

**ACPA Medications  
&  
Chronic Pain  
Supplement 2007**

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# Author and Contributors

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## INTRODUCTION

For over a quarter century, the American Chronic Pain Association, a non-profit, tax exempt organization, has offered a support system for people with chronic pain through education in pain management skills and self-help group activities. To learn more about the ACPA and how to become a member, please visit our web site at [www.theacpa.org](http://www.theacpa.org), or call the National Office at 800-533-3231.

The ACPA Medications & Chronic Pain 2007 Supplement is updated yearly and includes web links for certain medications and relevant Internet sites of interest. Generic names are primarily listed with brand names in parentheses.

**This supplement is not meant to serve as medical advice for your condition or regarding your medication needs.** Remember that the best source of information about your health and medication needs is from an open dialogue with your treating doctor.

**Prescription medications are lawfully available only from a health care professional licensed to prescribe them. Do not use them unless prescribed for you by such an individual.**

This ACPA Medications & Chronic Pain Supplement only deals with medications and does not mention the many other important treatment approaches to chronic pain. In fact, medications alone are rarely satisfactory absent the additional use of other approaches to treat the person with chronic pain. These other approaches include physical and occupational therapy, behavioral-psychological treatments, and a host of other modalities, devices, and interventional techniques including surgery. In fact, rehabilitation through cognitive, behavioral, and physical reactivation treatments often lessens the need for medications and other more invasive procedures.



The ACPA believes that people with chronic pain benefit from being well informed about their medications. This knowledge may relieve the fears that can interfere with receiving maximum benefits from medications. Information can also prevent unrealistic expectations that can lead to disappointment. People with pain should ask questions about the benefits and side effects when they are concerned about particular medications.

The ACPA Medications & Chronic Pain Supplement is a work in progress. Your comments and contributions are welcome by way of E-mail to [acpa@acpa.net](mailto:acpa@acpa.net).

In this document, the medical term "opioid" is used rather than the negatively perceived term "narcotic."

Many pain specialists recommend that the term "Chronic Pain" is better described as "Persistent Pain" – a condition which can be continuous or recurrent and of sufficient duration and intensity to adversely affect a patient's well being, level of function, and quality of life.

## **MEDICATIONS AND CHRONIC PAIN**

The use of analgesics (pain relievers) and other medications is the most common method of chronic pain treatment. Pain medications can be helpful for some patients in chronic pain, but they are not universally effective.

Short-term use of medications for pain is rarely worrisome, but prolonged use increases the possibility of adverse reactions including gastrointestinal distress, internal organ problems, balance troubles, and memory and concentration problems.

It is important to remember, everyone responds in a different manner to the same dose of medication.

Therefore, each person with chronic pain should be medically managed individually, and medication use should be determined by benefit, cost, potential side effects, and the person's other medical problems.

Partial rather than full relief of pain, sleep loss, or other symptoms is often a more realistic goal with using medications.

### **HOW MEDICATIONS CAN HELP & HARM**

Many people with chronic pain are able to manage adequately without medications and can function at a near-normal level. Others find that their overall quality of life, in terms of comfort and function, is improved with medications.

While medications can help relieve and cure symptoms, they also can cause unpleasant side effects that at a minimum can be bothersome and at their worst, can cause significant problems. These side effects can often be avoided or at least managed with the help of your physician.



All prescription medications, over-the-counter medications, or nutritional and herbal supplements, should be used carefully and appropriately because they can interact with each other and can cause side effects. Even the most potent medications used for pain do not always completely eliminate pain but rather may reduce the severity of pain. As such, medications may not be adequate treatments themselves but should be considered as part of a comprehensive approach to pain management and functional improvements.

It is critically important for you to tell your doctor about everything you are taking both for your pain and for other medical conditions, even when you may not think of it as a “medication.” This can include various supplements and vitamins you purchase without a prescription, items you grow from your garden or buy in a store, and other “substances” such as caffeine, alcohol, tobacco and even marijuana and illicit drugs.

It is strongly advised that you take all of your current medication bottles with you to any doctor appointments and be honest and forthcoming about any other substances you are using. Some drugs may cause serious side effects if they are combined with other medications. Even over-the-counter and herbal medications have the potential to have serious interactions with your prescription medications and each other.

#### **ADVICE FROM THE ACPA**

***The best advice the ACPA can offer is for you to discuss all medication questions with your physician!*** A physician who specializes in Pain Medicine may be best informed about the use of different medications for various chronic pain problems.

If you are a person with chronic pain, you may be on medications, and you should know why you are taking them. Medications can be confusing, especially if you take them for more than one condition. You should know what medications you are on, how much and how often you need to take them, and whether to take the medication before, with, or after meals or at bedtime. The dose you need depends on your medical condition, body size, age, and any other medications you take. Because of the possibility of interactions between drugs, some medications should not be generally taken together or should be taken at different times during the day to avoid unwanted reactions.

The label may show a brand name or the generic name. It is often less expensive to buy your prescription by its generic name than by the brand name. Although the color or shape of the pill may be different, there is no difference in quality between generic and brand name drugs. You can ask your doctor to prescribe generic drugs if they are available. Follow the dose and directions written on the prescription label. Do not change your dose without consulting your health care provider, and never use medication prescribed for someone else.

#### ***Warning from the ACPA about purchasing medicines over the Internet.***

Sites may purport to be legitimate or in a country with drug laws comparable to the US (e.g., Canada), but may (a) not be located in that country; (b) located in that country, but dispense prescriptions from another country that has no comparable law; (c) not handle and store



medicines in a manner that maintains potency and shelf life; or (d) purchase medicines from dubious sources, including knowingly or unknowingly selling counterfeit medicines that may contain amounts of the expected pharmaceutical ingredients that vary from those stated, may contain other unnamed pharmaceutical ingredients, may contain no active pharmaceutical ingredients or may contain toxic chemicals or microbial contaminants.

## **MEDICATION PICTURES**

It is always very important to be able to visually identify the medications you are taking. Pictures can be found at <http://www.healthsquare.com/drugmain.htm>. Type in the name of your medication and then click on the link for that medication. You may find a picture of the pill by shape, size, color, and dose at the bottom of the page. Note that not all links contain pictures.

Another useful site to identify pills is at <http://www.drugs.com/> where you can click on [Pill Identification](#), then click on “I Agree” at the bottom of the page. You then can find pills by drug form, shape, text imprint or drug name. If you know the drug name, you can click directly on [Image Search](#) and click on “I Agree” at the bottom of the page.

If you are unable to identify your pill(s), please contact your pharmacist and s/he should be able to help you identify your medication(s).

## **PAIN IN OLDER PERSONS**

Persistent or chronic pain is prevalent in older adults. The issue has been addressed in the American Geriatric Society ([www.americangeriatrics.org](http://www.americangeriatrics.org)) Clinical Practice Guideline: The Management of Persistent Pain in Older Persons at the following Internet Web site: <http://www.americangeriatrics.org/products/positionpapers/JGS5071.pdf>.

Some older individuals may be more sensitive to medications, more likely to experience side effects, and more likely to be using multiple drugs with the associated risk of interactions between the drugs. In older persons, the dose is often started low and adjusted slowly to optimize pain relief while monitoring and managing side effects. The use of multiple drugs can be seen as potentially advantageous. Combining smaller doses of more than one medication may minimize the dose-limiting adverse effects of a particular drug.



## OFF-LABEL MEDICATION USE

Prescription medications are often used for conditions not listed on their labels. This is called “off-label” use of the medication. It is legal for your physician to use a medication “off-label,” but your insurer, health plan or pharmacist may question its use as recommended by your doctor.

Most drugs have many effects, some desirable and others undesirable. Because of this, a drug may be used for a variety of unrelated conditions. For example, aspirin is used to reduce inflammation and pain in arthritis but is also used as a blood thinner to prevent heart attacks. Thus, it may be confusing to think of aspirin as an “arthritis” or “pain” medicine alone.

Similarly, many of the medicines used in chronic pain were originally designed and marketed for unrelated conditions, such as seizures. The fact that a physician recommends such a drug does not mean the doctor thinks you have epilepsy. The same is true with antidepressants; the fact that they are prescribed for chronic pain does not mean the physician has made a diagnosis of depression.

The Food and Drug Administration ([www.fda.gov](http://www.fda.gov)) allows drugs to be sold and advertised only for specific conditions in which they have been proven to be safe and effective. Once on the market, they can be used “off-label” for any condition in which there is evidence of effectiveness without the drug company proving to the FDA that the drug can treat the new “off-label” condition. The process of getting approval for another use of the medication can cost millions, so a company might not fund research studies to prove all the uses for a drug. This is especially true if the medication is no longer protected by a patent, and other companies can sell it.

Off-label prescribing is legal, and it is an accepted medical practice to use drugs in this way. However, a drug cannot be *advertised* for any condition unless the manufacturer goes to the expense of proving to the FDA that it is safe and effective for that condition. This is important because many of the drugs used for chronic pain have not been approved by the FDA for pain even though they may be useful for it.

It can be very frustrating if you are having trouble getting your prescription authorized by the insurer if it is being prescribed for off-label use. Try not to lose your temper or get angry as this only increases chronic pain problems. Ask your doctor to explain to the authorizing party that the medication is being prescribed off-label and for what reason.



## PAIN TYPES & CHRONIC PAIN CLASSIFICATION

Acute pain is distinguished as being of recent onset, transient, and usually from an identifiable cause.

Chronic pain can be described as persistent or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, and which adversely affects the individual's well-being. A simpler definition for chronic pain is pain that continues when it should not. It is usually treated with medicine that you take at specific times every day (rather than as needed) so that you get pain relief throughout the day.

Breakthrough or Flare-up pain can be described as transient pain beyond the normal pain baseline which is severe or excruciating. Breakthrough or flare-up pain consists of unpredictable pain flares that "break through" the medicine taken around-the-clock to treat persistent pain. Breakthrough or flare-up pain may be caused by changes in an underlying disease, including treatment, or involuntary or voluntary physical actions - such as coughing or getting up from a chair. Breakthrough or flare-up pain may also occur at the end of the scheduled pain medicine dose. Treatment for moderate-to-severe breakthrough pain is a strong, short-acting pain medicine, such as an opioid, that works quickly and lasts about as long as a breakthrough or flare-up pain episode. Some pain physicians feel that if you are taking pain medication for breakthrough or flare-up pain regularly, your regular long-acting pain medicine may not be effective. Alternative pain management strategies may be needed.

Chronic pain is classified by pathophysiology (the functional changes associated with or resulting from disease or injury) as nociceptive (due to ongoing tissue injury) or neuropathic (resulting from damage to the brain, spinal cord, or peripheral nerves), with mixed or undetermined causes as well. Pain relievers or analgesics are generally effective for nociceptive pain but less effective for neuropathic pain.

The American Academy of Pain Medicine has characterized pain by a new terminology, namely, *eudynia* for nociceptive pain, and *maldynia* for neuropathic pain.

Eudynia (nociceptive pain) is a normal physiologic response to noxious events and injury to somatic (muscle or soft tissue) or visceral (internal organ) tissue. It can be beneficial and serves as an early warning mechanism. Eudynia often is acute, but can also be persistent (e.g., cancer pain).

Maldynia or neuropathic pain often results in significant dysfunction. Whatever damage (pathology) exists, it is not well measured with our current testing abilities, and the physician often has difficulty correlating the pathology with the level of reported dysfunction and pain.





## OVER-THE-COUNTER (OTC) PAIN RELIEVERS

OTC drugs are those drugs that are available to consumers without a prescription. A trip to the local drug store reveals numerous tablets, suppositories, patches, sprays, creams and ointments, all with claims of providing pain relief.

