Pain

Hope Through Research

National Institute of Neurological Disorders
and Stroke
National Institutes of Health

Table of Contents

Pain

Pain is an unpleasant signal to us that something hurts. It is a complex experience and differs greatly from individual to individual, even between those with similar injuries and/or illnesses. Pain can be very light, almost unnoticeable, or explosive. Some people experience pain as pricking, tingling, stinging, burning, shooting, aching, or electric. Pain warns us that something is not quite right in our body and can cause us to take certain actions and avoid others. Pain also can significantly impact our quality of life—by adversely affecting our physical and emotional well-being; upsetting relationships with family, coworkers, and friends; and limiting our mobility and participation in daily activities.

Hundreds of pain syndromes or disorders make up the spectrum of pain. For example, there is the pain of childbirth, the pain of a heart attack, the pain of a headache or backache, and the pain that sometimes follows amputation of a limb. There also is pain that accompanies cancer and the pain that follows severe trauma, such as head and spinal cord injuries.

Pain is often a debilitating symptom of many diseases and is considered a disease itself when it persists beyond recovery from an injury or illness. Pain often goes away on its own or with treatment, but it can persist and develop into long-term chronic pain. Millions of Americans have pain every day. Chronic pain is one of the most common reasons adults in the U.S. seek medical care, affecting 50 million people.

A Pain Primer: What Do We Know About Pain?

Pain can be classified as acute or chronic, and the two kinds differ greatly.

- **Acute pain** usually results from a specific injury, disease, and/or inflammation. It generally comes on suddenly, for example, after physical trauma or surgery, and can be accompanied by anxiety or emotional distress. Normally, acute pain is a protective response to tissue damage resulting from injury, disease, overuse, or environmental stressors. The cause of acute pain usually can be diagnosed and treated. The pain is self-limiting, meaning it is confined to a given period of time and severity. Acute pain, however, can become chronic.

- **Chronic pain** is a medical disease that can be made worse by environmental and psychological factors. Chronic pain persists over a long period and can be challenging to manage. People with chronic pain often suffer from more than one painful condition. They also have an increased risk for developing problems with physical functioning, cognition, and emotional reactions. There may be common mechanisms that put some people at higher risk for developing multiple pain disorders. It is not known whether these disorders share a common cause.

Anatomy of Pain

Nociceptors

To sense pain, thousands of specialized sensory nerve cells or neurons—called nociceptors—throughout the body trigger a series of responses to a noxious (painful) stimulus. The stimulus triggers an electrical impulse

that travels through nerves from the site of the injury or diseased area to the spinal cord and up to the brain. Nociceptors in the head and face relay pain signals directly to the brain stem, where pain pathways converge.

The thalamus serves as a relay station that distributes signals to many other brain regions.

Brain Regions

One brain region that receives pain signals is the thalamus. The thalamus is a relay station that distributes sensory signals to many other brain regions, including those in the cortex—which process the nociceptive (reacting to or causing pain) information from the body and generates the complex experience of pain. This has multiple components including the: 1) sensory-discriminative aspect which helps us localize where on our body an injury has occurred, 2) affective-motivational aspect which conveys just how unpleasant the experience is, and 3) cognitive-evaluative aspect which involves thoughtful planning on how to avoid the pain.

Brain Systems

Many of the characteristics of pain have been associated with specific brain systems, although much remains to be learned. Additionally, researchers have found that many of the brain systems involved with the experience of pain overlap with the experience of basic emotions. Consequently, when people experience undesirable emotions (e.g., fear, anxiety, anger), the same brain systems responsible for these emotions also amplify the experience of pain.

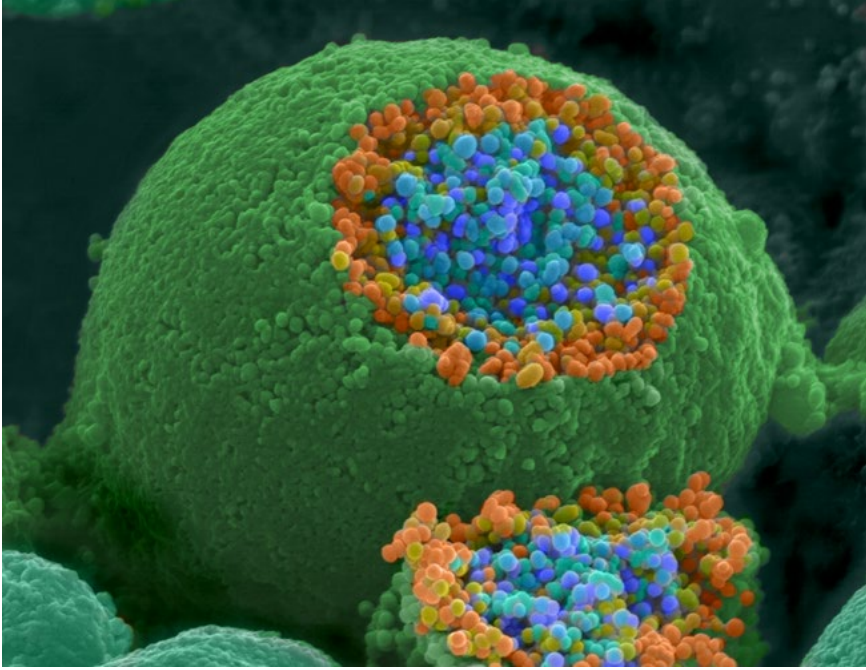
Fortunately, there also are systems in the brain that help to dampen or decrease pain. For example, there are descending signals from the brain that are sent back down the spinal cord that can inhibit (block or interfere with) the intensity of incoming nociceptive signals and reduce the pain experience. One way these descending signals result in pain reduction is by releasing molecules (such as endogenous or self-produced opioids) into the spinal cord that can prevent pain signals from being relayed to the brain from the nerves outside of the brain and spinal cord (peripheral nervous system).

