



Drugs for Arthritis Pain

by David Borenstein, MD

Although the term “arthritis” means “joint inflammation,” for most people the most common symptom of arthritis is pain. Whether arthritis is caused by cartilage breakdown (osteoarthritis, or OA) or a disordered immune system (rheumatoid arthritis, or RA), sooner or later it will cause pain. This article takes a look at the different types of pain that arthritis can cause and how various drugs are used to treat them.

What is pain?

Pain is defined as an unpleasant sensory and emotional experience that is brought on by damage — or the perception of damage — to the body’s tissues. But how does pain actually work in the body? The question has been asked for centuries. Today, our knowledge of the pain process is much more sophisticated than it was at the time of French philosopher René Descartes, who thought there was a single thread that attached a portion of each limb to the brain. This simplistic notion has been replaced by a model of complex nerve interconnections working together with chemicals produced by the nerves and surrounding tissues. These nerves and chemicals transmit pain signals from the site of tissue damage to the spinal cord and then the brain, where the signals are processed into physical sensations of pain. The communication chain by which pain signals are transmitted is known as a “pain pathway,” although, as we will see, there are different pathways for different types of pain.

The nervous system’s communications about pain don’t only travel one way — signals also travel back down the spinal cord, and some of these signals work to reduce pain. Pain-reducing signals travel along a “pain inhibitory pathway,” in which the nervous system produces pain-relieving chemicals. Endorphins, which block the transmission of pain signals to the brain, are among these chemicals. Increased activity in the pain inhibitory pathway decreases pain and promotes a feeling of well-being. For example, people with chronic pain experience less pain when they exercise regularly because exercise releases endorphins. The nerves in the pain inhibitory pathway also release the chemicals serotonin and norepinephrine in response to exercise. These chemicals, like endorphins, are thought to decrease pain, and medicines that increase levels of serotonin and norepinephrine have been shown to be effective in relieving pain.

Two types of pain

There are many ways to describe the characteristics of pain. One can talk of the onset of pain (when and how it begins), its location (where it is), its duration (how long it lasts), and its quality (what it feels like). In this article, I will concentrate on the duration and the quality of pain. Pain of short duration — that is, pain that lasts only a short time — is called *acute* pain. Long-lasting pain is chronic pain. Understanding the

difference between acute and *chronic* pain can help determine which drug or combination of drugs will work best for your arthritis.

Acute pain. Acute pain acts as a warning sign that you have an injury. When an injury occurs, the body releases a specific array of chemicals that signal tissue damage. These chemicals cause a part of your nervous system to recognize the injury immediately, which in turn causes the muscles to react in an attempt to limit the damage. This is the system that pulls your hand away when you touch a hot stove.

These acute events do not have a long-term effect on the nervous system. For example, you may have severe acute pain caused by an attack of gout. But once the attack is over, the pain goes away and the affected joint returns to feeling normal.

Chronic pain. In contrast, chronic pain does bring about changes to the nervous system that affect how you feel pain. Chronic pain was once thought to be acute pain that continued well beyond the period for normal healing. It was assumed the “acute” chemicals released in response to acute pain were simply being released over a longer period. However, research has shown that chronic pain involves a different set of chemicals and that chronic pain signals travel along a separate pathway to the brain. In addition, chronic pain can cause changes to structures within the nervous system, and these changes can increase sensitivity to painful stimuli. Because of these changes, chronic pain may persist even when there is no injury or after an initial injury has healed.

Another difference between acute pain and chronic pain is that chronic pain has effects on parts of the brain associated with emotions and mood. Chronic pain may therefore contribute to stress, anxiety, and depression.

Treating arthritis pain

For the purposes of discussing pain, the different forms of arthritis can be divided into two basic categories. In one category are the conditions that cause body-wide inflammation that includes the joints. RA is the prime example of this group; systemic lupus erythematosus is another well-known example. In the other category are conditions that involve a minimal amount of inflammation in the joints. OA is in this group.

These distinctions are important when it is time to decide on therapy to relieve arthritis pain. Pain associated with inflammatory arthritis is best controlled using drugs that decrease inflammation. For OA and other types of arthritis in which inflammation isn't the main problem, treatments that address only pain may be effective.