The traditional OTC pain group currently includes aspirin (Bayer<sup>®</sup>), acetaminophen (Tylenol<sup>®</sup>), naproxen sodium (Aleve<sup>®</sup>), ketoprofen (Orudis<sup>®</sup> KT), ibuprofen (Advil<sup>®</sup>, Motrin<sup>®</sup>), and various combinations.

Most OTC drugs are based on one of these FDA-approved ingredients. Many manufacturers add other ingredients in an effort to tailor the medication to particular symptoms. For example, a pain reliever and an antihistamine may be combined and sold as a nighttime pain and cold medication since the antihistamine induces drowsiness. Adding a decongestant makes a medication marketable for sinus problems.

When using OTC drugs, be aware that the brand name is often specific to the manufacturer and may not indicate the product's active ingredients. Look for active ingredients, usually listed by generic name, on the label. For example, this will tell you that Tylenol<sup>®</sup> PM not only contains acetaminophen but also contains diphenhydramine hydrochloride (Benadryl<sup>®</sup>).

Some OTC medications are labeled extra strength. This usually indicates that it contains more amounts (e.g., milligrams) of drug per dosage unit than the standard product by the same manufacturer.

The key to the effective use of OTC medications is understanding what you are taking and how much of it. You need to read the medication's ingredients to know what you are taking. Be sure the medication you select contains an appropriate amount of the drug you need for your symptoms and does not include medications or ingredients you do not need.

To do this, **you must read the label**. You also should discuss with your doctor any OTC medications you use or are considering using, especially if you also take a prescription medication. The pharmacist can be very helpful as well.

### THE SAFETY OF OTC MEDICATIONS

Used occasionally, OTC medications rarely cause significant health problems. In certain situations, however, they can be dangerous.

Acetaminophen (the ingredient in Tylenol<sup>®</sup> and a number of other OTC pain and cold remedies), can be toxic to the liver, especially with heavy alcohol use or those with liver problems, even at fairly low doses. The maximum recommended dose for acetaminophen is 4 grams or 8 extra-strength (500mg) tablets in 24 hours. Those who consume little alcohol can usually safely use as much as recommended on the package; however, the maximum recommended dose for heavy drinkers is 2 grams or 4 extra-strength tablets in 24 hours. If you already have liver disease, acetaminophen should only be consumed under your doctor's supervision.



The nonsteroidal anti-inflammatory drugs or NSAIDs (aspirin, ibuprofen, and others) cause an increase in stomach acid, but at the same time they reduce the stomach's protective mucous layer. Thus, they are associated with gastric bleeding, and such risk increases with dose and duration of use. They also may cause kidney failure in people with damaged kidneys, liver disease, and certain other conditions. Use with diuretics can increase this danger.

Over-the-counter pain medications can be useful and effective. Even though they are considered safe enough to be dispensed without a prescription, remember they are real medicines. It is important to discuss their use with a physician, especially if they are being combined with prescription medications.

Individuals taking medications for any of these conditions should check with their doctor before taking any NSAID medication.

## **PRESCRIPTION MEDICATIONS USED FOR CHRONIC PAIN**

In addition to typical analgesics, there is a wide variety of non-traditional drugs, called adjuvant analgesics, used for pain management. Adjuvant analgesics (pharmacological agents added to a drug to increase or aid its effect) represent a diverse group of drug classes that have other indications but relieve pain in specific circumstances. They should be used when specific indications exist.

**Prescription medications are lawfully available only from a licensed professional. Do not use them unless prescribed for you by such a professional.**

## **NON-OPIOID ANALGESIC PAIN RELIEVERS**

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the most widely used medications for most pain conditions. But these drugs are not without risk. NSAIDs can cause gastric distress with ulceration and bleeding while acetaminophen can cause liver toxicity. Fortunately, they do not produce physical or psychological dependence.

Aspirin and acetaminophen are available over-the-counter while most NSAIDs are available both by prescription and by non-prescription over-the-counter purchase.

The NSAIDs are indicated for pain that involves inflammation; acetaminophen does not have anti-inflammatory activity.

Some of these medications are more effective than others in some individuals, which indicate that it makes sense to try several different ones to determine which medication works best for you.

The cyclooxygenase (COX)-2 inhibitors are NSAIDs that have less gastrointestinal side effects with short term use. Currently available is celecoxib (Celebrex<sup>®</sup>); however, serious stomach ulceration can still occur without warning with this drug. As with other NSAIDs, patients should



be monitored during long-term use. There is no evidence that meloxicam (Mobic<sup>®</sup>) or other somewhat COX-2 selective NSAIDs are gastroprotective. These medications additionally have potential kidney effects and heart (cardiovascular) complications, especially when taken for prolonged periods.

The COX-2 inhibitor celecoxib (Celebrex<sup>®</sup>) is more expensive than some other NSAIDs and does not provide any better pain relief, but it does seem to be less risky for developing an ulcer when taken for less than 6 months. The COX-2 inhibitors rofecoxib (Vioxx<sup>®</sup>) and valdecoxib (Bextra<sup>®</sup>) were withdrawn from the market due to potential cardiovascular side effects.

While the increased risk of vascular events associated with cyclooxygenase-2 (COX-2) inhibitors has been well established, data are emerging that demonstrate similar risk increases associated with non-steroidal anti-inflammatory drugs (NSAIDs) that are not selective for COX-2. You are advised to discuss the risk-benefit ratio of NSAIDs with your physician.

Flavocoxid (Limbrel<sup>™</sup>) is a new prescription-only medical food/nutraceutical product, indicated for the clinical dietary management of osteoarthritis, including associated inflammation. It may also possess general analgesic and antioxidant properties, however currently no studies have shown whether flavocoxid is as effective as NSAIDs. Concomitant use with NSAIDs may increase the risk of stomach irritation.

## **GI PROTECTIVE MEDICATIONS**

Proton Pump Inhibitors (PPIs) such as omeprazole (Prilosec<sup>®</sup>) or esomeprazole (Nexium<sup>®</sup>) taken in addition to an NSAID can prevent associated ulcers but may not prevent long-term serious gastrointestinal problems. Data on misoprostol (Cytotec<sup>®</sup>) are stronger for a gastroprotective effect. Addition of high doses of H<sub>2</sub>-receptor antagonists such as ranitidine (Zantac<sup>®</sup>) may reduce NSAID related gastrointestinal distress, but there is no research data to show that it prevents drug-induced ulcers. For many individuals, acetaminophen (Tylenol<sup>®</sup>) may offer pain relief without gastrointestinal toxicity.

## **NON-OPIOID ANALGESIC DRUGS AND THEIR USES**

The following chart on the next page summarizes the uses and cautions that apply to many of the non-opioid analgesic medications now on the market.



<b>Medications and Their Common Brand Names*</b>	<b>May Be Useful for</b>	<b>Pros</b>	<b>Cons</b>	<b>Comments</b>
<b>Aspirin</b> Bayer® Bufferin®	Headache, muscle ache, fever, menstrual cramps, arthritis pain and inflammation. May reduce the risk of heart attack and stroke.	Anti-inflammatory; inexpensive.	May irritate stomach. Inhibits platelets and can cause prolonged bleeding. Can precipitate asthma in aspirin-sensitive patients.	May cause Reye's syndrome in children and teenagers and should not be used during viral syndromes; may be harmful for women in late pregnancy, people with kidney or liver disease, asthma, high blood pressure, or bleeding disorders.
<b>Salicylate Salts</b> Salicylate Trisalicylate		Fewer gastrointestinal side effects.	May irritate stomach.	Do not affect bleeding time or platelet aggregation.
<b>Acetaminophen</b> FeverALL® Tylenol®	Headache, muscle ache, backache, fever, and arthritis pain (especially osteoarthritis).	More gentle to the stomach; safer for children. Does not promote bleeding (or protect against heart attack, stroke).	Does not reduce inflammation; less effective than aspirin for soft tissue pain.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily.
<b>Ibuprofen</b> Advil® Motrin®	Headache, muscle ache, fever, sprains, menstrual cramps, backache, and arthritis pain.	Stronger and generally longer lasting than aspirin.	May irritate stomach.	May be harmful for people with kidney or liver disease, asthma, bleeding disorders, or those who drink alcohol heavily.
<b>Ketoprofen</b> Orudis® KT (OTC) Oruvail®	Headache, muscle ache, fever, menstrual cramps, cold or flu aches.	Helps reduce inflammation. More gentle to the stomach than aspirin.	Less gentle to the stomach than naproxen sodium, ibuprofen, acetaminophen.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily. Not recommended for children without doctor's supervision.
<b>Naproxen Sodium</b> Aleve® (OTC) Anaprox® Naprelan® Naprosyn®	Headache, muscle ache, fever, menstrual cramps, backache, arthritis pain and inflammation.	Stronger and generally longer lasting than aspirin for menstrual cramps, toothache, and inflammation.	May irritate stomach; tends to be higher in cost.	Not recommended for children without doctor's supervision.
<b>Meloxicam</b> Mobic®	Arthritis pain	Associated with less risk of ulcers than other NSAIDs.	Still a risk for stomach irritation. Tends to cost more.	Generally well-tolerated but still need to be concerned about gastrointestinal side effects.
<b>COX-2 Inhibitors</b> Celebrex®	Muscle aches, joint pain, arthritis, pain and inflammation.	Helps reduce inflammation; less stomach irritation.	Still a risk for stomach irritation. Tends to cost more.	Generally well-tolerated but still need to be concerned about gastrointestinal side effects. These agents are available by prescription only. Use caution with sulfa allergies and celecoxib.



Other NSAIDs include the following:

- Diclofenac (Cataflam<sup>®</sup>, Voltaren<sup>®</sup>, others)
- Diflunisal (Dolobid<sup>®</sup>)
- Etodolac (Lodine<sup>®</sup>, Lodine<sup>®</sup> XL)
- Fenoprofen (Nalfon<sup>®</sup>)
- Flurbiprofen (Ansaid<sup>®</sup>)
- Indomethacin (Indocin<sup>®</sup>, Indocin<sup>®</sup> SR)
- Ketorolac (Toradol<sup>®</sup>, others) – only U.S. NSAID in injectable formulation
- Mefenamic acid (Ponstel<sup>®</sup>)
- Nabumetone (Relafen<sup>®</sup>)
- Oxaprozin (Daypro<sup>®</sup>)
- Piroxicam (Feldene<sup>®</sup>)
- Sulindac (Clinoril<sup>®</sup>)
- Tolmetin (Tolectin<sup>®</sup>)

\* Brand names are the trademarked property of the medications' manufacturers.

## OPIOID ANALGESICS

### The Opioid Dilemma

Considerable controversy exists about the use of opioids for treatment of chronic pain of non-cancer origin. Many physicians feel that chronic pain is inadequately treated and that opioids can play an important role in the treatment of all types of chronic pain, including non-cancer pain. Others caution against the widespread use of opioids noting problems with tolerance, loss of benefit with time, and escalating usage with decreasing function in many individuals.

The use of opioids (or for that matter any treatment) makes sense when the benefits outweigh the risks and negative side effects. Benefit is suggested when there is a significant increase in the person's level of functioning, when there is a reduction or elimination of pain complaints, when there is a more positive and hopeful attitude and when side effects are minimal or controllable.

The dilemma with the long term use of opioids is that while there is a role for opioids in chronic, non-cancer pain, it is well known that prolonged use of opioids may result in problems including tolerance, hyperalgesia (abnormal pain sensitivity), hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses), depression, and suppression of the immune system. While opioid treatment may be prescribed to reduce pain and improve function, the treatment may actually result at times in just the opposite.