Neurochemistry of Pain

Neurotransmitters

Our ability to perceive pain involves intricate connections among many different brain regions. The nervous system uses a set of chemicals, called *neurotransmitters*, to communicate between neurons within and across these stations in the pain pathway. These chemicals are released by neurons in tiny packets (vesicles) into the space between two cells. When they reach their target, they bind to special proteins on the surface of the cells called *receptors*. The transmitter then activates the receptor, which functions much like a gate. The gate will either close to block (inhibitory receptor) the signal or open to send (excitatory receptor) the signal along to the next station. This is known as the gate control theory of pain.

There are many neurotransmitters in the human body and they play a role in normal function as well as in disease. In the case of nociception and pain, they act in various combinations at all levels of the nervous system to transmit and modify signals generated by noxious stimuli.



The nervous system uses chemicals called neurotransmitters to communicate between neurons within and across the pain pathway. These chemicals are released in tiny packets called vesicles into the space between two cells. The picture above shows a nerve ending that has been broken open to reveal vesicles (in orange and blue) that contain chemicals used to pass messages in the nervous system.

- **Glutamate**. Glutamate plays a major role in nervous system function and in pain pathophysiology. It heightens the process called central sensitization (see below) and contributes to making pain persist. Much attention has been given to developing molecules/drugs that block certain receptors for glutamate because of their potential in reducing pain.
- **GABA**. GABA (or gamma-aminobutyric acid) generally decreases or blocks the activity of neurons. Most of what is known of its role in pain is related to its function in inhibiting spinal cord neurons from transmitting signals and therefore dampening pain. Chemicals that are similar to GABA have been explored as possible analgesics, but because GABA is so widespread in the nervous system it is difficult to make a GABA-like drug without affecting other nervous system functions.

- **Norepinephrine and Serotonin**. Norepinephrine and serotonin dampen the incoming signals from painful stimuli from the site of the injury or inflammation. Drugs that modulate the activity of these transmitters, such as some antidepressants, are effective in treating some chronic pain conditions, likely by enhancing the availability of the transmitters through a recycling and reuse process. Serotonin receptors also are present on the nerves that supply the surface of the brain involved in migraines, and their modulation by a class of drugs called "triptans" is effective in acutely treating migraine.

- **Opioids**. Opioids are involved in pain control, as well as pleasure and addiction. Their receptors are found throughout the body and can be activated by endogenous opioid peptides (two or more amino acids that work together to interfere with pain signals) that are released by neurons in the brain. Enkephalins, dynorphins, and endorphins are some of the body's own natural pain killers. Endorphins may be familiar for their role in the feeling of well-being during exercise. Opioid receptors also can be activated by morphine, which mimics the effect of our endogenous opioids. Morphine is naturally produced by the body and like similar synthetic opioids, is a very potent, but potentially addictive pain killer that is widely used for severe acute and chronic pain management. However, there is limited research suggesting that the long-term use of opioids for chronic pain is an effective pain management tool. In addition, research suggests that opioid-induced hyperalgesia (an enhanced pain response) can occur with frequent and/or long-term use of opioids, which can result in a person becoming more sensitive to pain.

Central Sensitization

Central sensitization refers to changes in the nervous system that are associated with the development and maintenance of chronic pain. When this occurs, the nervous system goes through a process called *wind-up* and is in a continued state of high reactivity. This persistent state of reactivity lowers the threshold for a sensation to evoke a pain response and subsequently maintains pain even after the initial injury might have healed. People who experience *allodynia* and/or *hyperalgesia* may have a heightened sensitivity to pain and touch. Allodynia occurs when someone experiences pain as a result of stimuli that aren't normally painful. Hyperalgesia occurs when a stimulus is more painful than it should be.

