Patient Handouts

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Pain

The two faces of pain: acute and chronic

What is pain? The International Association for the Study of Pain defines it as: An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

It is useful to distinguish between two basic types of pain, acute and chronic, and they differ greatly.

Acute pain, for the most part, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or emotional distress. The cause of acute pain can usually be diagnosed and treated, and the pain is self-limiting, that is, it is confined to a given period of time and severity. In some rare instances, it can become chronic.

Chronic pain is widely believed to represent disease itself. It can be made much worse by environmental and psychological factors. Chronic pain persists over a longer period of time than acute pain and is resistant to most medical treatments. It can—and often does—cause severe problems for patients.

The A to Z of pain

Hundreds of pain syndromes or disorders make up the spectrum of pain. There are the most benign, fleeting sensations of pain, such as a pin prick. There is the pain of childbirth, the pain of a heart attack, and the pain that sometimes follows amputation of a limb. There is also pain accompanying cancer and the pain that follows severe trauma, such as that associated with head and spinal cord injuries. A sampling of common pain syndromes follows, listed alphabetically.

Arachnoiditis is a condition in which one of the three membranes covering the brain and spinal cord, called the arachnoid membrane, becomes inflamed. A number of causes, including infection or trauma, can result in inflammation of this membrane. Arachnoiditis can produce disabling, progressive, and even permanent pain.

Arthritis. Millions of Americans suffer from arthritic conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. These disorders are characterized by joint pain in the extremities. Many other inflammatory diseases affect the body's soft tissues, including tendonitis and bursitis.

Back pain has become the high price paid by our modern lifestyle and is a startlingly common cause of disability for many Americans, including both active and inactive people. Back pain that spreads to the leg is called sciatica and is a very common condition (see below). Another common type of back pain is associated with the discs of the spine, the soft, spongy padding between the vertebrae (bones) that form the spine. Discs protect the spine by absorbing shock, but they tend to degenerate over time and may sometimes rupture. **Spondylolisthesis** is a back condition that occurs when one vertebra extends over

another, causing pressure on nerves and therefore pain. Also, damage to nerve roots is a serious condition, called **radiculopathy**, that can be extremely painful. Treatment for a damaged disc includes drugs such as painkillers, muscle relaxants, and steroids; exercise or rest, depending on the patient's condition; adequate support, such as a brace or better mattress and physical therapy. In some cases, surgery may be required to remove the damaged portion of the disc and return it to its previous condition, especially when it is pressing a nerve root. Surgical procedures include discectomy, laminectomy, or spinal fusion (see section on surgery in How is Pain Treated? for more information on these treatments).

Burn pain can be profound and poses an extreme challenge to the medical community. First-degree burns are the least severe; with third-degree burns, the skin is lost. Depending on the injury, pain accompanying burns can be excruciating, and even after the wound has healed patients may have chronic pain at the burn site.

Central pain syndrome-see "Trauma" below.

Cancer pain can accompany the growth of a tumor, the treatment of cancer, or chronic problems related to cancer's permanent effects on the body. Fortunately, most cancer pain can be treated to help minimize discomfort and stress to the patient.

Headaches affect millions of Americans. The three most common types of chronic headache are migraines, cluster headaches, and tension headaches. Each comes with its own telltale brand of pain.

• migraines are characterized by throbbing pain and sometimes by other symptoms, such as nausea and visual disturbances. Migraines are more frequent in women than men. Stress can trigger a migraine headache, and migraines can also put the sufferer at risk for stroke.
• cluster headaches are characterized by excruciating, piercing pain on one side of the head; they occur more frequently in men than women.
• tension headaches are often described as a tight band around the head.

Head and facial pain can be agonizing, whether it results from dental problems or from disorders such as cranial neuralgia, in which one of the nerves in the face, head, or neck is inflamed. Another condition, **trigeminal neuralgia** (also called tic douloureux), affects the largest of the cranial nerve and is characterized by a stabbing, shooting pain.

Muscle pain can range from an aching muscle, spasm, or strain, to the severe spasticity that accompanies paralysis. Another disabling syndrome is **fibromyalgia**, a disorder characterized by fatigue, stiffness, joint tenderness, and widespread muscle pain. **Polymyositis, dermatomyositis**, and **inclusion body myositis** are painful disorders characterized by muscle inflammation. They may be caused by infection or autoimmune dysfunction and are sometimes associated with connective tissue disorders, such as lupus and rheumatoid arthritis.