## What are Opioids?

Opioids are morphine-like substances and have been available for centuries to relieve pain. The term opioid is derived from opium, which is an extract from the poppy plant. There are both naturally occurring and synthetic opioids. There are a number of opioid receptors in the body that mediate analgesia. In 1975, it was discovered that the body generates internal or endogenous opioids called endorphins, enkephalins, and dynorphins.

There are numerous opioids available by prescription. The potency, speed of onset, and duration are unique to each drug. All of the opioids have similar clinical effects that vary in degree from one drug to another.

Opioids are formulated as both short- and long-acting. Some opioids are used around-the-clock, while others are used as needed for breakthrough pain.

Most opioids are agonists, a drug that binds to a receptor of a cell and triggers a response by the cell. An agonist produces an action. It is the opposite of an antagonist, which acts against and blocks an action.

There are a number of opioid analgesics (pain relievers) that are partial agonists and mixed agonists/antagonists, which can simultaneously produce analgesia and precipitate withdrawal. These agents include buprenorphine (Buprenex<sup>®</sup>, Subutex<sup>®</sup>), butorphanol (Stadol<sup>®</sup>), nalbuphine (Nubain<sup>®</sup>), and pentazocine (Talwin<sup>®</sup>). They can be used for pain before surgery, pain during labor and delivery, migraine headache pain, and various other types of moderate to severe pain. Some are also used for the treatment of opioid dependence.

Given their agonist/antagonist nature, these medications should be used with caution in those taking other types of opioids. A partial agonist/antagonist is occasionally initiated in a person already taking another opioid. The doses should be adjusted gradually to avoid symptoms of withdrawal. If possible, these two types of agents should not be used together. Symptoms of withdrawal to monitor for include sweating, goose flesh, runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your doctor or pharmacist if you have these or other side effects.



These are examples of medical opioids:

<p><b>Hydrocodone</b> (with acetaminophen – Anexsia<sup>®</sup>, Lorcet<sup>®</sup>, Lortab<sup>®</sup>, Norco<sup>®</sup>, Vicodin<sup>®</sup>, Xodol, Zydone<sup>®</sup>; with ibuprofen – Reprexain<sup>™</sup>, Vicoprofen<sup>®</sup>; with aspirin—Azdone, Lortab ASA, Panasal)</p>	<p><b>Oxycodone</b> (OxyContin<sup>®</sup>, OxyIR<sup>®</sup>, Roxicodone<sup>™</sup>; with acetaminophen – Endocet<sup>®</sup>, Percocet<sup>®</sup>, Perloxx, Roxicet<sup>™</sup>, Tylox<sup>®</sup>; with aspirin – Endodan<sup>®</sup>, Percodan<sup>®</sup>, with ibuprofen - Combunox<sup>™</sup>)</p>
<p><b>Codeine</b> (with acetaminophen -Tylenol<sup>®</sup> with codeine No. 2, No. 3, No. 4)</p>	<p><b>Levorphanol</b> (Levo-Dromoran<sup>®</sup>)</p>
<p><b>Dihydrocodeine bitartrate, Aspirin, Caffeine</b> (Synalgos-DC<sup>®</sup>)</p>	<p><b>Methadone</b> (Dolophine<sup>®</sup>, Methadose<sup>®</sup>, Westadone)</p>
<p><b>Hydromorphone</b> (Dilaudid<sup>®</sup>)</p>	<p><b>Fentanyl</b> (Actiq<sup>®</sup> lozenge, Fentora<sup>®</sup> buccal tablet, Duragesic<sup>®</sup> patch) – FDA warning below</p>
<p><b>Morphine</b> (Avinza<sup>™</sup>, Duramorph<sup>®</sup>, Kadian<sup>®</sup>, MS—Contin<sup>®</sup>, MSIR<sup>®</sup>, Oramorph SR<sup>®</sup>, Roxanol<sup>™</sup>)</p>	<p><b>Butorphanol</b> (Stadol<sup>®</sup>)</p>
<p><b>Meperidine</b> (Demerol<sup>®</sup>)</p>	<p><b>Oxymorphone</b> (Numorphan<sup>®</sup>, Opana<sup>®</sup>)</p>
<p><b>Pentazocine</b> (Talwin<sup>®</sup>; with acetaminophen-Talacen<sup>®</sup>; with aspirin-Talwin Compound)</p>	<p><b>Buprenorphine</b> (Buprenex<sup>®</sup>, Subutex<sup>®</sup>) and <b>Buprenorphine and Naloxone</b> (Suboxone<sup>®</sup>)</p>



## OPIOID ADVERSE SIDE EFFECTS

Common opioid side effects, particularly with higher doses, include nausea, vomiting, constipation, thought and memory impairment, and drowsiness. The majority of these side effects are easily treated with dose adjustments, wane over time or can be offset by other alternate medications. Psychostimulants (see below) can be useful in selected patients to treat mild sedation. Constipation should be anticipated with a preventative bowel regimen including diet changes, stimulant laxatives and stool softeners. Mild sedation and impaired judgment or coordination also should be anticipated. Until tolerance or a baseline is reached, the patient and family need to be warned against driving and the potential for falls. Mild nausea can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be appropriate.

More serious side effects can include respiratory depression (slowed rate of breathing or loss of urge to breathe) and physical dependence.

In July 2005, the FDA issued a public health advisory to alert people of reports of death and other serious side effects from overdoses while on fentanyl transdermal patches. Deaths and overdoses have occurred in patients using both the brand name Duragesic® and the generic product. Some patients and health care providers may not be fully aware of the dangers of this drug. The directions for using the fentanyl skin patch must be followed exactly to prevent death or other serious side effects from overdose.

### Summary of Possible Opioid Adverse Effects

- Central nervous system
  - A sense of emotional well being and euphoria
  - Drowsiness, sedation, or hallucinations
  - Potential for diminished psychomotor performance
  - Dysphoria, agitation, and seizures
- Respiratory system
  - Respiratory depression is the major adverse effect and may result from toxicity
  - Diminution of pain or pain relief by other modalities may exacerbate respiratory depression
- Ocular system
  - Miosis stimulation occurs through the parasympathetic ganglion
- Gastrointestinal system
  - Constipation, nausea and vomiting
  - Delayed gastric emptying
- Genitourinary
  - Urinary retention
  - Sexual dysfunction
- Cardiovascular
  - Reduction in systemic vascular resistance
  - Decreased blood pressure but potentially increased cardiac output
  - Bradycardia due to vagal stimulation





- Musculoskeletal system
  - Muscle rigidity and myoclonus
- Immune system
  - Itching is common due to a direct histamine release (especially by morphine)
  - Not an allergic reaction
- Pregnancy
  - All opioids cross the placenta
  - Neonatal depression can occur if opioids are used during labor
  - No teratogenic effects have been observed
- Tolerance
  - Decreased duration of analgesia and then decreased effectiveness
- Physical dependence
  - Withdrawal symptoms include runny nose, shivering, “gooseflesh,” diarrhea, and mydriasis

## DRUG INTERACTIONS

A drug interaction occurs when the amount or the action of a drug are altered by the administration of another drug or multiple drugs. Always try to use the same pharmacy to pick up your prescriptions so the pharmacist can screen your health information and current medications to prevent drug interactions.

## TOLERANCE, FUNCTIONAL IMPAIRMENT, ADDICTION, WITHDRAWAL & PSEUDOADDICTION

**Tolerance** is a phenomenon in which one or more effects of a drug become less with repeated use at the same dose (many patients call this becoming “immune” to the drug). For example, a person might feel drugged after the first pain pill but, with continuous use a person might require, might require several pills to feel anything. With analgesics, the concern is that the individual will build up tolerance to the drug and therefore require more medication to achieve results. Unfortunately, in many cases, increasing doses of medications may lead to increased or unacceptable side effects. Analgesic tolerance is not addiction.

Although all of the questions are not yet answered, it is known that tolerance does not develop at the same rate to all of a drug’s effects. With opiates, for example, one rapidly becomes tolerant to the sedating effects of the drugs. It has been shown that cancer patients who are taking large but stable doses of morphine show little or no sedation. They do, however, continue to experience constipation, as patients will not develop tolerance to this side effect.

The real question, of course, is the extent to which tolerance develops to the *analgesic* effects of the drugs; that is, how soon do they lose their ability to reduce pain? This is unclear, and the answer seems different in different people and with different types of pain. Some people seem to benefit from the same dose of an opioid for years, while others rapidly increase the dose and still have unsatisfactory relief.

**Functional impairment** and physical inactivity are additional concerns that make physicians reluctant to provide chronic opioids. It is well known that a sedentary life decreases blood flow,



impedes healing, decreases muscle tone, and contributes to depression, bone loss, and fatigue. Clearly, some people become inactive and passive on opioids, while others become more active. It may be that some are able to obtain good analgesia without taking enough to produce intoxication, while others are not able to do so.

**Addiction** seems to be the primary fear that limits opioid prescribing. This is a term that requires clarification. Addiction is the traditional term used to identify the irresistible craving for, loss of control over use of, compulsive use of and continued use despite harm of certain types of drugs. Drugs capable of producing addiction do so by interacting with the biochemistry of the brain in such a way that the drug begins to seem essential – one feels a “need” for it as one does for food and water. While the media give the impression that the risk of addiction is inherent to the properties of opioids, experts in addiction generally recognize that it results from the interaction of the drug and various hereditary, psychological, and situational factors unique to the individual.

It was previously thought that addiction was demonstrated by the presence of tolerance and **withdrawal** (developing signs of illness/discomfort when the substance is unavailable). It is now thought that, while these two factors may be important signs of addiction to *recreational* drugs (alcohol, cocaine), they do not indicate addiction to *medical* drugs. This is because many people who have taken opioids or tranquilizers for more than a few doses will show some tolerance with use and withdrawal on abrupt drug cessation. In addition, numerous drugs can produce tolerance and withdrawal, yet do not produce addiction (e.g., epilepsy medications, some blood pressure drugs). Symptoms of withdrawal to monitor for include sweating, goose flesh, runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your doctor or pharmacist if you have these or other side effects.

**Addiction** should be distinguished from **physical dependence**. *Any person (or animal) that takes sufficient doses of certain types of drugs for a significant length of time can have withdrawal symptoms if the drug is suddenly stopped or reversed by another medicine. This shows the presence of physical dependence but does not constitute addiction.*

The risk of addiction is not well defined in chronic use. When it occurs, the drug is a liability rather than an asset to the person. There are four core elements in true addiction (the four C’s):

- ❑ **C**ompulsive use and preoccupation with the drug and its supply,
- ❑ **I**nability to consistently **C**ontrol the quantity used,
- ❑ **C**raving the psychic effects of the drug, and
- ❑ **C**ontinued use despite adverse effects from the drug.

Compulsive use or preoccupation may be demonstrated by taking the drug because it is available (as opposed to taking it exactly as a health care professional has instructed), inappropriate “stocking up,” having several physicians/pharmacists to guarantee a supply, and spending scarce resources on the drug.

Other examples of inappropriate use include selling the drug or changing the drug from pill to powder for injection or snorting.



Loss of control is demonstrated by the person who regrets his drunkenness and “pledges” to stop after two beers the next time; instead, he has six beers and behaves regrettably again. With pain medication, loss of control tends to take the form of using up a month’s supply in a week, so that the person must go without the medication for a long time.

Examples of use despite adverse consequences may consist of smoking despite emphysema, drinking despite convictions for driving under the influence, or using analgesics and tranquilizers despite their having an adverse effect on ability to function, mood, and family relationships.

Craving, in this sense, does not mean taking a medicine as directed to relieve pain, but rather, an intense desire for a mental effect (“buzz”, “high”, or “trip”) caused by a medicine.