Genetics of Pain

Differences in our genes highlight how differently we experience pain. Scientists believe that genetic variations can determine our risk for developing chronic pain, how sensitive we are to painful stimuli, whether certain therapies will reduce our pain, and how we experience acute and/or chronic pain. Many genes contribute to pain perception, and mutations in one or more pain-related genes account for some of the variability of pain experiences. Some people born insensate to pain—meaning they cannot feel pain—have a mutation in part of a gene that plays a role in electrical activity of nociceptors and other types of neurons. A different mutation in that same gene can cause a severe and disabling pain condition. Scientists have identified many genes involved in pain by screening large numbers of people with pain conditions for shared gene mutations. While genes play a role in determining our sensitivity to pain, they only account for a portion of this variability. Ultimately, our individual sensitivity to pain is governed by a

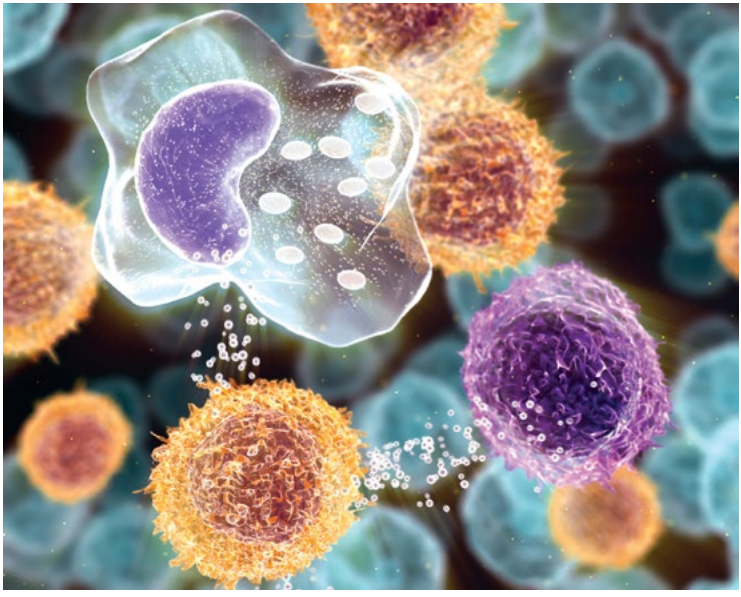
complex interaction of genes, cognitions, mood, our environment, and early life experiences.

Inflammation and Pain

The link between the nervous and immune systems also is important. Cytokines, a group of proteins found in the nervous system, are also part of the immune system—the body's shield for fighting off disease and responding to injury. Cytokines can trigger pain by promoting inflammation, even in the absence of injury or damage. After a trauma, cytokine levels rise in the brain and spinal cord and at the site of the injury. Improvements in our understanding of the precise role of cytokines in producing pain may lead to new classes of drugs that can block the action of these substances to produce analgesia.

Neural Circuits and Chronic Pain

The pain that we perceive when we have an injury or infection alerts us to the potential for tissue damage.



Cytokines can trigger pain by promoting inflammation, even in the absence of injury or damage.

Sometimes this protective pain persists after the healing occurs or may even appear when there was no apparent cause. This persistent pain is linked to changes in our nervous system, which responds to internal and external change by reorganizing and adapting throughout life. This phenomenon is known as neuronal plasticity, a process that allows us to learn, remember, and recover from brain injury. Following an injury or disease process, the nervous system sometimes undergoes a structural and functional reorganization that is not a healthy form of plasticity. Long-term, inappropriate, or inadequate changes in both the peripheral and central nervous system can make us hypersensitive to pain and can make it persist after injuries have healed. For example, sensory neurons in the peripheral nervous system, which normally detect noxious/painful stimuli, may alter the electrical or molecular signals they send to the spinal cord. This in turn triggers genes to alter production of receptors and chemical transmitters in spinal cord neurons, setting up a chronic pain state. Increased activity of neurons in the spinal cord, in turn enhance pain signaling pathways to the brain stem and in the brain. This central sensitization is difficult to reverse and makes pain persist beyond its protective role.

How is Pain Diagnosed?

There is no way to objectively measure pain. Only the person experiencing pain can describe how much pain he/she is feeling. After learning about a patient's pain history and other medical concerns, a healthcare provider may conduct physical exams, clinical assessments, and order diagnostic tests and imaging to assess pain intensity and diagnose or rule out any conditions.

Healthcare providers have many approaches and technologies to help identify the cause of a patient's pain. Primarily these include:

- A **musculoskeletal** and **neurological examination** in which the physician tests movement, reflexes, sensation, balance, and coordination.
- **Laboratory tests** (e.g., blood, urine, cerebrospinal fluid) can help the physician diagnose infection, cancer, nutritional problems, endocrine abnormalities, and other conditions that may cause pain.
- **Electrodiagnostic procedures** including **electromyography (EMG)**, **nerve conduction studies**, **evoked potential (EP) studies**, and **quantitative sensory testing** measure the electrical activity of muscles and nerves. They help physicians evaluate muscle symptoms that may result from a disease or an injury to the body's nerves or muscles. **EMG** tests muscle activity and identifies which muscles or nerves are affected by weakness or pain. **Nerve conduction studies** (usually performed along with an EMG) record how nerves are functioning. **EP** studies measure electrical activity in the brain in response to sight, sound, or touch stimulation. **Quantitative sensory testing** can establish thresholds for sensory perception which can then be compared to normal values. These tests are used to detect abnormalities in sensory function and nerve disorders.
- Imaging, especially **magnetic resonance imaging** or **MRI**, provides a look inside the body's structures and tissues, such as the brain and spinal cord. MRI uses magnetic fields and radio waves to differentiate between healthy and diseased tissue. **Ultrasound imaging** uses high-frequency sound waves to obtain images inside the body.