Myofascial pain syndromes affect sensitive areas known as trigger points, located within the body's muscles. Myofascial pain syndromes are sometimes misdiagnosed and can be debilitating. **Fibromyalgia** is a type of myofascial pain syndrome.

Neuropathic pain is a type of pain that can result from injury to nerves, either in the peripheral or central nervous system. Neuropathic pain can occur in any part of the body and is frequently described as a hot, burning sensation, which can be devastating to the affected individual. It can result from diseases that affect nerves (such as diabetes) or from trauma, or, because chemotherapy drugs can affect

nerves, it can be a consequence of cancer treatment. Among the many neuropathic pain conditions are **diabetic neuropathy** (which results from nerve damage secondary to vascular problems that occur with diabetes); **reflex sympathetic dystrophy syndrome** (see below), which can follow injury; **phantom limb** and **post-amputation pain**, which can result from the surgical removal of a limb; **postherpetic neuralgia**, which can occur after an outbreak of shingles; and **central pain syndrome**, which can result from trauma to the brain or spinal cord.

Reflex sympathetic dystrophy syndrome, or RSDS, is accompanied by burning pain and hypersensitivity to temperature. Often triggered by trauma or nerve damage, RSDS causes the skin of the affected area to become characteristically shiny. In recent years, RSDS has come to be called **complex regional pain syndrome** (CRPS); in the past it was often called **causalgia**.

Repetitive stress injuries are muscular conditions that result from repeated motions performed in the course of normal work or other daily activities. They include:

• writer's cramp, which affects musicians and writers and others,
• compression or entrapment neuropathies, including carpal tunnel syndrome, caused by chronic overextension of the wrist and
• tendonitis or tenosynovitis, affecting one or more tendons.

Sciatica is a painful condition caused by pressure on the sciatic nerve, the main nerve that branches off the spinal cord and continues down into the thighs, legs, ankles, and feet. Sciatica is characterized by pain in the buttocks and can be caused by a number of factors. Exertion, obesity, and poor posture can all cause pressure on the sciatic nerve. One common cause of sciatica is a herniated disc.

Shingles and other painful disorders affect the skin. Pain is a common symptom of many skin disorders, even the most common rashes. One of the most vexing neurological disorders is shingles or herpes zoster, an infection that often causes agonizing pain resistant to treatment. Prompt treatment with antiviral agents is important to arrest the infection, which if prolonged can result in an associated condition known as **postherpetic neuralgia**. Other painful disorders affecting the skin include:

• vasculitis, or inflammation of blood vessels;
• other infections, including herpes simplex;
• skin tumors and cysts, and
• tumors associated with neurofibromatosis, a neurogenetic disorder.

Sports injuries are common. Sprains, strains, bruises, dislocations, and fractures are all well-known words in the language of sports. Pain is another. In extreme cases, sports injuries can take the form of costly and painful spinal cord and head injuries, which cause severe suffering and disability.

Spinal stenosis refers to a narrowing of the canal surrounding the spinal cord. The condition occurs naturally with aging. Spinal stenosis causes weakness in the legs and leg pain usually felt while the person is standing up and often relieved by sitting down.

Surgical pain may require regional or general anesthesia during the procedure and medications to control discomfort following the operation. Control of pain associated with surgery includes presurgical preparation and careful monitoring of the patient during and after the procedure.

Temporomandibular disorders are conditions in which the temporomandibular joint (the jaw) is damaged and/or the muscles used for chewing and talking become stressed, causing pain. The condition may be the result of a number of factors, such as an injury to the jaw or joint misalignment, and may

give rise to a variety of symptoms, most commonly pain in the jaw, face, and/or neck muscles. Physicians reach a diagnosis by listening to the patient's description of the symptoms and by performing a simple examination of the facial muscles and the temporomandibular joint.

Trauma can occur after injuries in the home, at the workplace, during sports activities, or on the road. Any of these injuries can result in severe disability and pain. Some patients who have had an injury to the spinal cord experience intense pain ranging from tingling to burning and, commonly, both. Such patients are sensitive to hot and cold temperatures and touch. For these individuals, a touch can be perceived as intense burning, indicating abnormal signals relayed to and from the brain. This condition is called **central pain syndrome** or, if the damage is in the thalamus (the brain's center for processing bodily sensations), **thalamic pain syndrome**. It affects as many as 100,000 Americans with multiple sclerosis, Parkinson's disease, amputated limbs, spinal cord injuries, and stroke. Their pain is severe and is extremely difficult to treat effectively. A variety of medications, including analgesics, antidepressants, anticonvulsants, and electrical stimulation, are options available to central pain patients.

