

# ACPA Resource Guide

To

Chronic Pain Medication & Treatment

## 2013 Edition

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## **A Statement from the ACPA Board of Directors**

The American Chronic Pain Association (ACPA) advocates a multi-modal strategy for dealing with chronic pain. The ACPA focuses on pain management skills and self-help strategies that individuals can use with the approval of their healthcare providers.

The ACPA considers the use of medication and other treatments to be a matter for individuals to determine in conjunction with their healthcare provider. The ACPA takes no position on medical treatment choices. Thus, information the ACPA provides about medical care is educational and informative only.

The ACPA Resource Guide to Chronic Pain Medication & Treatment is an unbiased consensus document that combines practical clinical experience and the most recent scientific information.



## INTRODUCTION

For over a quarter century, the American Chronic Pain Association (ACPA), 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 <http://www.theacpa.org>, or call the National Office at 800-533-3231.

The ACPA Resource Guide to Chronic Pain Medication & Treatment is updated regularly and includes web links for certain medications and treatments and relevant Internet sites of interest. For medications, generic names are primarily listed with brand names in parentheses.

**This Guide is not meant to serve as medical advice for your condition or regarding your treatment needs.** Remember that the best source of information about your health and treatment needs is from an open dialogue with your health care professional (in this document the word “health care professional” includes physicians, prescribing advanced practice nurses, nurse practitioners, and physician assistants).

This ACPA Resource Guide to Chronic Pain Medication & Treatment covers medications and treatments. The topics covered are not exhaustive and because something is not mentioned does not imply that it is not useful. If you would like to see a topic covered in future editions of this ACPA Resource Guide to Chronic Pain Medication & Treatment, please notify us.

With the emerging and ever increasing growth of the Internet, large amounts of information are now available on almost every topic. Finding information is easy, but finding relevant factual information that meets a particular individual’s needs and educational level is not so easy.

The information in this ACPA Resource Guide to Chronic Pain Medication & Treatment is a summary of information from multiple sources. Sources and Internet links are provided for reference where appropriate. Any errors are those of the authors and recommendations for corrections, additions or deletions are welcomed at <http://www.theacpa.org/contactUs.aspx>.

There are many treatment approaches to chronic pain. These approaches include passive and active therapies, medications, behavioral-psychological treatments, and a host of other modalities, devices, and interventional techniques including surgery and other procedures. Medications, passive treatments, and invasive interventions alone are not always satisfactory absent the additional use of other active rehabilitation and educational approaches that treat the whole person with chronic pain.

In fact, rehabilitation through cognitive, behavioral, and physical reactivation treatments (also called functional restoration) 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 treatments and especially about their prescribed medications. This knowledge may relieve the



fears that can interfere with receiving maximum benefits from such treatment and medications. Information can also prevent unrealistic expectations that can lead to disappointment or even worse, a bad outcome.

Unfortunately, however hopeful the individual may be and however well-meaning the treatment may be, the reality is that there are risks associated with almost any treatment for chronic pain. The best approach is for people with pain to ask questions about the benefits and risks or side effects when they are about to embark on any particular treatment approach or new medication. Does the risk justify the possible benefit?

A “successful” person with chronic pain is someone who has learned to independently self-manage their condition in such a way as to achieve maximum function for everyday life activities while minimizing discomfort and avoiding a bad outcome from treatment.



## PAIN TYPES & CHRONIC PAIN CLASSIFICATION

Many pain specialists recommend that the term “chronic pain” should be described as “persistent pain” – which can be continuous or recurrent and of sufficient duration and intensity to adversely affect a person’s well-being, level of function, and quality of life. This document continues to use the term “chronic pain” given its universal acceptance.

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

Chronic or persistent pain can be described as ongoing 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 or persistent pain is **pain that continues when it should not**.

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 (analgesics) are generally effective for nociceptive pain but may be less effective for neuropathic pain.