Imaging such as MRI provides pictures of the body's structures and tissues to help locate the possible cause of pain.

- **Nerve blocks** not only can treat but also can help to diagnose the cause of pain. A person's response to a nerve block may help a provider to determine what is causing the pain or where it is coming from, since pain signals can spread throughout the body.
- **Psychological assessments** often are performed when assessing chronic pain. There is a high prevalence of depression, anxiety, and emotional distress associated with chronic pain (and vice versa), and often the diagnoses can be hard to separate. A provider may ask a patient to complete psychological questionnaires or ask how the person is feeling emotionally.
- **X-rays** produce pictures of the body›s structures, such as bones and joints. **Bone scans** can help diagnose and track infection, fractures, or other bone disorders.

How is Pain Treated?

The goal of pain management is to improve function—enabling individuals to work, attend school, and participate in daily activities. The many treatment options will vary depending on the type of pain, its duration, and patient access.

The best way to prevent, assess, and treat people who experience chronic pain is the biopsychosocial treatment model. This model allows patients, healthcare providers, and caregivers to view pain as a dynamic interaction among and within the biological, psychological, and social factors unique to that individual. It provides the best foundation for tailoring the most comprehensive pain management program for each person.

Interdisciplinary treatment—which involves team members from different healthcare specialties working collaboratively to set goals, make decisions, and share resources and responsibilities—is based on the biopsychological model that is important when assisting chronic pain sufferers.

For the most part, the medications, procedures, interventions, and therapies listed below have been shown in clinical trials to help relieve or manage pain associated with a specific condition(s), but none have been proven fully effective in relieving all types of pain. Discuss with your healthcare provider which treatment, or combination of treatments, will be most effective for you and your pain condition. It is important to remember that, while not all pain is curable, all pain can be treated. Common treatments include:

Acupuncture involves the application of needles to precise points on the body to relieve pain. It is part of a category of healing called traditional Chinese medicine. Evidence of the effectiveness of acupuncture

for pain relief is conflicting and clinical studies to investigate its benefits are ongoing.

Analgesic refers to the class of drugs that includes most "painkillers." This includes classes of **non-steroidal anti-inflammatory drugs** (NSAIDs) such as aspirin, ibuprofen, and naproxen, as well as acetaminophen and **opioids** (which have a narcotic effect and can induce sedation and pain relief). Nonprescription or over-the-counter pain relievers are generally used for mild to moderate pain. Prescription opioid pain relievers, sold through a pharmacy under the direction of a physician, are used for moderate to severe acute pain and are usually prescribed for short periods of time.

Anticonvulsants are used to treat seizure disorders because they dampen abnormally fast electrical impulses. They also are prescribed by physicians to treat various pain conditions, particularly neuropathic pain.

Non-prescription or over-the-counter pain relievers such as aspirin, ibuprofen, and acetaminophen often are used to relieve mild to moderate pain.

Antidepressants are often used to treat chronic pain and are particularly used to help manage musculoskeletal pain, neuropathic pain, and headache-related pain.

Anti-inflammatory diets (nutrition) are another approach to chronic pain management. Research suggests that some people with chronic pain can benefit from eating anti-inflammatory foods to help reduce their level of pain with limited negative side effects.

Beta-blockers are medications which inhibit one arm of the sympathetic nervous system and adrenal "fight or flight" hormones. Propranolol and timolol are used to prevent migraine headaches.

Biofeedback is used to treat many common pain problems, most notably headache and back pain. Biofeedback enables individuals to learn how to change physiological activity for the purpose of improving health and performance. The biofeedback machine provides rapid and accurate feedback that helps people become aware of, follow, and gain control over certain bodily functions, including muscle tension, heart rate, breath rate, and skin temperature. Feedback in conjunction with changes in thinking, emotions, and behavior leads to physiological changes that can be sustained over time without continued use of the biofeedback machine. Biofeedback is often used in combination with other treatment methods, generally without side effects.

Botox (botulinum toxin) is a Food and Drug Administration (FDA)-approved treatment for chronic migraines—those that last for or occur for 15 or more days a month. Botox is injected around pain fibers that are involved in headaches. Botox enters the nerve endings and blocks the release of chemicals involved in pain transmission.

Calcitonin gene-related peptide (CGRP) monoclonal antibodies are a class of FDA-approved medications to help prevent frequent migraines. Some of the new medications include Aimovig, Ajovy, and Emgality.

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 also may involve therapeutic and rehabilitative exercises. A review of numerous clinical trials to assess the effectiveness of spinal manipulations concludes that there is only low-quality evidence of their benefit for acute and sub-acute low back pain. For chronic back pain however, there is evidence of small to moderate treatment relief.