Vascular disease or injury-such as vasculitis or inflammation of blood vessels, coronary artery disease, and circulatory problems-all have the potential to cause pain. Vascular pain affects millions of Americans and occurs when communication between blood vessels and nerves is interrupted. Ruptures, spasms, constriction, or obstruction of blood vessels, as well as a condition called ischemia in which blood supply to organs, tissues, or limbs is cut off, can also result in pain.

How is pain diagnosed?

There is no way to tell how much pain a person has. No test can measure the intensity of pain, no imaging device can show pain, and no instrument can locate pain precisely. Sometimes, as in the case of headaches, physicians find that the best aid to diagnosis is the patient's own description of the type, duration, and location of pain. Defining pain as sharp or dull, constant or intermittent, burning or aching may give the best clues to the cause of pain. These descriptions are part of what is called the pain history, taken by the physician during the preliminary examination of a patient with pain.

Physicians, however, do have a number of technologies they use to find the cause of pain. Primarily these include:

• **Electrodiagnostic procedures** include **electromyography** (EMG), **nerve conduction studies**, and **evoked potential** (EP) studies. Information from EMG can help physicians tell precisely which muscles or nerves are affected by weakness or pain. Thin needles are inserted in muscles and a physician can see or listen to electrical signals displayed on an EMG machine. With **nerve conduction studies** the doctor uses two sets of electrodes (similar to those used during an electrocardiogram) that are placed on the skin over the muscles. The first set gives the patient a mild shock that stimulates the nerve that runs to that muscle. The second set of electrodes is used to make a recording of the nerve's electrical signals, and from this information the doctor can determine if there is nerve damage. **EP tests** also involve two sets of electrodes-one set for stimulating a nerve (these electrodes are attached to a limb) and another set on the scalp for recording the speed of nerve signal transmission to the brain.
• **Imaging**, especially **magnetic resonance imaging or MRI**, provides physicians with pictures of the body's structures and tissues. MRI uses magnetic fields and radio waves to differentiate between healthy and diseased tissue.
• A **neurological examination** in which the physician tests movement, reflexes, sensation, balance, and coordination.
• **X-rays** produce pictures of the body's structures, such as bones and joints.

How is pain treated?

The goal of pain management is to improve function, enabling individuals to work, attend school, or participate in other day-to-day activities. Patients and their physicians have a number of options for the treatment of pain; some are more effective than others. Sometimes, relaxation and the use of imagery as a distraction provide relief. These methods can be powerful and effective, according to those who advocate their use. Whatever the treatment regime, it is important to remember that pain is treatable. The following treatments are among the most common.

Acetaminophen is the basic ingredient found in Tylenol® and its many generic equivalents. It is sold over the counter, in a prescription-strength preparation, and in combination with codeine (also by prescription).

Acupuncture dates back 2,500 years and involves the application of needles to precise points on the body. It is part of a general category of healing called traditional Chinese or Oriental medicine. Acupuncture remains controversial but is quite popular and may one day prove to be useful for a variety of conditions as it continues to be explored by practitioners, patients, and investigators.

Analgesic refers to the class of drugs that includes most painkillers, such as aspirin, acetaminophen, and ibuprofen. The word analgesic is derived from ancient Greek and means to reduce or stop pain. Nonprescription or over-the-counter pain relievers are generally used for mild to moderate pain. Prescription pain relievers, sold through a pharmacy under the direction of a physician, are used for more moderate to severe pain.

Anticonvulsants are used for the treatment of seizure disorders but are also sometimes prescribed for the treatment of pain. Carbamazepine in particular is used to treat a number of painful conditions, including trigeminal neuralgia. Another antiepileptic drug, gabapentin, is being studied for its pain-relieving properties, especially as a treatment for neuropathic pain.

Antidepressants are sometimes used for the treatment of pain and, along with neuroleptics and lithium, belong to a category of drugs called psychotropic drugs. In addition, anti-anxiety drugs called benzodiazepines also act as muscle relaxants and are sometimes used as pain relievers. Physicians usually try to treat the condition with analgesics before prescribing these drugs.

Antimigraine drugs include the triptans- sumatriptan (Imitrex®), naratriptan (Amerge®), and zolmitriptan (Zomig®)-and are used specifically for migraine headaches. They can have serious side effects in some people and therefore, as with all prescription medicines, should be used only under a doctor's care.

Aspirin may be the most widely used pain-relief agent and has been sold over the counter since 1905 as a treatment for fever, headache, and muscle soreness.