Continuous pain is pain that is typically present for approximately half the day or more. In most cases, this type of pain is treated with an around-the-clock approach, such as regularly scheduled analgesic doses and a sustained exercise program.

Breakthrough or flare-up pain can be described as a transitory increase in pain in someone who has relatively stable and adequately controlled baseline pain. Breakthrough 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. It can also be caused by emotions such as increased stress, anxiety, or worry. Breakthrough pain may occur at the end of the scheduled pain medicine dose as well.

Treatment for moderate-to-severe breakthrough pain can consist of medication and/or the use of non-pharmacological tools. Non-pharmacological tools are recommended and include relaxation techniques, light stretching or activity, and positive self-talk. The treatment of breakthrough pain with a short-acting opioid is common in individuals with active cancer or other types of advanced medical illness for which opioid therapy is the mainstay for the long-term management of moderate to severe pain. However, there is no agreement among healthcare professionals on how best to treat breakthrough pain in people with non-cancer pain. It is important to tell your healthcare professional if you are experiencing breakthrough pain so that a treatment strategy that is right for you can be developed.



## PAIN IN CHILDREN

Chronic pain (defined as persistent and recurrent pain) is a significant problem in the pediatric population, conservatively estimated to affect 20% to 40% of children and adolescents around the world. The most common chronic pain conditions are musculoskeletal pain, headaches, and abdominal pain. Children may experience physical and psychological sequelae and their families may experience emotional and social consequences as a result of pain and associated disability.

Childhood pain brings significant direct and indirect costs from healthcare utilization and lost wages due to taking time off work to care for the child. In addition, longitudinal studies provide convincing evidence to suggest that childhood chronic pain predisposes both for the continuation of pain and the development of new forms of chronic pain in adulthood (from Assessment and Management of Children with Chronic Pain, A Position Statement from the American Pain Society - 1/4/12 [www.ampainsoc.org/advocacy/downloads/aps12-pcp.pdf](http://www.ampainsoc.org/advocacy/downloads/aps12-pcp.pdf) ).

## PAIN IN OLDER PERSONS

Persistent or chronic pain is prevalent in older adults. The issue has been addressed in the American Geriatrics Society (<http://www.americangeriatrics.org>) Pharmacological Management of Persistent Pain in Older Persons at the following Internet Web site: [http://www.americangeriatrics.org/files/documents/2009\\_Guideline.pdf](http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf).

In general, thirty percent of hospital admissions among the elderly may be linked to an adverse drug related event or toxic effect from a drug. Nearly one third of all prescribed medications are for patients over the age of 65 years. Unfortunately, many adverse drug effects in older adults are overlooked as age-related changes (general weakness, dizziness, and upset stomach) when in fact the patient is experiencing a medication-related problem.

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. Careful use of multiple drugs together can be seen as potentially advantageous. Combining smaller doses of more than one medication may minimize the dose-limiting adverse effects of using a particular single drug.

Beyond pharmacologic treatment, physical rehabilitation and other interventional therapies, including targeted injections and acupuncture, can be helpful to minimize side-effects and maximize physical function with pain relief.



## CLINICAL TRIALS

Clinical Trials (see <http://clinicaltrials.gov> for more information) are health-related medical research studies in human beings that follow a pre-defined plan. Choosing to participate in a clinical trial is an important personal decision. It is often helpful to talk to a physician, family members, or friends about deciding to join a trial. The results of the clinical trial can lead to new treatments or therapies becoming available for many people coping with chronic pain.

Information about Understanding Clinical Trials can be found at <http://clinicaltrials.gov/ct2/info/understand>.



## MEDICATIONS AND CHRONIC PAIN

**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. Do not use, buy or sell prescription drugs from family members, friends or others.**

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. In fact, in some individuals, pain medications may actually worsen their symptoms over time or cause unwanted or dangerous side effects.

Medication-related problems would rank fifth among the leading causes of death in the United States if they were considered a disease.