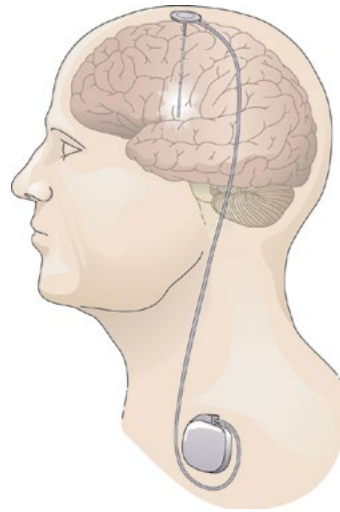
Cognitive-behavioral therapy is a well-established treatment for pain that involves helping an individual improve coping skills—pacing day-to-day activities, addressing negative thoughts and emotions that can amplify pain, and learning relaxation methods to help prepare for and cope with pain and changes in the nervous system. It is used for chronic pain, postoperative pain, cancer pain, and with transitions from acute to chronic pain.

Counseling can give an individual pain sufferer much needed support, whether it comes from family, group, or individual counseling. Support groups can provide an important supplement to drug or surgical treatment. Psychological treatment also can help people learn how to better handle physiological changes produced by pain.

Electrical stimulation, including implanted electric nerve stimulation, and deep brain or spinal cord stimulation, is the modern-day version of age-old practices in which the nerves or muscles are stimulated

by heat or massage. The following techniques require specialized equipment and trained personnel:

- **TENS** (transcutaneous electrical stimulation) 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. TENS can activate subsets of peripheral nerve fibers that can block pain transmission at the spinal cord level.
- **Peripheral nerve stimulation** uses electrodes placed surgically or percutaneously (injected through the skin) on a peripheral nerve. The individual is then able to send an electrical current as needed to the affected nerve, using a controllable electrical generator.
- **Spinal cord stimulation** uses electrodes surgically or percutaneously inserted between the spine's protective covering (the dura) and the spinal column. The individual can send a pulse of electricity to the spinal cord using an implanted electrical pulse generator that resembles a cardiac pacemaker.
- **Deep brain stimulation** is considered a more extreme treatment and involves surgical stimulation of the brain, usually the thalamus or motor cortex. It treats chronic pain in cases that do not respond or have stopped responding to less invasive or conservative treatments.



Deep brain stimulation, which involves surgical stimulation of the brain, is considered a more extreme pain treatment and is used for cases that do not respond to less invasive treatments.

Exercise may help individuals with pain better manage their symptoms and maintain flexibility and muscle strength.

- **Exercise** also may be part of the pain treatment regime for most people with pain. A physician or physical therapist can recommend an appropriate routine. Participation in some form of exercise, physical activity, and stretching may help individuals with pain better manage their symptoms, handle daily activities, and maintain flexibility and muscle strength. Exercise, sleep, and relaxation can all help reduce stress, thereby helping to alleviate pain. Supervised exercise has been proven to help many people with low back pain.

Hypnosis, in general, 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, and there is limited research suggesting its effectiveness. Some believe that hypnosis enables individuals to improve their ability to concentrate and/or relax.

Injections are sometimes used to deliver pain relief medication locally.

- **Facet injections** target the facet joints (small stabilizing joints in the spine between and behind vertebrae). A person may get pain relief from the local anesthetic and may notice longer lasting relief starting two to five days after injection.
- **Steroid injections** work by decreasing inflammation and reducing the activity of the immune system. Injecting steroids into one or two local areas allows doctors to directly deliver a high dose of medication.
- **Sacroiliac joint injection** is used to diagnose the source of a person's pain, as well as to provide therapeutic pain relief associated with sacroiliac joint dysfunction. The injection provides pain relief by reducing inflammation within the joint.
- **Trigger point injections** involve injecting a small amount of local anesthetic, sometimes with a steroid medication, directly into a painful trigger point (a specific site on the muscles that causes pain when pressed during an exam).

Low-power lasers have been used by some healthcare providers as a treatment for pain. This low intensity light therapy (not thermal) triggers biochemical changes within cells and may have an effect on pain, inflammation, and tissue repair, but this method is considered controversial.

Marijuana (*cannabis*) continues to remain highly controversial as a medical treatment to manage pain. Scientific studies are underway to test the safety and usefulness of cannabis for treating different medical conditions. Although marijuana has not been approved for any medical use at the federal level, several states and the District of Columbia permit the use of medical marijuana as a treatment.

- **Marinol** is an FDA-approved medication with the active ingredient dronabinol, a synthetic form of tetrahydrocannabinol (THC) used to treat chemotherapy-induced nausea and vomiting. Initial research has found that Marinol was no more effective than placebo for post-surgical and nerve-related pain, and only slightly more effective than placebo for chronic non-cancer pain.

Muscle relaxants are used to relax and reduce tension in muscles. Muscle relaxants are not a class of drugs, which means that they do not all have the same chemical structure or work the same way in the brain. The term "muscle relaxers" describes a group of drugs that act as central nervous system depressants and have sedative properties for musculoskeletal pain.