Biofeedback is used for the treatment of many common pain problems, most notably headache and back pain. Using a special electronic machine, the patient is trained to become aware of, to follow, and to gain control over certain bodily functions, including muscle tension, heart rate, and skin temperature. The individual can then learn to effect a change in his or her responses to pain, for example, by using relaxation techniques. Biofeedback is often used in combination with other treatment methods, generally without side effects. Similarly, the use of relaxation techniques in the treatment of pain can increase the patient's feeling of well-being.

Capsaicin is a chemical found in chili peppers that is also a primary ingredient in pain-relieving creams.

Chemonucleolysis is a treatment in which an enzyme, chymopapain, is injected directly into a herniated lumbar disc in an effort to dissolve material around the disc, thus reducing pressure and pain. The procedure's use is extremely limited, in part because some patients may have a life-threatening allergic reaction to chymopapain.

Chiropractic care may ease back pain, neck pain, headaches, and musculoskeletal conditions. It involves "hands-on" therapy designed to adjust the relationship between the body's structure (mainly the spine) and its functioning. Chiropractic spinal manipulation includes the adjustment and manipulation of the joints and adjacent tissues. Such care may also involve therapeutic and rehabilitative exercises.

Cognitive-behavioral therapy involves a wide variety of coping skills and relaxation methods to help prepare for and cope with pain. It is used for postoperative pain, cancer pain, and the pain of childbirth.

Counseling can give a patient suffering from pain much needed support, whether it is derived from family, group, or individual counseling. Support groups can provide an important adjunct to drug or surgical treatment. Psychological treatment can also help patients learn about the physiological changes produced by pain.

COX-2 inhibitors may be effective for individuals with arthritis. For many years scientists have wanted to develop a drug that works as well as morphine but without its negative side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) work by blocking two enzymes, cyclooxygenase-1 and cyclooxygenase-2, both of which promote production of hormones called prostaglandins, which in turn cause inflammation, fever, and pain. The newer COX-2 inhibitors primarily block cyclooxygenase-2 and are less likely to have the gastrointestinal side effects sometimes produced by NSAIDs.

In 1999, the Food and Drug Administration approved a COX-2 inhibitor-celecoxib-for use in cases of chronic pain. The long-term effects of all COX-2 inhibitors are still being evaluated, especially in light of new information suggesting that these drugs may increase the risk of heart attack and stroke. Patients taking any of the COX-2 inhibitors should review their drug treatment with their doctors.

Electrical stimulation, including transcutaneous electrical stimulation (TENS), implanted electric nerve stimulation, and deep brain or spinal cord stimulation, is the modern-day extension of age-old practices in which the nerves of muscles are subjected to a variety of stimuli, including heat or massage. Electrical stimulation, no matter what form, involves a major surgical procedure and is not for everyone, nor is it 100 percent effective. The following techniques each require specialized equipment and personnel trained in the specific procedure being used:

• TENS uses tiny electrical pulses, delivered through the skin to nerve fibers, to cause changes in muscles, such as numbness or contractions. This in turn produces temporary pain relief. There is also evidence that TENS can activate subsets of peripheral nerve fibers that can block pain transmission at the spinal cord level, in much the same way that shaking your hand can reduce pain.
• Peripheral nerve stimulation uses electrodes placed surgically on a carefully selected area of the body. The patient is then able to deliver an electrical current as needed to the affected area, using an antenna and transmitter.
• Spinal cord stimulation uses electrodes surgically inserted within the epidural space of the spinal cord. The patient is able to deliver a pulse of electricity to the spinal cord using a small box-like receiver and an antenna taped to the skin.

• Deep brain or intracerebral stimulation is considered an extreme treatment and involves surgical stimulation of the brain, usually the thalamus. It is used for a limited number of conditions, including severe pain, central pain syndrome, cancer pain, phantom limb pain, and other neuropathic pains.

Exercise has come to be a prescribed part of some doctors' treatment regimes for patients with pain. Because there is a known link between many types of chronic pain and tense, weak muscles, exercise-even light to moderate exercise such as walking or swimming-can contribute to an overall sense of well-being by improving blood and oxygen flow to muscles. Just as we know that stress contributes to pain, we also know that exercise, sleep, and relaxation can all help reduce stress, thereby helping to alleviate pain. Exercise has been proven to help many people with low back pain. It is important, however, that patients carefully follow the routine laid out by their physicians.