**Pseudoaddiction** describes a syndrome of poorly or under-treated pain. Patients develop feelings of anger and isolation, which lead to acting-out behavior. Inadequate pain management often leads to pseudoaddiction and commonly involves an ineffective medication or inadequate medication prescribing either by excessive intervals between allowed doses or inadequate doses. Pseudoaddiction may come about because the physician may be inadequately educated about pain management or have an excessive fear of causing addiction.

The American Pain Society ([www.ampainsoc.org](http://www.ampainsoc.org)) and the American Academy of Pain Medicine ([www.painmed.org](http://www.painmed.org)) have issued a joint consensus statement supporting the cautious use of chronic opioid analgesics (pain medications) for some people with persistent pain problems (<http://www.painmed.org/productpub/statements/pdfs/opioids.pdf>). Cautious use requires careful examination, discussion of risks and benefits with patients, thorough documentation, and sufficiently careful follow-up for the physician to be able to determine whether the drugs are actually improving the person’s overall status.

Taking opioids may or may not be in one’s best interest. The literature does not provide simple, clear guidelines for those who must face day-to-day pain. Research shows that chronic use of large quantities of opioids may interfere with the body’s natural pain relievers, the endorphins. Since physical activity is thought to promote release of endorphins, it is also possible that opioids could inhibit the body’s own mechanism of reducing pain by causing a person to be less active. Additionally, long-term opioid use may cause depression in some patients, which may impede their ability to recover.

## OPIOIDS AND THE GOALS OF PAIN MANAGEMENT

There has been disagreement as to whether the goal of pain management should be to reduce pain or to improve the way people function in their daily lives. The consensus of the members of the American Pain Society is that the primary goal in treating chronic pain patients with opioids is to **increase the level of function** rather than just to provide symptom relief.



It may be that this argument is not meaningful. When people are truly comfortable, they usually resume activities that they had previously avoided. If a person with pain fails to do this, it suggests that symptom relief has not occurred, even though the person may believe that the medications “take the edge off.” Clearly, maximizing quality of life entails both factors: minimizing suffering and maximizing function.

Pain management is essentially rehabilitation. The person experiencing pain and the family must ask to what end they want to be rehabilitated. What does rehabilitation mean to each of them? Webster defines rehabilitation as “*to restore to useful life through education and therapy.*” If a person’s goal is solely to reduce pain, then he or she may overlook the more important (and attainable) goal of rehabilitation. The essence of rehabilitation and maintaining wellness is for the person to take an active part in the recovery process.

It is important to mention that taking opioids precludes certain types of employment, even though one is tolerant and does not have side effects. People should be aware of the rules currently promulgated by Federal and State authorities.

## EVALUATING OPIOID USE

Some of the following questions may help clarify a person’s involvement with opioids and may help determine whether they are an asset or a liability:

- ❑ *Is the person’s day centered around taking medication?* If so, consultation with the health care professional may clarify long-term risks and benefits of the medication and identify other treatment options.
- ❑ *Does the person take pain medication only on occasion, perhaps three or four times per week?* If this is the case, then the likelihood of addiction is low.
- ❑ *Have there been any other chemical (alcohol or drug) abuse problems in the person’s life?* If so, then it is important to inform the health care professional, who will need to take that into consideration when prescribing.
- ❑ *Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed?* If so, that suggests the pain medication is failing to promote rehabilitation. Daily activity is necessary for the body to produce its own pain relievers, to maintain strength and flexibility, and to keep life full and meaningful. Encourage the person with pain to request recommendations from a physician for a graduated exercise program.
- ❑ *Is the person in pain able to function (work, household chores, and play) with pain medication in a way that is clearly better than without?* Chances are that the pain medication is contributing to wellness. Most people who are addicted to pain medications or other substances (excluding nicotine) do not function well. They are undependable and forgetful.



The following may be signs that a person is being harmed more than helped by pain medication.

- sleeping too much or having days and nights confused
- decrease in appetite
- inability to concentrate or short attention span
- mood swings (especially irritability)
- lack of involvement with others
- difficulty functioning due to drug effects
- use of drugs to regress rather than to facilitate involvement in life
- lack of attention to appearance and hygiene

While it is impossible to make generalized guidelines for when to provide opioids on a regular, ongoing basis, the person and his/her family can often help to determine whether these agents are useful. If family members see that the person with pain has lost control of his or her life, is less functional, and is more depressed when taking or increasing the dose of opioids than they were before, they should seek help.

Most research suggests that family members over-report the patient's pain, but they also may be the only ones who can accurately determine whether the person's life, mood, function, attitude, and comfort have changed for the better or worse. The person taking the medication may be so aware of the discomfort produced when they miss doses of pills that they incorrectly conclude that they need the medication. This severe pain may in fact only represent withdrawal due to physical dependence, as opposed to a persistent need for analgesic therapy.

What is the place of opioid pain medication? There is no question of the usefulness of opioids in acute pain and cancer pain. We do not yet know when they are most helpful in chronic use. Benefit is suggested when there is a significant increase in the person's level of functioning, reduction/elimination of pain complaints, a more positive and hopeful attitude and the side effects can be managed safely.

## **HYBRID PRESCRIPTION PAIN DRUGS**

Tramadol (Ultram<sup>®</sup>) and tramadol combined with acetaminophen (Ultracet<sup>™</sup>) are prescription pain medications indicated for the management of moderate to moderately severe pain. The combination of tramadol and acetaminophen produces greater analgesia than that produced by either administered alone.

Tramadol is a weak opioid analgesic that acts on the central nervous system in two ways. It binds modestly to opioid receptors and thus produces some analgesia by the same mechanism as opioids. It also affects certain neurotransmitters in the brain to decrease the perception of pain.



It blocks the reuptake of neurotransmitters, serotonin and norepinephrine, in the gaps between nerve cells, an action like that of some antidepressants that reduce pain. This may be the other mechanism by which tramadol relieves chronic pain.

Tramadol may cause fewer problems with drug addiction than do other opioids, however it is not completely free of this risk and may trigger addiction even in those without a history of drug abuse or previous addiction. However, this appears more likely to occur when used with carisoprodol (Soma<sup>®</sup>).

Tramadol reduces the respiratory rate to a lesser extent in overdoses and does not cause the sort of gastrointestinal irritation produced by NSAIDs. Tramadol reduces the threshold for seizures, which may occur in overdose. Seizures may also be provoked in those with a history of seizure disorders, head trauma, etc. or in those taking other drugs that reduce the seizure threshold. These include certain antidepressants such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs). They also include some antipsychotic medications (Thorazine<sup>®</sup>, Compazine<sup>®</sup>, etc.). Thus, caution is advised when tramadol is combined with these medications.

Since tramadol is a centrally acting synthetic analgesic, not a non-steroidal anti-inflammatory drug (NSAID), it has no anti-inflammatory activity. Also unlike NSAIDs, tramadol does not have the potential to compromise the efficacy of certain antihypertensive agents (diuretics and ACE-inhibitors). The tramadol dose should not exceed 400 mg (300 mg in the elderly) in divided doses a day.

Propoxyphene is a mild opioid analgesic structurally related to methadone. The potency of propoxyphene is from two thirds to equal that of codeine. Darvocet-N<sup>®</sup> 50, Darvocet-N<sup>®</sup> 100, and more recently Darvocet A500<sup>™</sup> tablets contain propoxyphene with acetaminophen. The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either drug alone. These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

Fiorinal<sup>®</sup> is a strong, non-opioid pain reliever and muscle relaxant. It is prescribed for the relief of tension headache symptoms caused by stress or muscle contraction in the head, neck, and shoulder area. It combines a non-opioid, sedative barbiturate (butalbital) with a pain reliever (aspirin) and a stimulant (caffeine).



## ANTIDEPRESSANTS

One of the most important classes of drugs used to treat chronic pain is the antidepressant group. It is important to note that a response to drugs that were originally developed for psychiatric illness does not mean that the pain is psychiatric in origin. Antidepressant drugs have been used for many years to relieve pain.

- They do not work for pain only by relieving depression. In fact, they work as well for non-depressed people with pain as for those with depression.
- They do not work equally well for all types of pain. For example, they tend to be helpful for fibromyalgia, headache, and pain due to nerve ("neuritic") damage (e.g., diabetic neuropathy), but generally are less helpful for most musculoskeletal sports-type injuries or back pain.
- How well they work has little to do with how effective they are as antidepressants. Some very effective antidepressants have virtually no ability to reduce pain.

Tricyclic antidepressants (TCAs) and related drugs can be roughly divided into those with additional sedative and relaxing properties and those that are less so. Agitated and anxious patients tend to respond best to antidepressants with sedative properties whereas withdrawn individuals and those with less energy will often obtain the most benefit from less sedating antidepressants.

### HOW ANTIDEPRESSANTS MAY HELP

While most people know that pain signals go up the spinal cord to reach the brain, they may not be aware that there are signals coming down the spinal cord that can increase or reduce pain transmission. By increasing levels of chemicals (norepinephrine and serotonin) at nerve endings, antidepressants appear to strengthen the system that inhibits pain transmission.

Some antidepressants may be useful in chronic pain because they effectively reduce anxiety and improve sleep without the risks of habit-forming medications. Some people with chronic pain are depressed, and treating the depression may also help reduce the perception of pain. Many people with chronic pain find that antidepressants, along with learning other pain management skills, can help them regain control of their lives and keep their pain under control.



## ANTIDEPRESSANT SIDE EFFECTS

The most common side effects of antidepressants are drowsiness, constipation, dry mouth, and blurred vision. Some people experience nightmares or an increased heart rate. While some people experience minimal side effects, for others, the side effects can be as bad as the pain. It is worth noting that different antidepressants have different side effects, and tolerance to these side effects can develop with use.

Some cause more sleepiness, some less. Although some lower sex drive, desire may actually increase as pain, sleep, and mood improve. Some may lower blood pressure, while others raise it. Some increase appetite while others do not. Several may cause dizziness.

If a person's pain is helped by an antidepressant but the side effects are troublesome, it may be possible to change medications. The benefit may be retained while reducing the undesirable side effects.

Some of these drugs, especially the tricyclic group, can be fatal in overdose and should only be available and prescribed in limited supply.

### **Alert: Mixing Anti-migraine Agents & Certain Antidepressants**

*In a News Review from Harvard Medical School -- Don't Mix Migraine, Depression Meds, Dr. Mary Pickett responded in July 2006 and some of her comments are summarized as follows.*

During the last year, the Food and Drug Administration warned people taking certain anti-migraine medications and certain drugs to treat depression that they may be at risk for a dangerous chemical imbalance. Antidepressant medications included in this warning are fluoxetine (Prozac<sup>®</sup>), sertraline (Zoloft<sup>®</sup>), paroxetine (Paxil<sup>®</sup>), escitalopram (Lexapro<sup>®</sup>), duloxetine (Cymbalta<sup>®</sup>), and venlafaxine (Effexor<sup>®</sup>). Migraine drugs include naratriptan (Amerge<sup>®</sup>), almotriptan (Axert<sup>™</sup>), sumatriptan (Imitrex<sup>®</sup>), and zolmitriptan (Zomig<sup>®</sup>).

Serotonin is a brain hormone that keeps our mood stable and our appetite in check, as well as serving other functions. More than 50 commonly prescribed medicines boost the amount or effect of serotonin in your system. When you take two or more drugs that affect serotonin levels, it can increase the amount of serotonin and may lead to bothersome or dangerous symptoms. This is called "serotonin syndrome."

The combination of a "triptan" anti-migraine medicine and almost any antidepressant may increase your brain serotonin level. You can have mild serotonin symptoms from even one medicine (common serotonin-related side effects from antidepressant medicines include headache, pain in the stomach, diarrhea, nausea, flushing or trembling).