In particular, the overuse, misuse and abuse of opioid (narcotic) pain medications has now become a national issue. Deaths due to overdoses of opioid prescription drugs have risen sharply, and now outnumber all other causes of accidental death. The abuse of prescription opioid pain medications now ranks second—only behind marijuana—as the nation’s most prevalent illegal drug problem. It is a federal crime to take a controlled substance that has not been prescribed for oneself.

Short-term use of opioid medications for pain is rarely worrisome, although side effects are most problematic while initiating treatment and tend to diminish with prolonged use. On the other hand, in some cases, prolonged use of opioids increases the possibility of adverse reactions including gastrointestinal distress including constipation, internal organ problems, balance troubles, endocrine problems, sexual dysfunction, and memory and concentration problems. After prolonged use, an increase in pain sometimes occurs due to an interaction between the brain and the opioids; stopping their use reduces this type of pain. In general, people who begin using other methods to relieve pain (such as those taught by ACPA) are sometimes able to reduce or quit chronic opioids entirely; most often they experience a reduction in suffering when they do.

It is important to remember, each person may respond in a different manner to any medication.

Therefore, each person with chronic pain should be medically managed individually, and medication use should be determined by weighing benefit compared to other alternatives, cost, potential side effects, and the person’s other medical problems

A realistic goal for pain relief medications is partial rather than full relief of symptoms.



## 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 health care professional.

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 health care professionals 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 bring all of your current medications in their original pill bottles or boxes and other items you are taking (including pills, vitamins and supplements you buy without a prescription) with you to any appointments with your health care professional and be honest and forthcoming about any other substances (even if they are not legal) you are using. You should also tell your health care professional whether you are taking your medications as prescribed or not. Some substances and drugs may cause serious side effects if they are combined with other medications. Even over-the-counter pills and herbal medications have possible side effects and the potential to cause serious interactions with your prescription medications and each other.

Keep a list of all of your medications in your wallet or purse. This list will be useful in case you are unable to speak in an emergency.

The following Internet Links may be helpful:

- *A Guide to Safe Use of Pain Medicine* from the Food and Drug Administration (FDA) is available at:

<http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm095742.pdf>



- *Consumer Education: What You Need to Know to Use Medicine Safely* from the FDA at:

<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm101467.htm>

If you are a person with chronic pain who is taking medications, you should know what they are and why you are taking them. Medications can be confusing, especially if you take them for more than one condition. You should know which ones you are supposed to take every day, and which ones you can just take when you need them. You should know how much and how often each medication should be taken, 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. You should know about potential side effects from the medications you are taking. Because of the possibility of interactions between drugs, some medications should not be taken together or should be taken at different times during the day to avoid unwanted reactions.

A Drug Interactions Checker is available at [http://www.drugs.com/drug\\_interactions.php](http://www.drugs.com/drug_interactions.php).

The label on your medication bottle may show a brand name (for example, Tylenol) or the generic name (for example, acetaminophen) or both. It is often less expensive to buy your prescription by its generic name rather than by the brand name. The color and shape of the pill may be different, but FDA-approved generic drugs are considered to be interchangeable with brand name drugs. If you notice any difference in drug benefit, you should discuss this with your health care professional.

You can ask your health care professional 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.

## **ADVICE FROM THE ACPA**

*The best advice the ACPA can offer is for you to discuss all medication questions with your health care professional!* Your primary physician is usually a good resource, but you may be referred to a physician who specializes in Pain Medicine and who may have more information or experience about the use of different medications for various chronic pain problems.



## WARNING ABOUT INTERNET MEDICATION PURCHASES

Sites may purport to be legitimate or in a country with drug laws comparable to the United States (e.g., Canada), but may (a) not be located in that country; (b) be 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.

Buying medication over the Internet may seem a good way to save money, but as many as 96% of online drugstores don't meet U.S. pharmacy laws or practice standards. The National Association of Boards of Pharmacy (NABP) Verified Internet Pharmacy Practice Sites (VIPPS) program evaluates and accredits pharmacy websites that meet state and federal laws and regulations and patient care standards. The NABP website maintains a [database of accredited online pharmacies](#) as well as a list of pharmacies that are *not* recommended. According to the NABP, the safest way to purchase drugs online is through pharmacies accredited by the VIPPS or Vet-VIPPS programs.