Hypnosis, first approved for medical use by the American Medical Association in 1958, continues to grow in popularity, especially as an adjunct to pain medication. In general, hypnosis is used to control physical function or response, that is, the amount of pain an individual can withstand. How hypnosis works is not fully understood. Some believe that hypnosis delivers the patient into a trance-like state, while others feel that the individual is simply better able to concentrate and relax or is more responsive to suggestion. Hypnosis may result in relief of pain by acting on chemicals in the nervous system, slowing impulses. Whether and how hypnosis works involves greater insight-and research-into the mechanisms underlying human consciousness.

Ibuprofen is a member of the aspirin family of analgesics, the so-called nonsteroidal anti-inflammatory drugs (see below). It is sold over the counter and also comes in prescription-strength preparations.

Low-power lasers have been used occasionally by some physical therapists as a treatment for pain, but like many other treatments, this method is not without controversy.

Magnets are increasingly popular with athletes who swear by their effectiveness for the control of sports-related pain and other painful conditions. Usually worn as a collar or wristwatch, the use of magnets as a treatment dates back to the ancient Egyptians and Greeks. While it is often dismissed as quackery and pseudoscience by skeptics, proponents offer the theory that magnets may effect changes in cells or body chemistry, thus producing pain relief.

Narcotics (see Opioids, below).

Nerve blocks employ the use of drugs, chemical agents, or surgical techniques to interrupt the relay of pain messages between specific areas of the body and the brain. There are many different names for the procedure, depending on the technique or agent used. Types of surgical nerve blocks include neurectomy; spinal dorsal, cranial, and trigeminal rhizotomy; and sympathectomy, also called sympathetic blockade.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (including aspirin and ibuprofen) are widely prescribed and sometimes called non-narcotic or non-opioid analgesics. They work by reducing inflammatory responses in tissues. Many of these drugs irritate the stomach and for that reason are usually taken with food. Although acetaminophen may have some anti-inflammatory effects, it is generally distinguished from the traditional NSAIDs.

Opioids are derived from the poppy plant and are among the oldest drugs known to humankind. They include codeine and perhaps the most well-known narcotic of all, morphine. Morphine can be administered in a variety of forms, including a pump for patient self-administration. Opioids have a

narcotic effect, that is, they induce sedation as well as pain relief, and some patients may become physically dependent upon them. For these reasons, patients given opioids should be monitored carefully; in some cases stimulants may be prescribed to counteract the sedative side effects. In addition to drowsiness, other common side effects include constipation, nausea, and vomiting.

Physical therapy and rehabilitation date back to the ancient practice of using physical techniques and methods, such as heat, cold, exercise, massage, and manipulation, in the treatment of certain conditions. These may be applied to increase function, control pain, and speed the patient toward full recovery.

Placebos offer some individuals pain relief although whether and how they have an effect is mysterious and somewhat controversial. Placebos are inactive substances, such as sugar pills, or harmless procedures, such as saline injections or sham surgeries, generally used in clinical studies as control factors to help determine the efficacy of active treatments. Although placebos have no direct effect on the underlying causes of pain, evidence from clinical studies suggests that many pain conditions such as migraine headache, back pain, post-surgical pain, rheumatoid arthritis, angina, and depression sometimes respond well to them. This positive response is known as the placebo effect, which is defined as the observable or measurable change that can occur in patients after administration of a placebo. Some experts believe the effect is psychological and that placebos work because the patients believe or expect them to work. Others say placebos relieve pain by stimulating the brain's own analgesics and setting the body's self-healing forces in motion. A third theory suggests that the act of taking placebos relieves stress and anxiety-which are known to aggravate some painful conditions-and, thus, cause the patients to feel better. Still, placebos are considered controversial because by definition they are inactive and have no actual curative value.

R.I.C.E.-Rest, Ice, Compression, and Elevation-are four components prescribed by many orthopedists, coaches, trainers, nurses, and other professionals for temporary muscle or joint conditions, such as sprains or strains. While many common orthopedic problems can be controlled with these four simple steps, especially when combined with over-the-counter pain relievers, more serious conditions may require surgery or physical therapy, including exercise, joint movement or manipulation, and stimulation of muscles.