You can have a much more severe form of serotonin syndrome if you combine several medicines with a serotonin effect. Severe serotonin syndrome (requiring a hospital stay or resulting in permanent harm) is quite rare. Serotonin can cause a variety of symptoms — no one gets all the symptoms at once, but anyone with too much serotonin will have at least a few symptoms. These symptoms can include mental changes such as anxiety, confusion, delirium, hallucinations, headaches, insomnia, mania (constant and sometimes senseless activity without rests) or coma; nerve or muscle symptoms such as tremor (shaking), unsteady coordination, muscle jerks, abnormally jumpy reflexes, jerking eye movements or changes in pupil size, restlessness or seizures, temperature or vital sign control problems which can include sweating or flushing, fevers, hyperventilation, slowed breathing, a change in heart rhythm, or high or abnormally low blood pressure; and digestive symptoms including abdominal pain, nausea, vomiting or diarrhea.

If you take an antidepressant or anti-anxiety medicine (or if a close friend or family member does), you should review the following list of drugs that can add to your serotonin load. This is a reasonably comprehensive list. Be very careful about overlapping medicines. You should also watch for serotonin symptoms when you increase your dose of any of these medicines.

Antidepressants, anti-anxiety, and certain sleep medicines including fluoxetine (Prozac<sup>®</sup>, Sarafem), paroxetine (Paxil<sup>®</sup>), sertraline (Zoloft<sup>®</sup>), citalopram (Celexa<sup>®</sup>), escitalopram (Lexapro<sup>®</sup>), trazodone (Desyrel<sup>®</sup>), venlafaxine (Effexor<sup>®</sup>), duloxetine (Cymbalta<sup>®</sup>) clomipramine (Anafranil<sup>®</sup>), buspirone (BuSpar<sup>®</sup>), mirtazapine (Remeron<sup>®</sup>), lithium, St. John's Wort, phenelzine (Nardil<sup>®</sup>), tranylcypromine (Parnate<sup>®</sup>), or isocarboxazid (Marplan<sup>®</sup>).

Anti-migraine medicines in either the 'triptan' or 'ergot' groups, including sumatriptan (Imitrex<sup>®</sup>), almotriptan (Axert<sup>™</sup>), eletriptan (Relpax<sup>®</sup>), frovatriptan (Frova<sup>®</sup>), naratriptan (Amerge<sup>®</sup>), rizatriptan (Maxalt<sup>®</sup>), zolmitriptan (Zomig<sup>®</sup>), ergotamine/caffeine (Cafergot<sup>®</sup>), or dihydroergotamine (DHE 45<sup>®</sup>, Migranal<sup>®</sup>).

Diet pills, specifically L-tryptophan (5-HTP), sibutramine (Meridia<sup>®</sup>), or phentermine.

Certain pain medicines including tramadol (Ultram<sup>®</sup>), fentanyl (Duragesic<sup>®</sup> patch), pentazocine (Talwin<sup>®</sup>), duloxetine (Cymbalta<sup>®</sup>), or meperidine (Demerol<sup>®</sup>).

Certain drugs for nausea, specifically ondansetron (Zofran<sup>®</sup>), granisetron (Kytril<sup>®</sup>), or metoclopramide (Reglan<sup>®</sup>).

Cough syrups or cold medicines if they contain the anti-cough ingredient dextromethorphan (DM) or linezolid (Zyvox<sup>™</sup>), an antibiotic for *Staphylococcus* or *Enterococcus* infections.



## BENEFITS OF ANTIDEPRESSANTS IN CHRONIC PAIN

The optimal role for antidepressants in chronic pain is still being defined as research progresses. These qualities seem clear, however.

- They do not have the potential to cause stomach inflammation and bleeding, as do the anti-inflammatory drugs.
- They do not seem to interfere with the body's internal pain fighting mechanisms; in fact, they probably strengthen them by increasing the effects of chemical messengers, such as norepinephrine and serotonin, in the nervous system.
- Many act as sedatives to promote a good night's sleep. Sleep deprivation is often one of the major obstacles in coping with chronic pain. In fact, with severe sleep deprivation, one cannot cope with much of anything.
- They may help to reduce depression.
- They may help to relieve anxiety and panic attacks.
- They may increase the effect of other pain relieving drugs or analgesics.
- They are non-addictive pain medications, and loss of effect due to tolerance does not occur after the optimal dose for a given person has been determined.
- They have a record of long-term safety and are among the most widely used drugs in medicine.

There is evidence that in chronic pain, antidepressants may work at lower doses and blood levels than are required for depression, and they may produce responses sooner than the three to five weeks which is typical for depression. This is not always true, however, and some people require full doses for maximum pain relief.

## PAIN STATES THAT MAY RESPOND TO ANTIDEPRESSANTS

Postherpetic neuralgia	Migraine & Tension Headache
Diabetic neuropathy	Chemotherapy induced peripheral neuropathy
Phantom limb pain	Fibromyalgia
Stump / neuroma pain	Irritable Bowel Syndrome
Central pain (following stroke)	Rheumatoid arthritis
Sympathetic dystrophy (CRPS / RSD)	Neuropathic pain



## **ANTIDEPRESSANTS COMMONLY USED FOR CHRONIC PAIN**

### **TRICYCLIC ANTIDEPRESSANTS (TCAs)**

The tricyclic antidepressants have been used to treat depression for a long time. They include amitriptyline (Elavil<sup>®</sup>), desipramine (Norpramin<sup>®</sup>), imipramine (Tofranil<sup>®</sup>), and nortriptyline (Aventyl<sup>®</sup>, Pamelor<sup>®</sup>).

These antidepressants have been proven to have pain-relieving effects. Desipramine is considered to have the lowest side effects profile of the TCAs.

The different tricyclic drugs have varied side effects and may sometimes be used to the patients' advantage. For the overweight patient with lethargy and tiredness, the clinician may choose a TCA with more noradrenergic selectivity (e.g., desipramine), which may be activating and can cause some anorexia. For others with poor sleep hygiene, the sedating properties of certain TCAs, such as amitriptyline may be helpful.

Common side effects caused by these tricyclic antidepressants include dry mouth, blurred vision, constipation, difficulty urinating, worsening of glaucoma, impaired thinking, and tiredness. These antidepressants can also lower blood pressure and may cause palpitations (pounding heart). They may increase appetite and be associated with weight gain. Go to the following web site for further information about tricyclic antidepressant toxicity: <http://www.emedicine.com/emerg/topic616.htm>

### **SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)**

The selective serotonin reuptake inhibitors have fewer side effects and are less sedating than the tricyclic antidepressants. They are also effective for headache prevention but less effective for other types of pain.

SSRIs are a group of antidepressants that includes drugs such as citalopram (Celexa<sup>™</sup>), escitalopram (Lexapro<sup>®</sup>), fluoxetine (Prozac<sup>®</sup>), fluvoxamine (Luvox<sup>®</sup>), paroxetine (Paxil<sup>®</sup>) and sertraline (Zoloft<sup>®</sup>).

Selective serotonin reuptake inhibitors (SSRIs) have been disappointing for neuropathic pain. Most studies of the serotonin-selective type (non-tricyclic) antidepressants have shown little or no pain relief. However, certain newer antidepressant agents such as duloxetine (Cymbalta<sup>®</sup>), venlafaxine (Effexor<sup>®</sup>) and mirtazapine (Remeron<sup>®</sup>) show some promise and have the advantage of a different, more benign side-effect and toxicity profile.



Some of the side effects that can be caused by SSRIs include dry mouth, stomach distress with nausea and vomiting, diarrhea, sweating, poor appetite, dizziness, tremors, drowsiness, anxiety, nervousness, insomnia, headache, increased blood pressure, increased heart rate, increased cholesterol levels and sexual problems.

SSRIs should be used with caution in patients with epilepsy, history of mania, cardiac disease, diabetes, angle-closure glaucoma, concomitant use of drugs that increase risk of bleeding, history of bleeding disorders (especially gastrointestinal bleeding), disorders of the liver and kidneys, pregnancy and breast-feeding. SSRIs, particularly paroxetine, may also impair performance of skilled tasks (e.g., driving) by causing drowsiness. Use within 14 days of an MAO inhibitor should be avoided.

Abrupt withdrawal of SSRIs should be avoided (associated with headache, nausea, burning or tingling sensation in the extremities, dizziness, and anxiety).

#### **OTHER ANTIDEPRESSANTS**

Other antidepressants exist that have different ways of working than the SSRIs and TCAs. Commonly used ones are nefazodone (Serzone<sup>®</sup>), bupropion (Wellbutrin<sup>®</sup> or Zyban<sup>®</sup>), and trazodone (Desyrel<sup>®</sup>). The monoamine oxidase inhibitors (MAOIs) are generally not used to treat chronic pain.

Bupropion (Wellbutrin<sup>®</sup>, Zyban<sup>®</sup>) can cause agitation, insomnia, headache and nausea. Although marketed for different indications, Wellbutrin<sup>®</sup> and Zyban<sup>®</sup> contain the same active ingredient and therefore should not be taken concurrently without close physician supervision. Serious cases of overdose have been reported in patients taking both agents.

Mirtazapine (Remeron<sup>®</sup>) can cause sedation, increased appetite, weight gain, increased cholesterol, dizziness, dry mouth, and constipation.

Some of the most common side effects of trazodone (Desyrel<sup>®</sup>) are sedation, dry mouth, and nausea. Although trazodone was developed for the treatment of depression, it is more frequently used today to alleviate insomnia.

The monoamine oxidase inhibitors (MAOIs) like phenelzine (Nardil<sup>®</sup>), tranylcypromine (Parnate<sup>®</sup>), isocarboxazid (Marplan<sup>®</sup>), and selegiline (Eldepryl<sup>®</sup>) commonly cause weakness, dizziness, headaches and tremor. While selegiline is used to treat Parkinson's disease, the other MAOIs are antidepressants. MAOIs generally are not effective as pain relievers and therefore are rarely used. They also have many drug-drug and drug-food interactions.



## ANTICONVULSANTS OR ANTIEPILEPTIC DRUGS

Several drugs that were developed for prevention of epileptic seizures have been found to help certain pain conditions. One of these drugs, carbamazepine (Carbatrol<sup>®</sup>, Tegretol<sup>®</sup>), is approved by the FDA for relieving the pain of trigeminal neuralgia, and gabapentin (Neurontin<sup>®</sup>) is approved for management of postherpetic neuralgia (PHN - the pain that lasts one to three months after shingles has healed). Nevertheless, most use of anticonvulsants for pain is “off label.” Although these medications are not habit forming, abrupt discontinuation can be hazardous. They should be stopped only after discussing how to do so with a physician. When used in migraine or cluster headache, they seem to reduce the frequency of headache more than the severity. Common side effects are drowsiness and unsteady gait or poor balance. These symptoms tend to diminish over time.

Gabapentin (Neurontin<sup>®</sup>) is widely utilized and has proven to be effective in many people for nerve injury or neuropathic pain. It is emerging as a first-line agent for the treatment of painful sensory neuropathy. Its use requires no more monitoring than other traditional medications, especially in elderly diabetic patients. However, decreased mental alertness or awareness is possible at higher doses. Generic gabapentin is now available. A similar but updated drug, pregabalin (Lyrica<sup>®</sup>), has been found effective in postherpetic neuralgia and diabetic neuropathy. Its primary advantage over gabapentin is thought to be Lyrica’s efficacy at smaller doses as well as twice a day dosing, however there is no evidence that this translates to an increased clinical effect. Pregabalin is not associated with significant drug interactions and can be used over a wide dose range (150-600mg/d). Its side effect profile is similar to gabapentin, and it is generally well tolerated. Side effects are mostly mild to moderate and transient, with dizziness and somnolence the most common. Other adverse effects include dry mouth, peripheral edema, blurred vision, weight gain, and concentration or attention difficulties.

