergency'

Most adult Americans had the chickenpox when they were young. Besides an itchy rash and fever – and perhaps a few days off from school – the illness came and went, just another chapter in our childhood. What most of us don't know is that the virus that caused our chickenpox –varicella–zoster–lay dormant in our body. For most of us, this is the end of the tale. For an estimated 20 percent of American adults, however, the virus reactivates and turns into shingles, a viral inflammation of the sensory ganglia associated with often intense neuralgic pain, rash and itching.

After chickenpox heals, the virus takes up latency in the sensory ganglia. When we are young and healthy, our immune system keeps the virus in check. As we get older or if our immune system becomes compromised, the virus can come out of latency. Age, in fact, is the leading risk factor for contracting shingles.

"Because it can damage or kill neurons, similar to what a stroke does in the brain," said Anne Louise Oaklander, M.D., Ph.D., an assistant professor of anesthesia at Harvard Medical School and one of the leading authorities on shingles, "shingles is a neurological emergency and requires immediate treatment."

Dr. Oaklander, who directs the Center for Shingles and Postherpetic Neuralgia at Massachusetts General Hospital (MGH), says most cases of shingles clear up after treatment with antiviral medications. However, she adds, the older a person is the higher the likelihood his or her shingles will be followed by postherpetic neuralgia (PHN) – persistent neuropathic pain in an area that has been affected by shingles.

The #1 Complication

Most older patients, says Dr. Oaklander, can expect to develop PHN, with about 50 percent of shingles patients over the age of 50 and 75 percent of shingles patients over the age of 70 developing PHN. This pain can last up to three months after the shingles rash has healed; however, for a number of individuals, PHN leads to chronic, often debilitating pain and disability.

In some cases, patients have preherpetic pain, a condition in which neuropathic pain presents prior to the onset of the shingles rash. These patients are more likely to develop PHN once the rash clears.

"Shingles is a great masquerader," said Dr. Oaklander, "because most people consider it a dermatologic disease [due to the rash]. But the important part of the disease is inside the body, where it kills neurons."

Early Treatment is Key

Immediate treatment of shingles can reduce a patient's pain and lower the risk of developing PHN. Four types of medications been proven effective in treating shingles and resultant PHN:

- Tricyclic antidepressants, which lessen pain from established PHN and, if given soon after shingles erupts, may prevent the development of PHN;
- Anticonvulsants, which are effective against diseases with excessive neuronal firing such as epilepsy and neuropathic pain;
- Topical local anesthetics, including creams, ointments and an FDA–approved patch; and
- Opioid medications, which have been shown in multiple clinical trials to be safe and effective.

The Bellwether of Neuropathic Pain

Because PHN has a well–defined etiology and onset, more is known about it than about most other causes of neuropathic pain. In fact, potential treatments for neuropathic pain are almost always evaluated in PHN patients, and treatments for PHN are almost always applicable to other neuropathic pain syndromes.

Dr. Oaklander's laboratory at MGH's Nerve Injury Unit has been testing the use of small skin biopsies to evaluate the pain–sensing neurons in them. These biopsies, says Dr. Oaklander, are the size of a pinhead and can measure the severity of nerve damage without opening the body to examine the nerves. "This is a very minimal procedure," she said, "which can oftentimes replace the old type of nerve biopsy in which the entire nerve is removed from the body for analysis."

Physicians at MGH are using this procedure to help diagnose small painful neuropathies such as those that occur with diabetes, HIV and other diseases. The procedure has benefits in the research laboratory, as well as in clinical care.

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Dr. Anne Louise Oaklander

Alternative Medicine and Pain Management

Dr. Ted Kaptchuk

Question: What exactly is the placebo effect?

Ted Kaptchuck: The placebo effect is the inherent possibility within a person, and especially present in the patient–physician encounter, that uses such mediums as belief, expectation, hope, imagination and conditioning to evoke renewed senses of intactness and health improvement. On a fundamental level, placebo research is very primitive and is usually undertaken as a secondary consideration to developing new drugs or other interventions. At this point, there is controversy within medicine on whether this healing phenomenon is clinically significant or even real.

Question: What types of placebo research are you conducting?

TK: My research in placebo has two levels. I am conducting clinical trials that are trying to unravel the placebo effect. One of my trials compares the ritual of sham needling [placing acupuncture needles near acupuncture points, but in sites that have no treatment effect] to the ritual of placebo pill. We also give real treatments, but we're concentrating on discovering whether ritual matters in health outcomes.

My other trial is a study in which we deliver different "doses" of the patient–physician relationship – attention, positive expectation, compassion, attentive listening, thoughtful silence, etc. – to see whether placebo effects and the patient–physician relationship can be delivered in a manner analogous to "dose dependent."

I'm also working on a third basic science experiment in which my colleagues and I see through brain imaging how a painful stimulation is modulated with different expectations.