Surgery, although not always an option, may be required to relieve pain, especially pain caused by back problems or serious musculoskeletal injuries. Surgery may take the form of a nerve block or it may involve an operation to relieve pain from a ruptured disc. Surgical procedures for back problems include **discectomy** or, when microsurgical techniques are used, **microdiscectomy**, in which the entire disc is removed; **laminectomy**, a procedure in which a surgeon removes only a disc fragment, gaining access by entering through the arched portion of a vertebra; and **spinal fusion**, a procedure where the entire disc is removed and replaced with a bone graft. In a spinal fusion, the two vertebrae are then fused together. Although the operation can cause the spine to stiffen, resulting in lost flexibility, the procedure serves one critical purpose: protection of the spinal cord. Other operations for pain include **rhizotomy**, in which a nerve close to the spinal cord is cut, and **cordotomy**, where bundles of nerves within the spinal cord are severed. Cordotomy is generally used only for the pain of terminal cancer that does not respond to other therapies. Another operation for pain is the **dorsal root entry zone operation**, or DREZ, in which spinal neurons corresponding to the patient's pain are destroyed surgically. Because surgery can result in scar tissue formation that may cause additional problems, patients are well advised to seek a second opinion before proceeding. Occasionally, surgery is carried out with electrodes that selectively damage neurons in a targeted area of the brain. These procedures rarely result in long-term pain relief, but both physician and patient may decide that the surgical procedure will be effective enough that it justifies the expense and risk. In some cases, the results of an operation are remarkable.

For example, many individuals suffering from trigeminal neuralgia who are not responsive to drug treatment have had great success with a procedure called microvascular decompression, in which tiny blood vessels are surgically separated from surrounding nerves.

Gender and pain

It is now widely believed that pain affects men and women differently. While the sex hormones estrogen and testosterone certainly play a role in this phenomenon, psychology and culture, too, may account at least in part for differences in how men and women receive pain signals. For example, young children may learn to respond to pain based on how they are treated when they experience pain. Some children may be cuddled and comforted, while others may be encouraged to tough it out and to dismiss their pain.

Many investigators are turning their attention to the study of gender differences and pain. Women, many experts now agree, recover more quickly from pain, seek help more quickly for their pain, and are less likely to allow pain to control their lives. They also are more likely to marshal a variety of resources-coping skills, support, and distraction-with which to deal with their pain.

Research in this area is yielding fascinating results. For example, male experimental animals injected with estrogen, a female sex hormone, appear to have a lower tolerance for pain-that is, the addition of estrogen appears to lower the pain threshold. Similarly, the presence of testosterone, a male hormone, appears to elevate tolerance for pain in female mice: the animals are simply able to withstand pain better. Female mice deprived of estrogen during experiments react to stress similarly to male animals. Estrogen, therefore, may act as a sort of pain switch, turning on the ability to recognize pain.

Investigators know that males and females both have strong natural pain-killing systems, but these systems operate differently. For example, a class of painkillers called kappa-opioids is named after one of several opioid receptors to which they bind, the kappa-opioid receptor, and they include the compounds nalbuphine (Nubain®) and butorphanol (Stadol®). Research suggests that kappa-opioids provide better pain relief in women.

Though not prescribed widely, kappa-opioids are currently used for relief of labor pain and in general work best for short-term pain. Investigators are not certain why kappa-opioids work better in women than men. Is it because a woman's estrogen makes them work, or because a man's testosterone prevents them from working? Or is there another explanation, such as differences between men and women in their perception of pain? Continued research may result in a better understanding of how pain affects women differently from men, enabling new and better pain medications to be designed with gender in mind.

Pain in aging and pediatric populations: special needs and concerns

Pain is the number one complaint of older Americans, and one in five older Americans takes a painkiller regularly. In 1998, the American Geriatrics Society (AGS) issued guidelines* for the management of pain in older people. The AGS panel addressed the incorporation of several non-drug approaches in patients' treatment plans, including exercise. AGS panel members recommend that, whenever possible, patients use alternatives to aspirin, ibuprofen, and other NSAIDs because of the drugs' side effects, including stomach irritation and gastrointestinal bleeding. For older adults, acetaminophen is the first-line treatment for mild-to-moderate pain, according to the guidelines. More serious chronic pain conditions may require opioid drugs (narcotics), including codeine or morphine, for relief of pain.

Pain in younger patients also requires special attention, particularly because young children are not always able to describe the degree of pain they are experiencing. Although treating pain in pediatric patients poses a special challenge to physicians and parents alike, pediatric patients should never be undertreated. Recently, special tools for measuring pain in children have been developed that, when combined with cues used by parents, help physicians select the most effective treatments.

Nonsteroidal agents, and especially acetaminophen, are most often prescribed for control of pain in children. In the case of severe pain or pain following surgery, acetaminophen may be combined with codeine.

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A pain primer: what do we know about pain?

We may experience pain as a prick, tingle, sting, burn, or ache. Receptors on the skin trigger a series of events, beginning with an electrical impulse that travels from the skin to the spinal cord. The spinal cord acts as a sort of relay center where the pain signal can be blocked, enhanced, or otherwise modified before it is relayed to the brain. One area of the spinal cord in particular, called the dorsal horn, is important in the reception of pain signals.