The NABP Web Site can be found at <http://www.nabp.net/programs/accreditation/vipps/find-a-vipps-online-pharmacy/index.php>

### Patient Tips for Safe Medication Purchasing\*

1. Purchase all medications from state-licensed pharmacies located in the United States.
2. When purchasing medications from online pharmacies, perform the following checks:
  - a. Ensure that the retailer is in good standing and is licensed to dispense medications in the United States. A pharmacy's status can be verified by contacting the appropriate state board of pharmacy or the National Association of Boards of Pharmacy (NABP) at <http://www.nabp.net> or 1-847-391-4406.
  - b. Examine the site to see if it has posted the Verified Internet Pharmacy Practice Sites (VIPPS) Accreditation Program seal of approval. The NABP established VIPPS to ensure that online pharmacies meet all appropriate state and federal regulatory and licensing requirements for proper operation. A list of VIPPS approved pharmacies can be found at <http://www.vipps.info>.
  - c. All legitimate online pharmacies will
    - i. Make available a licensed pharmacist to answer any medication related questions you may have.
    - ii. Require a prescription from a physician or other licensed health care professional who can prescribe medications.
    - iii. Provide accurate contact information for customer inquiries.
  - d. Notify the FDA about problematic websites at <http://www.fda.gov/buyonline>.
3. Be familiar with all of your medications, especially their physical characteristics such as size, color, shape, smell, hardness, taste, or texture. After refilling a medication, if anything appears suspicious, speak with your pharmacist immediately.



4. Be observant for any altered or open medication containers, variations in packaging, raised or hazy printing, flat printing (instead of imprinting or embossing), missing expiration dates or lot numbers on the package, or sticky residue on the container. All are signs of potential package tampering.
5. Carry a list of all medications you currently take (prescription, over-the-counter, herbal, dietary, and vitamin) with you when you visit your doctor or pharmacist so that they can screen for appropriate use and drug-drug interactions. Keep this list on your person at all times.
6. Be proactive. If you have questions about your medications, ask your pharmacist or physician.

\* Federal Food and Drug Administration (FDA). Buying Prescription Medicine Online: A Consumer Safety Guide. Available at <http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismAndDrugPreparedness/UCM133237.pdf>



## MEDICATION PICTURES

It is always very important to be able to visually identify the medications you are taking.

Unless otherwise noted by your prescriber or state law, pharmacies can dispense an FDA-approved generic version of your medication if available to help save you money. Since generic versions can be supplied by multiple manufacturers, your medication refill may look different. Generic medications can come in different sizes, shapes, colors, and packaging. You can use pill identification resources to confirm that the medication is correct. The most definitive tool for identifying a pill is the imprint code that can be on one or both sides of the pill.

On a computer, you can log onto the Internet and find pictures of most medications at <http://tinyurl.com/PillPicture>. You can type in the name of your medication and then click on the link for that medication.

Another useful site to identify pills is at [http://www.drugs.com/pill\\_identification.html](http://www.drugs.com/pill_identification.html) where you will find the Pill Identification Wizard. After clicking on “I Agree,” you can then type in the drug name, imprint(s), shape or color.

If you are unable to identify your pill, please contact or visit your pharmacist who should be able to help you identify your medication.



## MEDICATION SIDE EFFECTS, DRUG ALLERGIES, & DRUG INTERACTIONS

Consumers and health care professionals can now go to a single Web page on the U.S. Food and Drug Administration's Web site to find a wide variety of safety information about prescription drugs at <http://www.fda.gov/Cder/drugSafety.htm>.

### MEDICATION SIDE EFFECTS

Every person is unique in how they respond to a particular medication. Side effects are not uncommon but can usually be managed or tolerated. Some side effects though may be harmful to your health or even life-threatening. It is important that you notify your health care professional of any side effects from the medications you are taking.