- **Anxiolytics** include medications in the class of benzodiazepines, used to decrease central nervous system activity. These drugs can act as muscle relaxants and are sometimes used to manage anxiety.

Nerve blocks use drugs, chemical agents, or surgical techniques to interrupt the relay of pain messages between specific areas of the body and the brain. Nerve blocks may involve local anesthesia, regional anesthesia or analgesia, or surgery, and are routinely used for traditional dental procedures. Nerve blocks also can be used to prevent or even diagnose pain and may involve injection of local anesthetics to numb the nerve and/or steroids to reduce inflammation.

A local nerve block may use one of several local anesthetics such as lidocaine or bupivacaine. Peripheral nerve blocks involve targeting a nerve or group of nerves that affect a part of the body. Nerve blocks also may take the form of what is commonly called an epidural, in which a drug is administered into the space between the dura and the spinal column. This procedure is best known for its use

during childbirth. However, it is also used to treat acute or chronic leg or arm pain due to an irritated spinal nerve root.

- **Neurolytic blocks** employ injection of chemical agents such as alcohol, phenol, or glycerol, or the use of radiofrequency energy, to kill nerves responsible for transmitting nociceptive signals. Neurolytic blocks are most often used to treat cancer pain or pain in the cranial nerves.
- **Sympathectomy**, also called **sympathetic blockade**, typically involves injecting local anesthetic next to the sympathetic nervous system (involved with regulating heart rate, breathing, blood pressure, and response to stressful or dangerous situations). The procedure is often performed to treat neuropathic pain of a limb (e.g., complex regional pain syndrome) as well as vascular disease pain and other conditions.

- **Surgical blocks** are performed on cranial, peripheral, or sympathetic nerves. They are most often used to relieve cancer pain and extreme facial pain, such as that experienced with trigeminal neuralgia. There are several types of surgical nerve blocks and they are not without problems and complications. Nerve blocks can cause muscle paralysis and, in many cases, result in partial numbness. For that reason, the procedure should be reserved for a select group of individuals and should only be performed by skilled surgeons. Types of surgical nerve blocks include:
  - **Spinal dorsal rhizotomy**, in which the surgeon cuts the root or rootlets of one or more of the nerves radiating from the spinal cord. Other rhizotomy procedures include **cranial rhizotomy** and **trigeminal rhizotomy**, performed as a treatment for extreme facial or cancer pain.

Physical therapy and rehabilitation may help to decrease pain and improve mobility by increasing function, controlling pain, and aiding recovery. Individuals may engage in a number of physical therapy treatments simultaneously. A few of the most common forms (in addition to exercise, electrical stimulation, and ultrasound) are:

- Traction sometimes is used to decrease pain and improve mobility in the spine.
- Joint mobilization can occur when a physical therapist passively moves the joints of the body in specific directions to help decrease pain and improve mobility.
- Heat and ice are often used in physical therapy. Heat can increase circulation to the injured tissues, relax the muscles, and provide pain relief. Ice typically is used to help decrease pain and control inflammation.
- Kinesiology taping uses a flexible tape to support body parts and muscles to reduce bruising/swelling and provide pain relief.

Placebos are defined as substances without any therapeutic effect that are typically used as a control factor in clinical studies to determine the effectiveness of a medical treatment. Placebos are inactive substances, such as sugar pills, or harmless procedures such as saline injections, and may be prescribed more for the psychological benefit to the patient than for any physiological effect. Placebos, however, do offer some individuals pain relief. Although placebos have no direct effect on the underlying causes of pain, evidence from clinical studies suggests that many conditions such as migraine headache, back pain, post-surgical pain, rheumatoid arthritis, angina, and depression sometimes respond well to them. This is known as the placebo response, which is defined as the

observable or measurable change that can occur after administration of a placebo. One significant component responsible for the effect of placebo is the degree to which people expect the treatment to work. Placebos work in part by stimulating the brain's own analgesics.

Relaxation and mindfulness are ways for people to respond to the physical sensation of pain, which can have a major impact on how the body's nervous system creates and perceives pain. An individual's automatic reactions to pain, often unconsciously, can amplify the pain-generating activity of the nervous system. Relaxation strategies (e.g., imagery, progressive muscle relaxation, autogenic relaxation) and mindfulness techniques (e.g., exercises that help the individual observe physical, cognitive, and emotional reactions and make skillful choices to relieve pain) are evidence-based practices to help shift the nervous system back toward a normal non-pain state.

R.I.C.E.—**R**est, **I**ce, **C**ompression, and **E**levation—are four components prescribed by many orthopedists, coaches, trainers, nurses, and other professionals for *temporary* muscle or joint injuries, such as sprains or strains.

The four components—Rest, Ice, Compression, and Elevation—often are prescribed for temporary muscle or joint injuries, such as sprains or strains.

Radiofrequency ablation (RFA) uses an electrical current produced by a radio wave to heat up a small area of nerve tissue, thereby decreasing pain signals from that specific area. The degree of pain relief can vary depending on the cause and location of the pain. Some individuals can experience pain relief for up to 6-12 months.