The most common destination in the brain for pain signals is the thalamus and from there to the cortex, the headquarters for complex thoughts. The thalamus also serves as the brain's storage area for images of the body and plays a key role in relaying messages between the brain and various parts of the body. In people who undergo an amputation, the representation of the amputated limb is stored in the thalamus.

Pain is a complicated process that involves an intricate interplay between a number of important chemicals found naturally in the brain and spinal cord. In general, these chemicals, called neurotransmitters, transmit nerve impulses from one cell to another.

There are many different neurotransmitters in the human body; some play a role in human disease and, in the case of pain, act in various combinations to produce painful sensations in the body. Some chemicals govern mild pain sensations; others control intense or severe pain.

The body's chemicals act in the transmission of pain messages by stimulating neurotransmitter receptors found on the surface of cells; each receptor has a corresponding neurotransmitter. Receptors function much like gates or ports and enable pain messages to pass through and on to neighboring cells. One brain chemical of special interest to neuroscientists is glutamate. During experiments, mice with blocked glutamate receptors show a reduction in their responses to pain. Other important receptors in pain transmission are opiate-like receptors. Morphine and other opioid drugs work by locking on to these opioid receptors, switching on pain-inhibiting pathways or circuits, and thereby blocking pain.

Another type of receptor that responds to painful stimuli is called a nociceptor. Nociceptors are thin nerve fibers in the skin, muscle, and other body tissues, that, when stimulated, carry pain signals to the spinal cord and brain. Normally, nociceptors only respond to strong stimuli such as a pinch. However, when tissues become injured or inflamed, as with a sunburn or infection, they release chemicals that make nociceptors much more sensitive and cause them to transmit pain signals in response to even gentle stimuli such as breeze or a caress. This condition is called allodynia -a state in which pain is produced by innocuous stimuli.

The body's natural painkillers may yet prove to be the most promising pain relievers, pointing to one of the most important new avenues in drug development. The brain may signal the release of painkillers

found in the spinal cord, including serotonin, norepinephrine, and opioid-like chemicals. Many pharmaceutical companies are working to synthesize these substances in laboratories as future medications.

Endorphins and enkephalins are other natural painkillers. Endorphins may be responsible for the "feel good" effects experienced by many people after rigorous exercise; they are also implicated in the pleasurable effects of smoking.

Similarly, peptides, compounds that make up proteins in the body, play a role in pain responses. Mice bred experimentally to lack a gene for two peptides called tachykinins-neurokinin A and substance P-have a reduced response to severe pain. When exposed to mild pain, these mice react in the same way as mice that carry the missing gene. But when exposed to more severe pain, the mice exhibit a reduced pain response. This suggests that the two peptides are involved in the production of pain sensations, especially moderate-to-severe pain. Continued research on tachykinins, conducted with support from the NINDS, may pave the way for drugs tailored to treat different severities of pain.

Scientists are working to develop potent pain-killing drugs that act on receptors for the chemical acetylcholine. For example, a type of frog native to Ecuador has been found to have a chemical in its skin called epibatidine, derived from the frog's scientific name, Epipedobates tricolor. Although highly toxic, epibatidine is a potent analgesic and, surprisingly, resembles the chemical nicotine found in cigarettes. Also under development are other less toxic compounds that act on acetylcholine receptors and may prove to be more potent than morphine but without its addictive properties.

The idea of using receptors as gateways for pain drugs is a novel idea, supported by experiments involving substance P. Investigators have been able to isolate a tiny population of neurons, located in the spinal cord, that together form a major portion of the pathway responsible for carrying persistent pain signals to the brain. When animals were given injections of a lethal cocktail containing substance P linked to the chemical saporin, this group of cells, whose sole function is to communicate pain, were killed. Receptors for substance P served as a portal or point of entry for the compound. Within days of the injections, the targeted neurons, located in the outer layer of the spinal cord along its entire length, absorbed the compound and were neutralized. The animals' behavior was completely normal; they no longer exhibited signs of pain following injury or had an exaggerated pain response. Importantly, the animals still responded to acute, that is, normal, pain. This is a critical finding as it is important to retain the body's ability to detect potentially injurious stimuli. The protective, early warning signal that pain provides is essential for normal functioning. If this work can be translated clinically, humans might be able to benefit from similar compounds introduced, for example, through lumbar (spinal) puncture.