When you are taking any medicine, it is important to be aware of any change in your body. Tell your health care professional if something unusual happens.

It may be hard to know if an adverse reaction is caused by a medical problem or by your medicine. Tell your health care professional when your symptoms started and whether they are different from other symptoms you have had from an illness. Be sure to remind your health care professional of all the medicines you are taking.

The following are some adverse drug reactions that you might notice:

- |   |   |
|---|---|
| <input type="checkbox"/> Skin rash or itching (pruritus)            | <input type="checkbox"/> Drowsiness                             |
| <input type="checkbox"/> Headache                                   | <input type="checkbox"/> Confusion, mental / behavioral changes |
| <input type="checkbox"/> Dry mouth                                  | <input type="checkbox"/> Breathing difficulties                 |
| <input type="checkbox"/> Easy bruising or bleeding                  | <input type="checkbox"/> Abnormal heartbeat                     |
| <input type="checkbox"/> Edema (swelling)                           | <input type="checkbox"/> Increased blood pressure               |
| <input type="checkbox"/> Stomach distress - pain, nausea / vomiting | <input type="checkbox"/> Urinary retention                      |
| <input type="checkbox"/> Diarrhea or constipation                   |   |

### DRUG ALLERGIES

If you have a drug allergy, the medication can trigger an immune response. In other cases, as in a type of reaction to drugs such as aspirin or niacin, allergy-like symptoms may occur but do not involve the immune system. Like many other allergies, a drug allergy can cause a range of responses from a mild rash to life-threatening effects on many body systems.

When reviewing drug allergy information with your health care provider, it is important to differentiate drug intolerance or side effects (e.g., stomach upset) from true allergic reactions. Drug allergies should be documented appropriately in your medical record and should include a description of the reaction.



Some pain medicines such as opiate analgesics (e.g., morphine and meperidine) can stimulate histamine release that may seem like an allergic reaction. You may feel symptoms such as lightheadedness, dizziness, a fast heart rate, facial flushing, sweating, or itching. In some cases, the opiate analgesic can be continued with an antihistamine to treat these symptoms. If symptoms are severe, an opioid that is not associated with histamine release or a non-narcotic alternative may be substituted.

Allergic reactions to drugs can occur within hours or days to as much as three weeks after drug treatment is started. If you are allergic to a drug, you may experience itching, welts, swelling, and wheezing. An uncommon effect of drug allergy is a life-threatening reaction called anaphylaxis, which is a severe whole-body allergic reaction. Symptoms of anaphylaxis develop very quickly, usually in a matter of minutes. Symptoms may include abdominal pain or cramping, anxiety, confusion, difficulty breathing, dizziness, hives/itchiness, nausea/vomiting, skin redness, slurred speech, and wheezing.

You should notify your health care professional immediately or possibly seek emergency medical help depending on your symptoms. More information about drug allergies can be found at the Mayo Clinic web site at <http://www.mayoclinic.com/health/drug-allergy/HQ00582>. Another good source of information is on the National Jewish Medical and Research Center at <http://nationaljewish.org/disease-info/diseases/allergy/about/allergic-to/medications.aspx>.

## **DRUG INTERACTIONS**

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



## 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 health care professional to use a medication “off-label,” but your insurer, health plan, or pharmacist may question its use as recommended by your health care professional.

A drug is used off-label when the health care professional prescribes that drug for a medical use for a diagnosis other than the one that received FDA approval. Off-label prescribing is a commonly used and accepted medical practice. These drugs do have FDA approval, but for a different use. For example, health care professionals frequently prescribe FDA-approved anticonvulsant medications for persons who do not have seizures, but who have irritated nerves that need to be stabilized for improvement of mood and pain relief. When your health care professional prescribes an anticonvulsant medication for use as a mood stabilizer or for pain, it may be considered an off-label use.