Tiagabine (Gabitril<sup>®</sup>) has also been found to be useful for nerve injury or neuropathic pain. Its most common side effects include nonspecific dizziness, drowsiness, and difficulty with concentration. Tiagabine use has been associated with new onset seizures and status epilepticus in patients without epilepsy.

Topiramate (Topamax<sup>®</sup>) has shown some use in treating neuropathic and sympathetically maintained pain. It is also being used for the prevention or prophylaxis of migraines. Topiramate may cause secondary angle closure glaucoma and, if left untreated, may lead to permanent vision loss. Use should be discontinued, and medical attention should be sought immediately in cases of blurred vision or eye pain. Topiramate can also impair mental concentration, cause dose-related weight loss, and cause or predispose to kidney stones.



## ANTICONVULSANTS USED IN CHRONIC PAIN

Carbamazepine (Tegretol <sup>®</sup> ):	Best studied, interacts with some other drugs, can affect the liver, white blood cells.
Valproic acid (Depakote <sup>®</sup> ):	Used in headache or nerve pain.
Gabapentin (Neurontin <sup>®</sup> ):	Has proven to be effective in some people for nerve injury or neuropathic pain. Seems safer, easier to use, costly. Some mental fuzziness possible at higher doses.
Phenytoin (Dilantin <sup>®</sup> ):	Stronger evidence supports the use of the above agents over phenytoin. The risk of adverse effects and drug interactions also precludes its regular use.
Clonazepam (Klonopin <sup>®</sup> ):	A benzodiazepine (Valium <sup>®</sup> , Xanax <sup>®</sup> family).
Lamotrigine (Lamictal <sup>®</sup> ):	May be useful for pain refractory to carbamazepine. Used in trigeminal neuralgia, central pain. May cause dizziness, constipation, nausea, decreased mental awareness, etc.
Tiagabine (Gabitril <sup>®</sup> )	Used in combination with other anticonvulsant agents in the management of partial seizures. Useful for neuropathic pain.
Pregabalin (Lyrica <sup>®</sup> )	Found effective in postherpetic neuralgia and diabetic neuropathy. Some advantage over gabapentin. It is generally well tolerated.
Topiramate (Topamax <sup>®</sup> )	Generally well tolerated but sometimes causes confusion, dizziness, fatigue, and problems with coordination and concentration. Possibly useful in treating neuropathic and sympathetically maintained pain. It is also being used as a preventive migraine treatment. Side effects include strange sensations and loss of appetite.
Levetiracetam (Keppra <sup>®</sup> )	Indicated for use as adjunctive therapy in the treatment of partial seizures in adults. It is possibly effective in neuropathic pain.
Oxcarbazepine (Trileptal <sup>®</sup> )	Indicated for the treatment of partial seizures. Its improved safety and tolerability profile suggests that it may be an important addition to the treatment of neuropathic pain.
Zonisamide (Zonegran <sup>®</sup> )	Indicated for use as adjunctive therapy for treatment of partial seizures (or <i>focal seizures</i> ) in adults with epilepsy. Research suggests that zonisamide may be useful for treating neuropathic pain.



## **SODIUM CHANNEL BLOCKING & ORAL ANTI-ARRHYTHMIC AGENTS**

Intravenous lidocaine has strong sodium channel blocking properties and has demonstrated efficacy in several uncontrolled studies on neuropathic pain. Some pain centers used intravenous lidocaine both as a diagnostic tool to assess responsiveness to a subsequent oral sodium channel blocker (e.g. mexiletine, oxcarbazepine, and carbamazepine) as well as a therapeutic tool when delivered in an inpatient setting.

Those antiarrhythmics with local anesthetic properties are occasionally used in chronic pain. They are approved for the prevention of disturbances in heart rhythm but, just as they interrupt premature firing of heart fibers, they also diminish premature firing of damaged nerves.

Due to safety concerns, the only antiarrhythmics that are used often for chronic pain are mexiletine (Mexitil<sup>®</sup>) and flecainide (Tambocor<sup>™</sup>). They reduce pain in diabetic neuropathy, post stroke pain, complex regional pain syndrome or reflex sympathetic dystrophy, and traumatic nerve injury.

Mexiletine is chemically similar to lidocaine, an anesthetic frequently used by dentists. Common side effects of mexiletine include dizziness, anxiety, unsteadiness when walking, heartburn, nausea, and vomiting. It should be taken with food to lessen stomach irritation. Infrequent adverse reactions include sore throat, fever, mouth sores, blurred vision, confusion, constipation, diarrhea, headache, and numbness or tingling in the hands and feet. Serious symptoms occur with over-dosage including seizures, convulsions, chest pain, shortness of breath, irregular or fast heartbeat, and cardiac arrest. Immediate discontinuation of the medication followed by emergency treatment is appropriate in these conditions.

Flecainide (Tambocor<sup>™</sup>) was approved to treat arrhythmias and can slow a fast heart rate. It has also been effective for treating certain painful conditions related to neuropathic pain. Although cardiac side effects with flecainide may be infrequent, an ECG is recommended before treatment is started.



## TOPICAL PAIN RELIEVERS

Creams, gels, sprays, liquids, patches, or rubs applied on the skin over a painful muscle or joint are called *topical pain relievers* or *topical analgesics*. Many are available without a prescription.

Topical agents should be distinguished from transdermal medications, which are also applied directly to the skin, but the drug may have effects throughout the body and work away from the area of pain (currently available transdermal drugs include fentanyl and clonidine). Transdermal medication in a patch is absorbed through the skin by the bloodstream over a period of time (you should never cut a transdermal patch into smaller pieces).

Some of the over-the-counter topical agents contain salicylates, a family of drugs that reduce inflammation and pain. They come from the bark of the willow tree and are the pain relieving substances found in aspirin. Small amounts relieve mild pain. Larger amounts may reduce both pain and inflammation. Salicylates decrease the ability of the nerve endings in the skin to sense pain.

Counterirritants, another group of topical agents, are specifically approved for the topical treatment of minor aches and pains of muscles and joints (simple backache, arthritis pain, strains, bruises, and sprains). They stimulate nerve endings in the skin to cause feelings of cold, warmth, or itching. This produces a paradoxical pain-relieving effect by producing less severe pain to counter a more intense one. Some topical pain relievers are methyl salicylate, menthol, camphor, eucalyptus oil, turpentine oil, histamine dihydrochloride, and methyl nicotinate.

Topical agents have also gained popularity for use in certain neuropathic pain conditions such as diabetic neuropathy, postherpetic neuralgia, or neuroma pain. They are also prescribed in Complex Regional Pain Syndrome (CRPS) states.

Aspirin in chloroform or ethyl ether, capsaicin (Zostrix<sup>®</sup>, Zostrix<sup>®</sup>-HP), EMLA<sup>®</sup> (eutectic mixture of local anesthetics) cream, and local anesthetics such as the lidocaine patch 5% (Lidoderm<sup>®</sup>) are topical treatments for neuropathic pain. Of these, the topical lidocaine patch is the only FDA-approved treatment for neuropathic pain. There are additional topical agent combinations which can be compounded at your local pharmacy. These compounded mixtures are prepared uniquely for each individual but have not passed rigorous scientific study. Any benefit from such compounded creams is anecdotal.

Capsaicin is the active ingredient in hot peppers. Several studies have suggested that capsaicin (cap-SAY-sin) can be an effective analgesic in at least some types of neuropathic pain. An adequate trial of capsaicin usually requires four applications daily, around the clock, for at least three to four weeks. Some individuals may experience a burning sensation, which usually lessens within 72 hours with repeated use. Gloves should be worn during application, and hands should





be washed with soap and water after application to avoid contact with the eyes or mucous membranes.

Topical anesthetics, such as EMLA<sup>®</sup> (Eutectic Mixture of Local Anesthetic) cream, is used primarily prior to painful procedures such as venipuncture (blood drawing), lumbar puncture (spinal tap), and wart removal. EMLA<sup>®</sup> cream may be effective in the treatment of postherpetic neuralgia, ischemic (decreased blood supply) neuropathy, and a variety of other neuropathic conditions.

EMLA<sup>®</sup> cream is a combination of the local anesthetics lidocaine and prilocaine. This combination results in a relatively constant release of dissolvable local anesthetics that can diffuse through the skin and soft tissue. A thick layer of EMLA<sup>®</sup> cream is applied to intact skin and covered with an occlusive dressing. The minimal application time to obtain reliable superficial pain relief is one hour. However, the cream may be left on the skin for up to two hours, depending on the degree of the procedure performed. Analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream.

Lidoderm<sup>®</sup> 5% (lidocaine) patches can be cut to fit over the area of pain. The 5% lidocaine patch is the only topical anesthetic agent to receive FDA approval for the treatment of a neuropathic pain condition, specifically postherpetic neuralgia (PHN). It measures 10 cm x 14 cm and has a polyethylene adhesive backing. Up to three patches can be applied simultaneously to intact skin for up to 12 hours in any 24-hour period.

Side effects of topical local anesthetics are minimal and include localized skin irritation and swelling that generally disappear within two to three hours after the local anesthetic(s) is removed from the skin. As a rule, blood concentrations of topical local anesthetics are well below toxic levels.



## SEDATIVES, ANTI-ANXIETY MEDICATIONS, & TRANQUILIZERS

Proper sleep hygiene is critical to the individual with chronic pain and often is hard to obtain. Various medications may provide short-term benefit. While sleeping pills, so-called minor tranquilizers, and anti-anxiety agents are commonly prescribed in chronic pain, pain specialists rarely, if ever, recommend them for long-term use. They can be habit-forming, and they may impair function and memory more than opioid pain relievers. There is also concern that they may increase pain and depression over the long-term.

Zolpidem tartrate (Ambien<sup>®</sup>) is a non-benzodiazepine and is used for the short-term treatment of insomnia (difficulty falling asleep or staying asleep, or early awakening). Side-effects that are more common may include allergy, daytime drowsiness, dizziness, drugged feeling, headache, indigestion, and nausea. Some people using Ambien<sup>®</sup>, especially those taking serotonin-boosting antidepressants, have experienced unusual changes in their thinking and/or behavior. Ambien<sup>®</sup> and other sleep medicines can cause a special type of memory loss. Older adults, in particular, should be aware that they may be more apt to fall. Ambien<sup>®</sup> should be used with caution in people who have liver problems. If it is taken for more than a week or two, it should not be stopped abruptly. It should not be used in people who use alcohol. It can increase the drug's side effects. If you have breathing problems, they may become worse when you use Ambien<sup>®</sup>.

Another sleeping medication, eszopiclone (Lunesta<sup>™</sup>), reportedly has fewer side effects and can be taken for longer periods of time. Initial testing suggests fewer side effects than other sleep medication but individuals taking eszopiclone or any other sedative drug may develop dependence on the drug for sleep. They may also experience withdrawal symptoms when the drug is discontinued. The most common side effects of eszopiclone are dizziness and loss of coordination.

A newer sleeping medication, ramelteon (Rozerem<sup>™</sup>) is a melatonin receptor agonist with high affinity for MT-1 and MT-2 receptors. These receptors are believed to regulate the body's circadian rhythm. It is indicated for the treatment of insomnia characterized by difficulty with sleep onset. According to the manufacturer, the most common adverse effects are somnolence, dizziness and fatigue. The recommended dose is 8mg nightly, taken within 30 minutes of going to bed. Ramelteon has been shown to be safe and effective to use for up to one year. Ramelteon should not be taken with fluvoxamine (Luvox<sup>®</sup>) or given to patients with severe liver disease.