My research is trying to bridge the gap between what is usually considered the art of medicine – ritual and the patient–physician relationship – and the science of medicine – quantitative outcomes and measurable physiology. My goal is to bring the "soft" stuff into mainstream, "hard" medical research.

Question: What role does the placebo effect play in pain management?

TK: In terms of pain, no one – even the most skeptical critic – has doubted that there is a placebo effect in pain, that the ritual of treatment changes how a person feels. The debate here is on the magnitude and clinical importance of this effect. I hope that my research will also clarify this.

Question: Is the placebo effect considered a form of alternative medicine?

TK: I don't think this is a form of alternative medicine. Placebo effects, if they exist, underlie all health care. The confusion is that the National Center for Complementary and Alternative Medicine [at the National Institutes of Health] has undertaken to lead the NIH to investigate placebo effects.

Question: What role do alternative therapies – chiropractic, acupuncture, massage, etc. – play in the treatment of acute and, perhaps more importantly, chronic pain?

TK: There is some controversy here. The evidence for acupuncture and pain relief, outside of dental pain where it is more robust, is equivocal or contradictory. The optimism with acupuncture is that its purported effects are explainable with basic science mechanisms, such as the release of endogenous opioids. But the clinical evidence for pain – as opposed to nausea and vomiting – is probably still unclear.

There are more than 75 randomized clinical trials investigating chiropractic. Most of the systematic reviews say that the evidence is not very well designed, methodologically, and that more evidence is needed. On the other hand, what evidence we do have shows that it is certainly not inferior to any other treatment that we have for, say, chronic back pain.

Massage is just beginning to be investigated. Two large randomized clinical trials have recently demonstrated massage as having value for low back pain. In a scientific sense, however, more research is needed.

Question: As alternative approaches gain more acceptance in Western medical practice, will some of these methods become more "mainstream" methods of pain management?

TK: Pain clinics routinely use methods that have not been impressively demonstrated to be effective. A physician treating chronic pain often has to try various options and let the patient's experience be the guide. Acupuncture has been used in many pain units for some time. I think there is a tendency for health centers to increasingly utilize alternative medicine. I'm not sure if science is leading the way on this or if the market is. But patients clearly like having these services in a hospital.

[In its March 28 edition, the *Wall Street Journal* published an article on the growth of alternative medicine programs at some of the nation's leading hospitals. The paper reported that the number of

medical centers with alternative clinics jumped to almost 100 last year, up from fewer than a dozen in 2000, and that one-third of the nation's medical schools are now offering elective courses in alternative medicine. Since 1993, Harvard Medical School has been offering courses in alternative medicine and therapies. It has established a Division for Education and Research in Complementary and Alternative Medicine and the Osher Institute.]

Ted Kaptchuk, O.M.D., assistant professor of medicine at Harvard Medical School, is a well-known scholar and researcher on placebo, alternative medicine and research methodology. His background is unconventional. He holds a doctorate from the Macau Institute of Chinese Medicine in China. Dr. Kaptchuk serves as director of complementary services at Harvard Medical School's Osher Institute and the Division for Education and Research in Complementary and Alternative Therapies at HMS. In addition, he serves on the national advisory council of the National Center for Complementary and Alternative Medicine at the National Institutes of Health.

Focus on the Future: The Next Generation of Neuroscientists

The study of the human brain helps researchers to define and understand neurological disorders such as stroke, addiction, depression, epilepsy, Parkinson's and Alzheimer's diseases. Thanks to the generosity of donors, Harvard Medical School is able to provide critical financial support to exceptional researchers who represent the next generation of neuroscientists. In each issue of *On the Brain,* we will spotlight some of these outstanding fellows in the neurosciences at Harvard Medical School.

Dr. Weiyuan Ma

WEIYUAN MA, PH.D. is a postdoctoral fellow in the Department of Neurobiology at Harvard Medical School. Dr. Ma has been working in the lab of HMS professor Gary Yellen, Ph.D., over the past year studying the therapeutic mechanisms of ketogenic diet on pediatric epilepsy. The ketogenic diet, a high fat/low carbohydrate and protein regimen, is a remarkably effective, but difficult therapy for severe childhood epilepsy. It has been employed in a number of centers in the United States and around the world. If the patients and their families are able to stay with the diet, weaning after one or two years can often permit the patients to remain seizure-free with little or no medication. Though it has been used in its modern form for over 70 years, there is essentially no understanding of how the ketogenic diet works to suppress seizures. Based on its properties, Dr. Yellen hypothesized a role for the metabolically sensitive ATP (Adenosine Triphosphate)-inhibited K+(potassium) channels – KATP – in quieting electrical behavior in the brains of patients treated with the diet. Dr. Ma's current research is focusing on establishing an in vitro model system to test the effect of the diet on central neurons. Preliminary data strongly support Dr. Yellen's hypothesis. Understanding the basic mechanism of the ketogenic diet should translate directly into improved treatment for epilepsy, a very common disease affecting one to two percent of the human population.