Drugs can have more than one effect. 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, cardiac arrhythmias, and depression. The fact that a health care professional recommends such a drug does not mean that you have epilepsy or some other condition. The same is true with antidepressants; the fact that they are prescribed for chronic pain does not mean that the health care professional has made a diagnosis of depression.

The FDA (<http://www.fda.gov>) allows drugs to be sold and advertised for specific conditions in which data prove the drug is safe and effective for its intended use. Once on the market, drugs prescribed for “off-label” usage for any condition, particularly those with some clinical data of effectiveness. The process of obtaining approval for another use of the medication can be costly, so a company cannot fund research studies to prove all the uses for a drug. This approval issue 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 process of proving to the FDA that it is safe and effective for that condition. Some of the drugs used for chronic pain have not been approved by the FDA for pain even though they may have supportive clinical data. Indeed, drugs that have been FDA approved for a specific type of pain (e.g., diabetic nerve pain or postherpetic neuralgia) cannot be marketed for use in other pain conditions.

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 health care professional to explain to the authorizing party that the medication is being prescribed off-label and for what reason.

Further discussion about off-label medication use can be found at [http://www.painaction.com/members/article.aspx?id=4529&utm\\_source=patientnewsletter174&utm\\_medium=email&utm\\_campaign=offlabel\\_medication](http://www.painaction.com/members/article.aspx?id=4529&utm_source=patientnewsletter174&utm_medium=email&utm_campaign=offlabel_medication)



## IF MEDICATIONS ARE NOT WORKING

There are many treatments for chronic pain but unfortunately some people get worse, not better, with the use of pain medications.

If you have been taking pain medicine every day for a long time and they don't seem to be working to reduce pain and allowing you to do more – maybe something is wrong. After all, successful treatments should relieve distress and restore health, function, and well-being – so life gets back to normal or as close to normal as possible.

At the beginning, you probably went to the doctor because you were concerned about pain from an injury or medical condition that was disrupting your daily life. It is common for healthcare practitioners to prescribe various tests and treatments including medications. If months or even years have passed since then how well are the medications working for you now?

Some treatment methods other than the pain medications mentioned in this ACPA Resource Guide have been shown to work well and can be less hazardous – and more likely to restore a satisfying everyday life. Some methods are medical treatments and some are things you can do by yourself. Suffering can usually be greatly relieved by learning how the nervous system works, and by learning new skills. Multidisciplinary pain programs and organizations like this one, the American Chronic Pain Association, teach many specific self-care techniques. Mastering them will allow you to find relief and minimize the things that often make pain worse: stress, inactivity, uncertainty, feeling powerless, being out of shape, lack of sleep, boredom, fear, anger -- all the normal human reactions to pain and life disruption. Combining several methods often works the best.

If your life is still on hold and your pain level is still high after months or years of pain medicine use, it may be time to think about changing treatments. Your doctor may be able to prescribe other treatments with fewer side effects to help you manage the pain while you learn the self-care approaches that will help you get your life back on track. You can talk to your doctor about reducing or stopping prescribed medications so you can see whether you feel better overall. It can be dangerous as well as uncomfortable to do this rapidly or without medical supervision, especially if you are on high doses or are taking more than one medication.

The goal of pain care should be to find the right treatment or combination of treatments that allow you to increase your ability to function and regain the ability to engage in and enjoy everyday life activities. If that's not possible for you now, it's time to reconsider what you are doing, and try something else.

For a more detailed discussion and article, “If Opioids Have not Relieved Your Chronic Pain” go to <http://tinyurl.com/8aeas78>.



## MEDICATIONS FOR THE TREATMENT OF PAIN

There are four major classes of medications used in the treatment of chronic pain:

1. **Non-opioids:** aspirin, NSAIDs, and acetaminophen.
2. **Opioids** (also called narcotics, but the term narcotic should be avoided as it suggests illicit drug use to some). Examples of opioids include morphine, codeine, hydrocodone, oxycodone, etc.
3. **Adjuvant analgesics:** Medications originally used to treat conditions other than pain but now also used to help relieve specific pain problems; examples include some antidepressants and anticonvulsants.
4. **Other:** Medications with no direct pain-relieving properties may also be prescribed as part of a pain management plan. These include medications to treat insomnia, anxiety, depression, and muscle spasms.