Another promising area of research using the body's natural pain-killing abilities is the transplantation of chromaffin cells into the spinal cords of animals bred experimentally to develop arthritis. Chromaffin cells produce several of the body's pain-killing substances and are part of the adrenal medulla, which sits on top of the kidney. Within a week or so, rats receiving these transplants cease to exhibit telltale signs of pain. Scientists, working with support from the NINDS, believe the transplants help the animals recover from pain-related cellular damage. Extensive animal studies will be required to learn if this technique might be of value to humans with severe pain.

One way to control pain outside of the brain, that is, peripherally, is by inhibiting hormones called prostaglandins. Prostaglandins stimulate nerves at the site of injury and cause inflammation and fever. Certain drugs, including NSAIDs, act against such hormones by blocking the enzyme that is required for their synthesis.

Blood vessel walls stretch or dilate during a migraine attack and it is thought that serotonin plays a complicated role in this process. For example, before a migraine headache, serotonin levels fall. Drugs for migraine include the triptans: sumatriptan (Imitrix®), naratriptan (Amerge®), and zolmitriptan (Zomig®). They are called serotonin agonists because they mimic the action of endogenous (natural) serotonin and bind to specific subtypes of serotonin receptors.

Ongoing pain research, much of it supported by the NINDS, continues to reveal at an unprecedented pace fascinating insights into how genetics, the immune system, and the skin contribute to pain responses.

The explosion of knowledge about human genetics is helping scientists who work in the field of drug development. We know, for example, that the pain-killing properties of codeine rely heavily on a liver enzyme, CYP2D6, which helps convert codeine into morphine. A small number of people genetically lack the enzyme CYP2D6; when given codeine, these individuals do not get pain relief. CYP2D6 also helps break down certain other drugs. People who genetically lack CYP2D6 may not be able to cleanse their systems of these drugs and may be vulnerable to drug toxicity. CYP2D6 is currently under investigation for its role in pain.

In his research, the late John C. Liebeskind, a renowned pain expert and a professor of psychology at UCLA, found that pain can kill by delaying healing and causing cancer to spread. In his pioneering research on the immune system and pain, Dr. Liebeskind studied the effects of stress-such as surgery-on the immune system and in particular on cells called natural killer or NK cells. These cells are thought to help protect the body against tumors. In one study conducted with rats, Dr. Liebeskind found that, following experimental surgery, NK cell activity was suppressed, causing the cancer to spread more rapidly. When the animals were treated with morphine, however, they were able to avoid this reaction to stress.

The link between the nervous and immune systems is an important one. Cytokines, a type of protein found in the nervous system, are also part of the body's immune system, the body's shield for fighting off disease. Cytokines can trigger pain by promoting inflammation, even in the absence of injury or damage. Certain types of cytokines have been linked to nervous system injury. After trauma, cytokine levels rise in the brain and spinal cord and at the site in the peripheral nervous system where the injury occurred. Improvements in our understanding of the precise role of cytokines in producing pain, especially pain resulting from injury, may lead to new classes of drugs that can block the action of these substances.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
http://www.ninds.nih.gov

Information also is available from the following organizations:

National Institute of Dental and Craniofacial Research (NIDCR)
National Institutes of Health, DHHS

31 Center Drive, Room 5B-55
Bethesda, MD 20892
http://www.nidcr.nih.gov
301-496-4261

American Chronic Pain Association (ACPA)
P.O. Box 850
Rocklin, CA 95677-0850
http://www.theacpa.org
916-632-0922, 800-533-3231

American Headache Society Committee for Headache Education (ACHE)
19 Mantua Road
Mt. Royal, NJ 08061
http://www.achenet.org
856-423-0043

National Headache Foundation
820 N. Orleans, Suite 217
Chicago, IL 60610-3132
http://www.headaches.org
312-274-2650, 888-NHF-5552 (643-5552)

Mayday Fund [For Pain Research]
c/o SPG
136 West 21st Street, 6th Floor
New York, NY 10011
http://www.painandhealth.org
212-366-6970

American Pain Foundation
201 North Charles Street, Suite 710
Baltimore, MD 21201-4111
http://www.painfoundation.org
888-615-PAIN (7246)

Arthritis Foundation
P.O. Box 7669
Atlanta, GA 30357
http://www.arthritis.org
Tel: 800-283-7800, 404-872-7100, 404-965-7888

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National Institute of Neurological Disorders and Stroke. Pain: Hope Through Research. Available at: http://www.ninds.nih.gov/disorders/chronic_pain/detail_chronic_pain.htm. Last accessed July 20, 2012.

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← Back