Before coming to the United States and Harvard Medical School, Dr. Ma was most recently in Israel at the Department of Life Sciences and the Zlotowski Center for Neuroscience at Ben-Gurion University of the Negev, where he earned his Ph.D., *summa cum laude.* There he aimed to elucidate some of the mechanisms by which extracellular ATP regulates airway ciliary function. Dr. Ma and his colleagues identified an ATP-gated ion channel in rabbit airway ciliated cells, which is an important mediator in mucociliary activation. The mucociliary system is responsible for maintaining airways, keeping them clean of inhaled particles and pathogens. This discovery may change the understanding of the fatal, hereditary disease cystic fibrosis (CF) and open new avenues of treatment for the respiratory disorder that marks it.

Originally from China, Dr. Ma earned a bachelor's degree in biomedical engineering from the Huazhong University of Science and Technology in Wuhan, China and went on to receive his master's degree in biophysics at Peking University's School of Medicine in Beijing. Dr. Ma was awarded a fellowship for each year of his doctorate program at Ben Gurion University and at the completion of his

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Mr. Nathaniel Blair

Direct-to-Consumer Advertising: An Unnecessary Expense or Better-Informed Consumers?

Dr. Richard Frank

Most of us have seen the commercials: the senior couple dancing, Dorothy Hamill figure skating, various star athletes promoting its benefits. In the four years between 1996 and 2000, annual spending on this type of advertising, called direct-to-consumer (DTC), for prescription medications tripled to nearly $2.5 billion and has become common fare on American television screens.

While this spending accounts for only about 15 percent of pharmaceutical company promotions, says Richard G. Frank, Ph.D., the Margaret T. Morris professor of health care policy at Harvard Medical School, broadcast advertising of drugs is so pervasive because television is such a visible – and visual – medium.

"Everyone," said Dr. Frank, "is aware of these drugs. They have become a part of the public consciousness."

In a study published in the *New England Journal of Medicine* in February, Dr. Frank and his colleagues examined the growing controversy surrounding the promotion of prescription medications to consumers, especially so-called "designer" drugs.

The issue of direct-to-consumer advertising is two fold. Proponents argue that such advertising leads to better-informed health care consumers and improved quality of care. Critics, on the other hand, claim that it causes physicians to waste valuable time with patients and promotes the unnecessary use of expensive medications.

This wave of DTC advertising was unleashed in 1997 following the Food and Drug Administration's clarification of guidelines regarding broadcast advertisements of drugs. Prior to 1997, drug companies, in both print and broadcast advertising, were required to disclose most of the information contained on their package inserts. The new guidelines said that these companies were no longer required to include all such information, but rather had to make a fair representation of key benefits and side effects of their medications, as well as provide a place for providers to go to get the full medication information.

"The positive news from all this," said Dr. Frank, "is that the advertising has created a greater awareness that some problems may be an illness and is helping to get people to see their doctor. People who have symptoms or some level of disability from such illnesses as high cholesterol, depression or allergies now know that they have a problem and there is something they can do about it."

Pain Drugs Lead Advertising Spending

Pain medications are among the leaders in DTC advertising. Merck, the maker of the anti-inflammatory drug Vioxx, spent nearly $161 million in advertising in 2000. Celebrex, Pfizer's anti-inflammatory, ranked seventh, with $79 million in advertising costs.

"There is a huge market for pain medication," said Dr. Frank. "Over the past several years, there has been a large increase in demand for these drugs. And what this has done is create a sort of 'arms race' amongst the competition."

In fact, he says, dollars spent on advertising by one drug company help to raise sales of competitors' drugs in the same class.

DTC advertising of these medications, however, is largely responsible for an increased awareness among consumers that there are treatments for pain. Pain, said Dr. Frank, is "one of those things that people don't understand is an illness." A study conducted a few years ago showed that pain is under-recognized and under-reported, and that physicians tend to downplay pain with their patients and under-dose them. Now, says Dr. Frank, patients are raising the issue of pain with their doctors because they are better informed.

Advertising Does Not Guarantee Prescriptions

One of the dangers of such advertising is that patients may go off "half-cocked with this information." Dr. Frank says only 30 percent of the people who ask their doctor for a drug they've seen advertised on television even know what it is for. "Confusion about these drugs is an issue," he says. The other side of the coin, he adds, is that "people who ask for certain drugs explicitly are much more likely to have a condition for which they are seeking treatment and to then be treated for it."

Despite the ubiquitousness of drug advertising, by no means is it 100 percent effective in generating prescriptions. In a 2001 study, the Henry J. Kaiser Family Foundation found that of the 30 percent of respondents who had asked their doctor for a specific advertised medication, only 44 percent received a prescription for that drug.