Some medications are available over-the-counter without a prescription and some require a prescription.

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



## 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 following article is from the FDA: **Over-the-Counter Medicines: What's Right for You?** It can be found at

<http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/Choosingtherightover-the-countermedicineOTCs/UCM150312.pdf>.

The two most common types of OTC pain relievers are acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs).

Acetaminophen is an active ingredient found in more than 600 OTC and prescription medicines, including pain relievers, and for pain relief and fever reduction in cough suppressant and cold medication combinations.

NSAIDs are common medications used to relieve fever and minor aches and pains. They include aspirin, naproxen, and ibuprofen. They can be found in many combination medicines taken for colds, sinus pressure, and allergies. They act by inhibiting an enzyme that helps make specific chemicals in the body responsible for pain and inflammation.

The traditional OTC pain group currently includes aspirin (Bayer®), acetaminophen (Tylenol®), naproxen sodium (Aleve®), ibuprofen (Advil®, Motrin® IB), and various combinations.

Most analgesic 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® PM not only contains acetaminophen but also contains diphenhydramine hydrochloride (Benadryl®).

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 to understand what drug(s) you are taking and the maximum dosage. You need to read the medication's ingredients to know what you are



taking. Be sure that 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 health care professional 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.

You can find further information about OTC medicines from the American Academy of Family Physicians at <http://familydoctor.org/online/famdocen/home/otc-center.html>.

## THE SAFETY OF OTC MEDICATIONS

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

As mentioned, the most common OTC medications used for pain are nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.

The NSAIDs (aspirin, ibuprofen, and others) can reduce the stomach's protective mucous layer and natural protection against irritation of the stomach lining from stomach acid. Thus, they can be associated with gastric bleeding, and such risk increases with age, dose and duration of use. They also may cause kidney failure in people with damaged kidneys, liver disease, and certain other conditions such as high blood pressure. Use with diuretics can increase this danger. Finally, the use of these medications has been associated with increased risk of cardiovascular disease (CVD), particularly in patients with risk factors for CVD or a prior history of CVD. Individuals with any of these conditions should check with their health care professional before taking any NSAID medication.

The American Heart Association (AHA) recommends health care professionals change their approach to prescribing pain relievers for patients with or at risk for heart disease. Research in the AHA journal *Circulation* found that heart attack survivors who take NSAIDs face a significantly increased risk of a second heart attack or death.

OTC 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. There is often a mistaken belief that because the medication can be obtained without a prescription, that they are safe and without potential for harm. Nothing could be further from the truth.

For instance, acetaminophen is the medication most involved in overdoses which can be fatal but it is important to recognize the relative risk when compared to taking NSAIDs for chronic pain.

Remember OTC acetaminophen has been proven to be safe and effective when used as directed. When the labeled dosing of acetaminophen is not followed (overdose), serious liver damage may occur. In contrast, GI bleeds, injury and death from NSAIDs has been known to occur at labeled doses, especially in cases where it is used chronically.



Just remember that these OTC drugs are real medications and need to be taken as directed. It is important to discuss their use with a health care professional or pharmacist, especially if they are being combined with prescription medications.



## ACETAMINOPHEN SPECIAL COMMENTS

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 in those with liver problems, even at fairly low doses. The maximum recommended adult dose for acetaminophen is 4000 mg or 8 extra-strength 500 mg tablets in 24 hours (the FDA Panel on acetaminophen recommends up to 3000 mg or 3 grams a day in older persons). Patients can have elevations in liver enzymes (although often asymptomatic) at 2000 mg (2 grams), and some health care professionals encourage patients to stay well below the 4000 mg (4 grams) cut off. The FDA has reviewed the data on acetaminophen extensively and may establish new guidelines with a maximum dosage of 2600 mg (2.6 grams) per day

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.pdf>. (pg 9).