Four major types of drugs are used to relieve arthritis pain: nonsteroidal anti-inflammatory drugs (NSAIDs), pure analgesics, antidepressants, and anticonvulsants. To make your pain relief regimen as simple as possible, your doctor will try to use only one drug to improve your condition. In many circumstances, acute pain can be relieved in this way. Unfortunately, it is often necessary to use two or more drugs from different categories to control chronic pain. (See [“Common Arthritis Pain Drugs”](#) for a list of commonly prescribed pain relievers.)

NSAIDs

NSAIDs are the class of medicines most frequently prescribed for all types of pain, whether acute or

chronic, inflammatory or noninflammatory. NSAIDs reduce fever, swelling, and blood clotting in addition to pain. They work by blocking an enzyme in the body called cyclooxygenase-2 (COX-2). COX-2 produces substances called prostaglandins, and at sites of inflammation these prostaglandins are associated with the heat, swelling, and pain that accompany tissue damage.

In addition to blocking COX-2, most NSAIDs block another enzyme called cyclooxygenase-1 (COX-1), which also produces prostaglandins. The prostaglandins made by COX-1 help preserve the stomach lining, regulate kidney function, and maintain normal blood pressure. NSAIDs that block both COX-1 and COX-2 are known as nonselective NSAIDs, and they include common drugs such as ibuprofen (Advil). Nonselective NSAIDs are effective at decreasing pain and swelling associated with all forms of arthritis. The difficulty with nonselective NSAIDs is that by blocking COX-1 as well as COX-2, they raise the risk of several gastrointestinal problems, including heartburn and bleeding ulcers.

A second type of NSAID, known as a COX-2 inhibitor, was designed to address this problem. By targeting only COX-2 and leaving COX-1 alone, COX-2 inhibitors can reduce the risk of these gastrointestinal side effects. The only COX-2 inhibitor currently on the market in the United States is celecoxib (Celebrex). The COX-2 inhibitors valdecoxib (Bextra) and rofecoxib (Vioxx) were removed from the market several years ago over concerns that they increased the risk of heart attack and stroke. In recent years, the labels of all NSAIDs have been required to include a warning of the potential for increased cardiovascular risk.

NSAIDs fall into a number of different chemical groups. You may respond to one chemical group and not another. Any particular NSAID will help only about two-thirds of people who try it, and some people have to try three or more NSAIDs before finding one that works for them.

Although NSAIDs are usually taken by mouth, topical NSAIDs, including gels and patches, have become available in recent years. These formulations allow the medicine to be applied directly onto a painful joint. The downside of the topical NSAIDs is that they have to be applied up to four times a day to have an effect, whereas many oral NSAIDs can be taken once or twice a day. Unfortunately, even though applying NSAIDs topically means that less of the medicine circulates to other parts of the body, they still carry a risk of side effects.

Pure analgesics

Pure analgesics reduce pain but, unlike NSAIDs, have no effect on inflammation. The pure analgesic category is divided into two groups: nonopioid and opioid medicines.

Nonopioid analgesics. Acetaminophen (Tylenol) is a popular nonopioid analgesic that works by decreasing prostaglandin production in the brain and spinal cord (but has no effect on prostaglandin production in other parts of the body). It has pain-relieving effects similar to those of NSAIDs but without the gastrointestinal side effects. For this reason, it's often the first drug tried for relieving the pain of OA. When acetaminophen alone doesn't relieve pain, or when inflammation is the underlying problem, acetaminophen is often used in combination with drugs in other categories. Acetaminophen carries a risk of liver damage when it is taken in higher-than-recommended doses, so people taking acetaminophen should avoid other over-the-counter pain relievers and cold medicines unless they have discussed those medicines with their doctor.

Opioid analgesics. Opioids, also known as narcotics, work by mimicking the action of endorphins in the pain inhibitory pathway. Endorphins, which can be found in the brain, spinal cord, and elsewhere

throughout the body, latch onto opioid receptors in the nervous system and block pain signals. The strength of an opioid drug is related to how well it binds to these receptors.

Opioid analgesics are available in multiple formulations and combinations, both short-acting and long-acting. Short-acting opioids are most appropriate for acute pain concentrated in a particular area, as can occur with OA and other forms of arthritis that involve minimal inflammation. In this case, the medicine would be discontinued once the symptoms were resolved.

Long-term opioid therapy is prescribed for people whose pain persists despite the use of NSAIDs and nondrug treatments. People taking short-acting opioids often have to transition to long-acting opioids if they are taking a steady dose of short-acting opioids that cannot be decreased without a marked worsening in their physical function.