Diazepam (Valium<sup>®</sup>) is widely prescribed, even though it is widely recognized for causing depression and physical dependence when used for long periods.

Many pain specialists believe that anxiety and insomnia in those with chronic pain are best treated with antidepressants when possible. Non-medication approaches to proper sleep hygiene are best but are not the focus of this Medications & Chronic Pain Supplement.



Most people experience anxiety at one time or another in their lives. Anxiety can present as nervousness or sweaty palms before an interview, irritability, uneasiness, feelings of apprehension, tight muscles, and difficulty sleeping. Anxiety is often mild, but if it becomes severe, counseling or medications may be needed. The most widely prescribed drugs for anxiety are benzodiazepines, like diazepam (Valium<sup>®</sup>), lorazepam (Ativan<sup>®</sup>), clonazepam (Klonopin<sup>®</sup>), flurazepam (Dalmane<sup>®</sup>), triazolam (Halcion<sup>®</sup>), temazepam (Restoril<sup>®</sup>), and alprazolam (Xanax<sup>®</sup>). They are also used as muscle relaxants and for insomnia (difficulty sleeping). Their use as sleep aids is limited as they do not work well when used continuously each night to produce sleep.

Side effects are similar to those of alcohol and include sedation, slurred speech, and gait unsteadiness. Other adverse reactions include chest pain and a pounding heartbeat, psychological changes, headache, nausea, restlessness, vision problems, nightmares, and unexplained fatigue. Alcohol and tobacco should be avoided while taking these drugs.

Because of withdrawal symptoms, these drugs should be discontinued slowly under a physician's supervision. Withdrawal reactions may be mistaken for anxiety since many of the symptoms are similar. Left unattended, benzodiazepine withdrawal can be associated with seizures or even death.

Two common drugs for migraine, Fiorinal<sup>®</sup> and Fioricet<sup>®</sup>, contain aspirin or acetaminophen (Tylenol<sup>®</sup>), respectively, with caffeine and butalbital, a barbiturate. These drugs may cause a high level of physical dependence and rebound headaches in frequent use. But they are probably harmless in those who use one of them for infrequent migraines.



## MUSCLE RELAXANTS

Many drugs have been marketed as muscle relaxants, even though most do not seem to have any direct effect on muscle. Perhaps they should be called “brain relaxants,” since they are all sedating and this may be how they actually work. Some also have analgesic (pain reducing) properties. Cyclobenzaprine (Flexeril<sup>®</sup>) is chemically similar to the tricyclic antidepressants and may have a similar mechanism. Muscle relaxants have limited efficacy in chronic pain, but may be used to treat acute flare-ups.

### DRUGS USED AS MUSCLE RELAXANTS IN CHRONIC PAIN

Carisoprodol (Soma <sup>®</sup> )	Converted by the body into meprobamate, a barbiturate-like drug. It may cause physical dependence. It should be avoided in kidney or liver disease. With prolonged use, it is associated with dependence. Long-term use in chronic pain should be avoided.
Cyclobenzaprine (Flexeril <sup>®</sup> )	Skeletal muscle relaxant that is structurally similar to the TCAs. Side effects include dizziness, drowsiness, dry mouth, constipation, confusion, and loss of balance. Long-term use in chronic pain should be avoided.
Methocarbamol (Robaxin <sup>®</sup> )	Skeletal muscle relaxant with sedative properties. Side effects include drowsiness and urine discoloration to brown, black, or green.
Metaxalone (Skelaxin <sup>®</sup> )	Skeletal muscle relaxant. It should be used with caution in liver disease.
Chlorzoxazone (Parafon Forte <sup>®</sup> DSC)	Skeletal muscle relaxant with sedative properties. It should be used with caution in liver disease.
Baclofen (Lioresal <sup>®</sup> )	Reduces spasticity after neurological illness or injury. Withdrawal should not be abrupt. Inhibits transmission at the spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side effects of sedation and muscle weakness (other adverse events are uncommon). Baclofen is known to be safer for long-term use.
Dantrolene (Dantrium <sup>®</sup> )	A true muscle relaxant that acts directly on skeletal muscle and produces fewer central adverse effects. Can have significant liver toxicity. The dose should be increased slowly.
Orphenadrine (Norflex <sup>™</sup> )	A skeletal muscle relaxant with analgesic properties.
Tizanidine (Zanaflex <sup>®</sup> )	A drug indicated for spasticity associated with multiple sclerosis or spinal cord injury but being used off label for chronic pain.
Diazepam (Valium <sup>®</sup> )	Other benzodiazepines also have muscle-relaxant properties. Most pain physicians avoid prescribing diazepam for muscle spasm. Toxicity of benzodiazepines is discussed at <a href="http://www.emedicine.com/emerg/topic58.htm">www.emedicine.com/emerg/topic58.htm</a> .



## ANTI-PSYCHOTIC MEDICATIONS

This class of drugs was marketed primarily because of its ability to reduce hallucinations and psychotic thinking, although some members of the class are used to treat nausea and migraine.

Common ones include chlorpromazine (Thorazine<sup>®</sup>), aripiprazole (Abilify<sup>™</sup>), clozapine (Clozaril<sup>®</sup>), haloperidol (Haldol<sup>®</sup>), olanzapine (Zyprexa<sup>®</sup>, Zydys<sup>®</sup>), quetiapine (Seroquel<sup>®</sup>), risperidone (Risperdal<sup>®</sup>), and ziprasidone (Geodon<sup>®</sup>).

In general, their use in chronic pain is poorly established, and they have the potential to cause a permanent neurological condition called tardive dyskinesia. In mild cases, this consists of movements of the mouth and tongue, which is mostly a cosmetic problem; however, in more severe cases there can be severe muscle activity that interferes with ability to function and even to breathe. For these reasons, they are usually considered “last resort” drugs. Toxicity of anti-psychotics is discussed at [www.emedicine.com/EMERG/topic338.htm](http://www.emedicine.com/EMERG/topic338.htm).

## ANTI-HYPERTENSIVE MEDICATIONS

Clonidine (Catapres<sup>®</sup>, Catapres-TTS<sup>®</sup> patch) is a centrally-acting alpha-agonist that lowers blood pressure and has also been shown to have pain-relieving properties in sympathetically maintained pain conditions such as Complex Regional Pain Syndrome (CRPS) or Reflex Sympathetic Dystrophy (RSD). It is available as tablets for oral administration, as an injectable solution for administration in an epidural or implanted pump, or as a once-weekly patch.

Side effects can include dry mouth, drowsiness, dizziness, and constipation. Transient localized skin reactions can occur with the patch.

It should not be discontinued suddenly as this can result in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure. Some individuals can develop an allergy to clonidine with a generalized rash, itching, or swelling. It should be used with caution in patients with severe heart disease, cerebrovascular disease (stroke), or chronic kidney failure. To avoid hypertensive crisis, clonidine should not be used with tricyclic antidepressants.



## **BOTULINUM TOXIN**

Botulinum toxin (Botox<sup>®</sup> & Myobloc<sup>®</sup>) has been found to be effective in decreasing overactive (hypercontractile) muscles, which may be present in a number of chronic pain conditions. There appears to be pain relieving properties of botulinum toxin irrespective of muscle relaxation. Chronic headache, back, neck, and extremity muscle pain has been shown to respond to botulinum toxin injection.

Botulinum toxin works within 3 to 5 days after intramuscular administration and lasts for an average of 12 weeks.

The occurrence of side effects after receiving botulinum toxin is rare. Muscle weakness may occur and is the most common side effect. Swallowing problems can develop when treating cervical muscle problems. Other possible adverse effects include dry mouth, pain at the injection site, swallowing problems, headache, and flu-like symptoms. Additionally, adverse effects may include local bruising, generalized fatigue, lethargy, dizziness, and difficulty speaking with hoarseness, but these side effects are extremely rare.

## **NMDA INHIBITORS**

Numerous new compounds that specifically target mechanisms mediating neuropathic pain such as the N-methyl-D-aspartate (NMDA) receptor complex are currently in clinical trials. NMDA inhibitors appear to help prevent sudden acute pain from progressing into chronic pain. These act by blocking receptors of neurotransmitters that are essential for making long-term memories. The NMDA antagonists also reduce opioid tolerance and may enhance opioid analgesia. However, side effects are the biggest problem with this drug class.

The utility of these agents has been limited by their significant side effect profile. Agents that have clinically relevant NMDA blocking properties include ketamine, amantadine (an anti-influenza medication), memantine (an Alzheimer drug; Namenda<sup>™</sup>), dextromethorphan (an anti-cough medication), and methadone (an opioid).

Ketamine is a strong NMDA antagonist that has been used orally and intravenously for the treatment of CRPS and other neuropathic pain conditions. Adverse effects reported in studies of lower doses given to adults by the oral route include lightheadedness, dizziness, tiredness, headache, nervous floating sensation, bad dreams, and sensory changes. More formal study is needed to assess both the efficacy and safety of ketamine for neuropathic pain.

Dextromethorphan, memantine and amantadine are weaker NMDA receptor blockers, and consequently, are also thought to have fewer CNS side effects.



The basic concept of NMDA antagonism in neuropathic pain remains sound, but there is a strong need for more studies and perhaps development of newer agents with fewer CNS side effects.

Some pain physicians have been prescribing NMDA inhibitor drugs for chronic neuropathic pain, but further studies are needed to determine their effectiveness.

## **ADRENERGIC DRUGS, BISPHOSPHONATES & THALIDOMIDE**

Alpha adrenergic antagonists (e.g. phentolamine, phenoxybenzamine, reserpine, and others) have been used clinically for the treatment of CRPS without good evidence from clinical research studies. The rationale for their use is the recognized role of the sympathetic nervous system in CRPS and the theory that blockade will provide pain relief. Oral clonidine has not demonstrated significant efficacy in neuropathic pain and is challenging to use for due to its side effect profile. It is more widely utilized in implanted pumps as an intrathecal agent.

Bisphosphonates (e.g. pamidronate, clodronate, alendronate) inhibit bone resorption and have demonstrated efficacy in the treatment of CRPS in several studies. While the primary mechanism of these agents has been thought to be reduction in pain by preventing the osteoporosis associated with CRPS, other peripheral and central mechanisms may be responsible and deserve investigation.

Recently, there has been significant interest in the use of thalidomide as a treatment for CRPS. There are no published clinical trials on thalidomide use in CRPS and only case reports demonstrating benefit. The drug is currently being studied in clinical trials but due to its history of causing birth defects, women of child bearing age have been excluded and extensive monitoring is required.

## **ACTIVATING MEDICATIONS (CENTRAL NERVOUS SYSTEM STIMULANTS)**

Side effects from medications prescribed for chronic pain can be bothersome at the least and, if significant enough, may cause the need to discontinue the offending medication. One of these side effects is daytime drowsiness, making it difficult for the individual to function and carry out day to day activities and work. Rather than give up the benefits of the prescribed medication, some physicians will try to treat the side effect of sleepiness and lethargy by prescribing an "activating" medication such as methylphenidate (Ritalin<sup>®</sup>, Concerta<sup>®</sup>, and Metadate<sup>®</sup>), dextroamphetamine (Dexedrine<sup>®</sup>), modafinil (Provigil<sup>®</sup>), and combination products (Adderall<sup>®</sup>).