"A doctor may say, 'Well, that's a good idea, but not the best treatment for you,'" said Dr. Frank. "Or the doctor may prescribe another drug in the same class that is better suited for the patient for a number of reasons."

As competition among drug manufacturers escalates, the issues of advertising content and the spread to other classes of drugs will also likely increase. The FDA is recommending a Q&A format in drug advertising to create a better balance of information on benefits and side effects.

Dr. Frank says the larger issue may be the spread of advertising across different classes of drugs. "Right now," he said, "this advertising is not happening with drugs for heart disease and certain other illnesses with which mistakes can be more consequential. It's an open question how far this spread will go."

What is not a question, though, is that pharmaceutical manufacturers will continue to promote their products, targeting those who increasingly demand them – the consumers.

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Additional Complications

In addition to PHN, other potential complications of shingles include postherpetic itch (PHI) and direct invasion of the brain and spinal cord. PHI is a severe, chronic itch mediated by thin, unmyelinated sensory axons, most commonly on the head and neck, and is a common complaint of patients both during and after shingles. In some cases, PHI can lead to self-injury by excessive scratching of desensitized skin.

In rare cases, says Dr. Oaklander, the varicella-zoster virus can directly invade the brain and spinal cord, leading to stroke, encephalitis or spinal cord damage. Immunosuppressed patients are at higher risk of developing this potentially fatal complication.

While shingles are most common on the torso (from the Latin *cingulum,* meaning girdle), where the rash appears in band across only one half of the body, other areas are susceptible to eruptions, says Dr. Oaklander. The area around the eyes and forehead is the second most common location. Patients with this type of shingles, called ophthalmic zoster, require immediate ophthalmologic evaluation because of the risk of acute eye problems, including blindness.

Nearly three million Americans, primarily women, develop shingles affecting the genitalia. "This often goes undiagnosed," said Dr. Oaklander, "because gynecologists confuse it with herpes simplex, a sexually transmitted disease." Left untreated, this type of shingles can damage internal organs such as the bladder.

In rare cases, shingles affects the VII cranial nerve in the face (also known as Bell's palsy), which can produce pain in the outer ear and a portion of the cheek, as well as affect adjacent cranial nerves, causing double vision, hearing loss or vertigo.

"The lesson [about shingles] to take away," said Dr. Oaklander, "is three fold. First, it is a serious neurological disease that can cause significant disability. Second, immediate treatment can reduce pain and lessen the risk of developing PHN. And third, consultation with a pain-relief specialist is essential for patients with established PHN."

Harvard Medical School and MGH are clinical and research centers of excellence for shingles. For more information, please feel free to visit Dr. Oaklander's Web site, *www.shingles.mgh.harvard.edu.*

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degree, Dr. Ma won an award from the Israeli Chemistry Society and the Keitman Prize for excellent graduate students. He has co-authored a number of articles for publication in scientific journals as well as a chapter for a medical text.

NATHANIEL T. BLAIR is a doctoral degree candidate in the Program in Neuroscience at HMS. He is one of five fellows supported by the Stuart H.Q. and Victoria Quan Fellowship Fund in Neurobiology. Mr. Blair has been working with Neurobiology professor Bruce P. Bean, Ph.D., studying the ion channels that underlie the excitability of nociceptors, the neurons that sense pain.

The goal of Mr. Blair's doctoral thesis is to understand the role of individual ionic currents in the generation of nociceptor action potentials and how the properties of these currents govern nociceptor firing. An ion channel is a molecular pore in the membrane of the neuron.

In his research, Mr. Blair is studying a voltage-gated sodium channel that is specifically expressed in nociceptors to determine how this channel contributes to the transmission of pain. "I am also examining how the activity of this voltage-gated sodium current is modified by mediators of inflammation," he said. "Since this sodium channel seems to be expressed only in nociceptors, strategies to decrease its activity are a great target for reducing pain."

Before coming to HMS in 1999, Mr. Blair was at Stanford University's Department of Molecular and Cellular Physiology. He received his bachelor's degree, with honors, in 1996 from the University of Chicago, where he was an undergraduate research assistant. In addition to the Quan Fellowship, he has received the Albert J. Ryan Fellowship at HMS and the Smith-Stanford Graduate Fellowship at Stanford.

The Harvard Mahoney Fellows Program provides annual support for training and research to pre- and postdoctoral students in the Department of Neurobiology. The Stuart H.Q. and Victoria Quan Fellowship Fund in Neurobiology at Harvard Medical School was established to financially support the investigative efforts of predoctoral students in the vital area of neuroscience research. For more information on these and other fellowship funds in neuroscience at Harvard Medical School, please contact Patricia Flint at 617 384-8444.

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