Although opioids can be very effective at relieving pain, they are not doctors' first choice for chronic pain because of their potential to cause adverse effects. Possible side effects of opioids include sedation, dizziness, nausea, vomiting, itching, sweating, and constipation. In rare cases, opioids can bring on a slowed rate of breathing — known as respiratory depression — which can cause death. This is most likely in people just beginning opioid treatment and becomes less of a concern with regular opioid use.

If you take an opioid for an extended period, you will become physically dependent on it, meaning that your body will come to rely on the drug for normal functioning. For this reason, people who have taken an opioid for a long time experience symptoms of withdrawal, such as sweating, abdominal cramps, or diarrhea, if they stop the medicine abruptly. People taking an opioid may also become tolerant to the drug, so that they need increasing doses to achieve the same effect in treating chronic pain. Physical dependence and tolerance are not addiction; among addiction's hallmarks is a *psychological* dependence on a drug (or other substance or behavior) that causes people to compulsively seek it out. Addiction to opioids is rare in people who do not have a history of addiction and who use opioids as directed.

Another option is a “weak” opioid such as tramadol (Ultram). “Weak” opioids are so called because they bind only modestly to opioid receptors. Unlike most other opioids, tramadol also increases levels of serotonin and norepinephrine in the pain inhibitory pathway, which may account for part of its pain-relieving ability. The primary side effects of tramadol include dizziness and nausea.

The recommended opioid dose varies from person to person, but the general rule of thumb is to use the lowest effective dose. Short-acting opioids, which are absorbed and cleared from the body relatively quickly, must be taken several times a day. Long-acting opioids, which are designed to be released slowly and stay in the body longer, need to be taken less often and typically in a lower dose. If you use an opioid for chronic pain, it's important to use it as directed. You should also keep you doctor updated on how well it is controlling your pain and what, if any, side effects you are experiencing.

Antidepressants

Antidepressant medicines have been shown to be helpful for chronic pain, even in people who do not have depression. How these drugs relieve pain is not entirely known. The current thinking is that antidepressants relieve pain by increasing levels of serotonin and norepinephrine in the pain inhibitory pathway.

Tricyclic antidepressants, such as amitriptyline, increase low levels of serotonin and norepinephrine. The doses of tricyclics that are effective for pain relief are significantly lower than the doses required to improve

depression. A second class of antidepressants called serotonin–norepinephrine reuptake inhibitors (SNRIs), which includes duloxetine (Cymbalta) and milnacipran (Savella), has pain-relieving properties similar to those of tricyclics and is used for treating chronic pain. In fact, Cymbalta has recently won approval to treat OA pain, and both Cymbalta and Savella are approved to treat the chronic pain condition fibromyalgia. A third class known as selective serotonin reuptake inhibitors (SSRIs), including sertraline (Zoloft) and fluoxetine (Prozac), is not as effective for pain relief.

Antidepressants have several potential side effects. Tricyclics' side effects can include dry mouth, blurred vision, dizziness and drowsiness. SNRIs and SSRIs can increase the risk for headache, nausea, nervousness, and insomnia. Side effects are often more pronounced with tricyclics than with SNRIs and SSRIs.

Anticonvulsants

The list of options for treating chronic pain has grown to include a variety of drugs that were developed to treat neurologic conditions that are not usually associated with pain. For example, drugs originally used to treat seizures — examples are gabapentin (Neurontin) and pregabalin (Lyrica) — can also relieve pain. These drugs, called anticonvulsants, have effects on structures in the nervous system known as calcium channels, which allow cells to transmit electrical signals. Blocking calcium channels reduces the number of chemical messengers known as neurotransmitters in the central nervous system. Because they have an entirely different mechanism of action from other pain relievers, anticonvulsants are usually taken along with NSAIDs or pure analgesics. In this case, the drugs are started one at a time so that any side effects can be correctly attributed to the most recently added medicine. Side effects associated with anticonvulsants include dizziness, sleepiness, blurred vision, and weight gain.

The right pain therapy for you

No single drug or combination of drugs works for all types of arthritis pain. Your pain is unique. It may be acute or chronic, and it may be caused by an inflammatory or a noninflammatory condition. In addition, some people have particular sensitivities that can make specific drug side effects intolerable. You and your doctor will take all of these factors into account when deciding on a pain regimen that is effective and tolerable for you. The hope is that, as your physical function improves and you gain better control of your arthritis, you will be able to take your focus away from pain and enjoy a better quality of life.

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