Methylphenidate (Ritalin<sup>®</sup>, Concerta<sup>®</sup>, and Metadate<sup>®</sup>) is a medication prescribed for individuals (usually children) who have an abnormally high level of activity or attention-deficit hyperactivity



disorder (ADHD). It is a central nervous system (CNS) stimulant. It has effects similar to, but more potent than, caffeine and less potent than amphetamines. It is occasionally used off-label as a stimulant when daytime sleepiness from chronic pain medications is a problem. When used appropriately, it can be effective, but it does have potential for abuse ([www.nida.nih.gov/Infofax/ritalin.html](http://www.nida.nih.gov/Infofax/ritalin.html)). Marked anxiety, tension, and agitation are contraindications to methylphenidate since the drug may aggravate these symptoms. Methylphenidate should be given cautiously to emotionally unstable patients and those with a history of drug dependence or alcoholism, as they may increase the dose on their own initiative.

Dextroamphetamine (Dexedrine<sup>®</sup>) is an amphetamine used to treat narcolepsy and attention-deficit hyperactivity disorder in children. In some cases, this drug has been used to treat depression or as an adjunct in the treatment of exogenous obesity. This drug is from a family of drugs known as central nervous system stimulants.

Modafinil (Provigil<sup>®</sup>) is approved by the FDA to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. It is also being used off-label for persons with chronic pain and excessive daytime sleepiness. It is generally well tolerated, with mild to moderate side effects. It reportedly does not affect nighttime sleep. Provigil<sup>®</sup> has been known to cause headaches. Less frequent side effects include nausea, nervousness, anxiety, and insomnia.

## **IMPLANTED DRUG DELIVERY SYSTEMS**

Delivery of pain relievers directly to the area of the spinal cord and nerve roots is another route of drug delivery. In this case, the approach offers dosage reductions, potentially fewer side effects and in some instances, is the only route possible for certain drugs.

Ziconotide (Prialt<sup>®</sup>) is a non-opioid analgesic used for the management of severe chronic pain and is reserved for patients intolerant or refractory to other therapies. It is delivered intrathecally (directly to the spinal nerves). The drug is delivered by continuous infusion through an infusion pump directly into the fluid surrounding the spinal cord. Common side effects include dizziness, nausea, vomiting, constipation, diarrhea, loss of appetite, and muscle weakness.





## HERBAL MEDICINES

*The following information about Herbal Medicine was abstracted from an article written by Kate O'Hanlan, M.D., Use of Herbal Medicine and Quality Medical Care, in the Drug Information Service Newsletter, The Department of Pharmacy, Stanford Hospital & Clinics, Volume 21, Issue 5, November/December 2002. Herbal medicines are unproven regarding treating chronic pain and further, have the potential to interfere and interact with other prescription medications.*

Herbal medicines are broadly defined as medicinal agents derived from plant substances. Nutraceuticals are nutrient products such as fish oils and megavitamins. While many currently used prescription medications may also fall into this category, all prescriptive agents have been critically evaluated with regard to evidence of their efficacy, cross reactions, and undesired side effects and are closely monitored by the Federal Food and Drug Administration (FDA).

Consumption of herbal medicines bought over-the-counter from a virtually unregulated pharmaceutical and vitamin industry is increasing yearly. The 1994 Dietary Supplement Health and Education Act permits herbal remedies and medicinal agents to be categorized with vitamins, minerals, and food additives, with no FDA oversight of safety or efficacy data required prior to marketing or listed on the label. Additionally, there is no oversight of the sterility of production, bio-equivalency, or durability of product life.

All medications have the potential for toxic side effects and cross reactions with other medications. Unexpected toxicity or drug interaction from any medication may accrue due to many variables such as age, gender, nutritional status, other illnesses, and surgery. While such knowledge is part of clinical medicine, this information is not as readily available for herbal remedies and nutraceuticals, even though some have been used for centuries. In addition, standard preparation and dosing instructions have not been elucidated for the use of herbal medicines.

The American Society of Anesthesiologists recommends that patients discontinue or taper off of herbal medicines and nutraceuticals at least two weeks prior to surgery, and that patients taking herbal medicinals having urgent or emergency surgery bring the original containers to the hospital for review by the anesthesiologist and surgeon.

Many adverse events from herbal medicines have been reported including hypersensitivity reactions, anaphylaxis (shock), hepatitis, nausea, vomiting, diarrhea, platelet inhibition, increased and decreased clotting time, lower seizure threshold, elevated digoxin levels, central nervous system depression, phototoxicity, myocardial ischemia, electrolyte alterations, hypotension, arrhythmias, renal failure, carcinogenicity, and autoimmune effects. Some of the undesirable effects of a few of the more commonly used herbals are shown below.



Adverse Events with Commonly Used Herbal Medications	
Aloe vera	Nausea, vomiting, diarrhea
Astragalus	Autoimmune disease
Belladonna	Atropine effects
Chaparral	Hepatitis
Ephedra	Cardiac arrhythmias, death
Ginkgo biloba	Excess bleeding

Familiarity with the growing list of herbal remedies and a detailed understanding of their possible side effects and cross reactions with anesthetic drugs and medications are no longer possible, if they ever were possible.

The National Institutes of Health (NIH) National Center for Complimentary and Alternative Medicine (NCCAM) and the National Library of Medicine (NLM) has partnered to create *CAM on PubMed*, a subset of NLM's PubMed. [PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&orig_db=PubMed&cmd_current=Limits&pmfilter_Subsets=Complementary+Medicine) provides access to citations from the MEDLINE database and additional life science journals. It also includes links to many full-text articles at journal Web sites and other related Web resources. More information can be found at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&orig\\_db=PubMed&cmd\\_current=Limits&pmfilter\\_Subsets=Complementary+Medicine](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&orig_db=PubMed&cmd_current=Limits&pmfilter_Subsets=Complementary+Medicine).

## MIGRAINE HEADACHES

Migraine headache treatment has been revolutionized with the advent of the triptans. These include sumatriptan (Imitrex<sup>®</sup> – also available by injection or nasal spray), zolmitriptan (Zomig<sup>®</sup> – also available by nasal spray or as orally-disintegrating tablets), naratriptan (Amerge<sup>®</sup>), rizatriptan (Maxalt<sup>®</sup> – also available as orally-disintegrating tablets) and almotriptan (Axert<sup>™</sup>). More recently introduced triptans include frovatriptan (Frova<sup>®</sup>) and eletriptan (Relpax<sup>®</sup>).

The key to effective treatment, however, is still a combination of avoidance of migraine triggers, stress management and relaxation techniques, and non-medication symptom relief through the use of locally applied heat or cold, massage, hot showers, and rest in a quiet, darkened room. Some people benefit from complementary or alternative therapies such as relaxation techniques, training in self-hypnosis, biofeedback, yoga, aromatherapy, acupuncture, spinal manipulation, and homeopathic remedies.



Unfortunately, while migraine headaches can now be better controlled, it is unrealistic to expect instant, complete or permanent pain relief for what is essentially a chronic, recurring disease.

Effective migraine treatment begins with the early recognition that an attack is pending followed by immediate treatment. Migraine sufferers are encouraged to take an active role in managing their headaches by avoiding common triggers, making lifestyle changes, and taking their medication at the first sign of migraine pain.

Patients taking certain migraine and depression medications together may be at risk for a dangerous chemical imbalance. Depression medications included in this warning are Prozac<sup>®</sup>, Zoloft<sup>®</sup>, Paxil<sup>®</sup>, Lexapro<sup>™</sup>, Cymbalta<sup>®</sup> and Effexor<sup>®</sup>. Migraine drugs include Amerge<sup>®</sup>, Axert<sup>™</sup>, Imitrex<sup>®</sup>, and Zomig<sup>®</sup>. Serotonin is a brain hormone that keeps our mood stable and our appetite in check, as well as serving other functions. When you take two or more drugs that affect serotonin levels, it can increase the amount of serotonin and may lead to bothersome or dangerous symptoms. This is called "serotonin syndrome." Please see in the discussion of antidepressant medication of this APCA Medications Supplement for more detailed comments about mixing migraine and certain antidepressant medications.

An excellent medical review on migraine headaches can be found in the Cleveland Clinic Medical Journal in January 2003 at [www.ccmj.org/pdffiles/Mannix103.pdf](http://www.ccmj.org/pdffiles/Mannix103.pdf).

## **ALCOHOL & CHRONIC PAIN**

Alcohol is also a drug. The use of alcohol has no place in the treatment of chronic pain, although some individuals turn to alcohol for relief when they perceive their pain as intolerable.

Alcohol can enhance the effect of certain prescription drugs as well as markedly increase potential toxic side effects (such as liver damage when used in conjunction with acetaminophen).

Alcohol affects the nervous system as a depressant, not as a stimulant. It depresses normal mental activity and normal muscle function. Short-term effects of an average amount of alcohol include relaxation, breakdown of inhibitions, euphoria, and decreased alertness. Short-term effects of large amounts of alcohol include nausea, stupor, hangover, unconsciousness, and even death. Alcohol increases stomach acid and impairs liver function. Chronic alcoholism frequently leads to permanent damage to the liver. Alcohol also affects the heart and blood vessels by decreasing normal function leading to heart disease. Bleeding from the esophagus and stomach frequently accompany liver disease caused by chronic alcoholism. Many medications cannot be given to patients with abnormal liver function, thus making it more difficult to treat chronic pain.



The early signs of alcoholism include the prominent smell of alcohol on the breath and behavior changes such as aggressiveness, passivity, lack of sexual inhibition, poor judgment, and outbursts of uncontrolled emotion such as rage or tearfulness. Intoxication signs of alcoholism include unsteady gait, slurred speech, poor performance of any brain or muscle function, stupor or coma in severe alcohol intoxication, with slow, noisy breathing, cold and clammy skin, and an increased heart beat.

The long-term effects of alcohol addiction include the compulsive use of it. When alcohol is unavailable to persons who are severely addicted, severe withdrawal symptoms are noticed and may be life threatening if not treated immediately. Even with successful treatment, individuals addicted to alcohol have a high tendency to relapse.

Alcohol and chronic pain medications do not mix.

## **ILLICIT DRUGS & MARIJUANA**

Reputable pain physicians will not prescribe opioids and other medications to individuals who procure or sell drugs illicitly. The potential for serious medication interactions and side effects is great.

There is no place for the use of illicit drugs in the treatment of chronic pain.

The use of marijuana is controversial, including for chronic pain relief. Some states allow the legal use of marijuana for health purposes including pain, while the federal government continues to threaten physicians with prosecution for prescribing it.

The use of marijuana, alcohol, or other substances should be discussed openly between you and your physician.

## **CONCLUSION**

An essential concept in pain management is that each person is different and will respond differently to situations, interventions, and medications. It is important for the person with pain, family members, and others to avoid quick judgments based on what they hear or read about medications. The best place to get advice about medications is from the health care provider assisting the person with pain. Families need to be good reporters – observant, truthful, and honest about what they see in the person who is taking medication. Often the person taking the medication does not realize the changes that are produced. Family member observations will be helpful to the health care provider.



This ACPA Medications & Chronic Pain Supplement only deals with medications but it is important to understand that there are many other important treatment approaches to chronic pain. In fact, medications alone are rarely satisfactory absent the additional use of other approaches to treat the person with chronic pain. These other approaches include physical and occupational therapy, behavioral-psychological treatments, and a host of other modalities, devices, and interventional techniques including surgery. In fact, rehabilitation through cognitive, behavioral, and physical reactivation treatments often lessens the need for medications and other more invasive procedures.

There is no question that medications play an important role in the treatment of chronic pain, but they should be used judiciously. Benefit should be based on less pain, more function and return to everyday activities with the least, manageable, medication side effects possible.

The ACPA once again reminds you that this 2007 Medications & Chronic Pain Supplement is not meant to serve as medical advice for your condition or regarding your medication needs. Remember that the best source of information about your health and medication needs is from an open dialogue with your doctor.

## **REFERENCES ON THE INTERNET**

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