Serotonergic agonists—the triptans (including sumatriptan, naratriptan, and zolmitriptan)—are used specifically for acute migraine headaches because they block pain pathways in the brain. Taken as pills, shots, or nasal sprays, they can relieve many symptoms of migraine.

Surgery may be recommended for some people with pain that significantly impacts their daily functioning. Surgery may be considered when less invasive treatments have not been helpful. However, surgical procedures are not always successful and may not be appropriate for all people.

Topical pain creams/gels are sprayed on or rubbed into the skin over painful muscles or joints. Although they are all designed to relieve pain, they have different ingredients. Topical pain creams and gels (e.g., compounded pain creams to treat specific pain) are sometimes prescribed by a physician, while others can be bought over the counter. There is limited evidence about the effectiveness of such creams. Below are the most common ingredients in products available without a prescription.

- **Capsaicin** (pronounced cap-SAY-sin) is a chemical found in chili peppers and is also a primary ingredient in prescription or over-the-counter pain-relieving creams as a treatment for several pain conditions, including shingles. This topical cream may be helpful for deep pain. It works by reducing the amount of substance P—a compound

Capsaicin, a chemical found in chili peppers, is a key ingredient in pain-relieving creams used to treat a number of pain conditions.

thought to be involved in the synaptic transmission of pain and other nerve impulses—that is found in nerve endings and interferes with the transmission of pain signals to the brain. Individuals can become desensitized to the compound, however, perhaps because of long-term capsaicin-induced damage to nerve tissue. Some people cannot tolerate the burning sensation they experience when using capsaicin cream.

- **Counterirritants** include ingredients such as menthol, methylsalycylate (oil of evergreen), and camphor. They are called counterirritants because they create a burning or cooling sensation that distracts the person from the pain.
- **Salicylates** are the same ingredients that give aspirin its pain-relieving quality and are found in some creams. When absorbed into the skin, they may help with pain, particularly in joints close to the skin, such as fingers, knees, and elbows.

Sex/Gender and Pain

According to the Institute of Medicine's (IOM) 2011 report: *Relieving Pain in America* (https://www.nap.edu/catalog/13172/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care), women

often report a higher prevalence of chronic pain than men and are at a greater risk for many pain conditions. Women also are likely to have more pain from certain diseases, such as cancer. In addition, some chronic pain disorders occur only in women while others occur predominantly in women. These include chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, vulvodynia, and temporomandibular disorders.

The IOM report notes three theories that might explain the gender differences in pain experience:

- A gender-role theory that assumes that it is more socially acceptable for women to report pain;
- An exposure theory that suggests that women are exposed to more pain risk factors; and
- A vulnerability theory proposing that women are more vulnerable to developing certain types of pain, such as musculoskeletal pain.

Of these, the vulnerability theory is best supported by scientific evidence.

Race/Ethnicity and Pain

According to the 2011 IOM report, cultural perspectives and identification in a specific racial or ethnic group can influence a patient's report of pain. Initial research also indicates that healthcare providers' expectations of a person's pain can be influenced by race or ethnicity. People of different races/ethnicities often experience different rates of clinically painful conditions. Some research has shown that African Americans, Asians, and Hispanics demonstrate lower pain tolerance compared to Caucasians. Stereotypes also have resulted in the undertreatment of racial/ethnic minorities. Some studies suggest that there are

such disparities in pain management for a variety of conditions and treatment settings. They indicate that African Americans and Hispanics are more likely to have their pain undertreated than Caucasians.

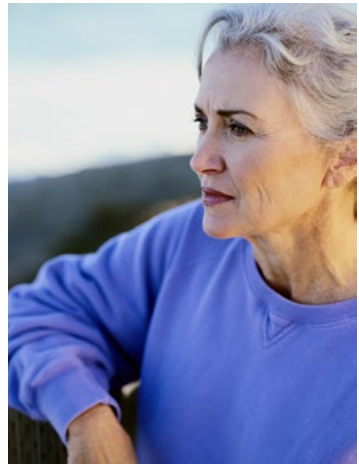
Pain in the Older Population and Children

According to the 2011 IOM report, the likelihood of experiencing pain and the type of care one receives differs for children and the very old, compared to young and middle-aged adults.

Older people

Pain is the number one medical complaint of older Americans. Research suggests that more severe pain and pain that interferes with activities increases with age. Evidence also shows that older people are more vulnerable to severe or persistent pain and that the inability to tolerate severe pain also increases with age. Some of the most common causes of pain in older adults include joint pain, post-surgical pain, chronic disease, and conditions associated with aging.

Pain management in the older population differs from that in younger people. For example, older people are much more likely to experience medication-related side effects than younger people.



Pain affects men and women differently. It is the number one medical complaint of older Americans.

Children

Pain in children also requires special attention. Identifying the problem and getting a proper diagnosis can be particularly difficult because young children often are not able to describe the degree of pain that they are experiencing. Also, a child's pain is often undertreated for various reasons, one being there are few evidence-based recommendations regarding medication-prescribing practices for children and adolescents. Although treating pain in children poses challenges to physicians and parents alike, children should never be undertreated. Specific tools and questionnaires for measuring pain in children have been developed that, when combined with feedback from parents, can help physicians select the most effective treatments.

What is the Future of Pain Research?

At the forefront of pain research are scientists supported by the National Institutes of Health (NIH), including the National Institute of Neurological Disorders and Stroke (NINDS), which is the primary federal supporter of research on the brain and nervous system. More than 20 institutes and centers at NIH support pain research and are members of the NIH Pain Consortium, which identifies, coordinates, and supports pain research initiatives, activities, and strategic planning at NIH.

NINDS funds a broad range of pain research, including exploration of pain neural pathways and the mechanisms of the perception of pain, neuropathic pain, inflammatory pain, and the transition from acute to chronic pain. NINDS also supports the exploration and development of new therapies for pain, and funds research on potential new targets for pain treatments.

NIH introduced the **HEAL** (Helping to End Addiction Long-term) **Initiative** SM in April 2018. The HEAL Initiative is an aggressive trans-NIH effort to improve prevention and treatment strategies for opioid misuse and addiction and to enhance pain management. While many strategies currently are being used to reverse the opioid overdose epidemic, there is an urgent need to develop more effective treatments for pain while reducing the potential for addiction and abuse. The HEAL Initiative focuses on understanding the biological underpinnings of chronic pain and accelerating the discovery and development of novel non-addictive and effective pain treatments through the clinical pipeline. NIH awarded $945 million in fiscal year 2019 funding for grants, contracts, and cooperative agreements across 41 states through the HEAL Initiative. For more information on HEAL, visit https://heal.nih.gov.

The NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative® is a national effort to accelerate the development and application of new technologies to provide unprecedented access to the inner workings of the nervous system. Scientists working with the BRAIN Initiative are studying ways

The primary aims of pain research include to prevent chronic pain and develop better treatments for pain.

to modulate neural circuitry to reduce pain. For more information on the BRAIN Initiative, visit https://braininitiative.nih.gov/.

In addition to NINDS, other NIH Institutes fund research on pain. Research projects on pain and other disorders can be found using NIH RePORTER (http://projectreporter.nih.gov), a searchable database of current and past research projects supported by NIH and other federal agencies. RePORTER also includes links to publications from these projects and other resources.

Clinical Studies offer an opportunity to help researchers find better ways to safely detect, treat, or prevent pain and therefore hope for individuals now and in the future. NINDS conducts clinical studies on pain at the NIH research campus in Bethesda, Maryland, and supports pain studies at medical research centers throughout the United States. But studies can be completed only if people volunteer to participate. By participating in a clinical study, healthy individuals and people living with pain can greatly benefit the lives of those affected by this disorder. Talk with your doctor about clinical studies and help to make the difference in improving the quality of life for all people living with pain. For more information about NINDS clinical trials on pain, see http://www.clinicaltrials.gov and search for "pain AND NINDS."

Over the centuries, science has provided us with a remarkable ability to understand and control pain. Today, scientists know a great deal about the causes and mechanisms of pain, and research has led to improved diagnosis and treatment of several painful disorders. For people who fight every day against the limitations imposed by pain, the work of NINDS-supported scientists holds the promise of even greater knowledge of pain in the coming years. Their research offers a powerful weapon in the battle to prolong and improve the lives of people with pain: hope.

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
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
301-496-4261
www.nidcr.nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
National Institutes of Health, DHHS
31 Center Drive, Room 4C02
Bethesda, MD 20892-2350
301-496-8190 or 877-226-4267
www.niams.nih.gov

National Institute on Drug Abuse (NIDA)
National Institutes of Health, DHHS
6001 Executive Boulevard, Room 5213
Rockville, MD 20892-9561
301-443-1124; 800-729-6686 (Publications)
www.drugabuse.gov

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

American Headache Society/
American Migraine Foundation
19 Mantua Road
Mt. Royal, NJ 08061
856-423-0043
https://americanmigrainefoundation.org/

Arthritis Foundation
1355 Peachtree Street, N.E., Suite 600
Atlanta, GA 30309
844-571-4357 or 404-872-7100
www.arthritis.org/

Migraine Research Foundation
300 East 75th Street, Suite 3K
New York, NY 10021
212-249-5402
www.migraineresearchfoundation.org

National Headache Foundation
820 N. Orleans, Suite 411
Chicago, IL 60610-3132
312-274-2650 or 888-643-5552
www.headaches.org

Credits

Illustrations and photos:
Page 5, Tina Carvalho, University of Hawaii at Manoa
Page 8, Courtesy of Roche
Page 11, John Crawford, MedArts, NIH
Page 17, Bill Branson, NIH, for NCI
Page 28, NINDS DIR, NIH

National Institute of Neurological Disorders and Stroke

NIH . . . Turning Discovery Into Health

Prepared by:

Office of Neuroscience Communications and Engagement
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20892

NIH Publication No. 20-NS-2406
July 2020