Those who consume little alcohol can usually safely use as much as is recommended on the package; however, the maximum recommended dose for heavy drinkers is 2000 mg (2 grams) or 4 extra-strength 500 mg tablets in 24 hours. If you consume moderate amounts of alcohol or already have liver disease, acetaminophen should only be taken under your health care professional's supervision.

If you see the abbreviation "APAP" on the label of a drug, it means the medicine contains acetaminophen. However, not all OTC and prescription drugs with acetaminophen will say APAP, so be sure to ask what is in the medicines you are prescribed *before* you take them. Some prescription medications have acetaminophen in them, see list below. You may see something like this written on the label on the bottle, Hydrocodone/APAP 5/500. The way to tell how much acetaminophen is in each tablet is to look at the number after the "/". In the example above, each tablet has 500 milligrams of acetaminophen in it. When calculating how much acetaminophen you take daily, be sure to include acetaminophen from all sources, both from prescription and OTC medications.

When acetaminophen is used in combination with NSAIDs, there is an increased risk of developing kidney abnormalities. This adverse event is often only seen with long-term use.

On January 13, 2011, the U.S. Food and Drug Administration (FDA) asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, including combination acetaminophen and opioid products, to no more than 325 mg per tablet, capsule, or other dosage unit. The FDA has stated that limiting the amount of acetaminophen per dosage unit in prescription products may reduce the risk of severe liver injury from acetaminophen overdosing.

Please visit the FDA website for more information on acetaminophen dosing: <http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm>

Acetaminophen is an ingredient in many OTC and prescription medicines. Here are some - *but not all* - of the most common *OTC and prescription drugs* that contain acetaminophen.



### Prescription Drugs with Acetaminophen\*

- Acetaminophen and Butalbital (Axocet<sup>®</sup>)
- Acetaminophen and Codeine Phosphate Oral Solution and Tablets (Tylenol<sup>®</sup> with Codeine)
- Acetaminophen, Isometheptene, and Dichloralphenazone Capsules (Midrin<sup>®</sup>)
- Butalbital, Acetaminophen and Caffeine Tablets (Esgic<sup>®</sup>, Fioricet<sup>®</sup>, Zebutal<sup>®</sup>)
- Hydrocodone Bitartrate and Acetaminophen Tablets, Capsules, Elixir (Lorcet<sup>®</sup>, Lortab<sup>®</sup>, Vicodin<sup>®</sup>, Norco<sup>®</sup>, Zydone<sup>®</sup>, Hydrocet<sup>®</sup>, Anexsia<sup>®</sup>)
- Oxycodone and Acetaminophen Tablets, Capsules, Elixir (Percocet<sup>®</sup>, Endocet<sup>®</sup>, Roxicet<sup>®</sup>, Tylox<sup>®</sup>)
- Pentazocine HCl and Acetaminophen Tablets (Talacen<sup>®</sup>)
- Tramadol and Acetaminophen Tablets (Ultracet<sup>™</sup>)

### OTC Drugs with Acetaminophen

- **Backaid<sup>®</sup>** Maximum Strength Backache Relief
- **Benadryl<sup>®</sup>** Allergy and Sinus Headache Caplets
- **Contac<sup>®</sup>** Day or Night Cold/Flu Caplets
- **CVS<sup>®</sup>** 8 Hour Acetaminophen Extended-Release Caplets/Cold and Flu Relief – Day- or Night-time Softgels/Infants' Non-Aspirin Suspension Drops/Non-Aspirin Children's Suspension/Non-Aspirin Extra Strength Gelcaps or Caplets/Sinus Headache Decongestant Caplets
- **Duane Reade<sup>®</sup>** Acetaminophen Tablets, Caplets, or Geltabs/Children's Acetaminophen Elixir/Extra Strength Acetaminophen Gelcaps, Geltabs, Caplets, or Tablets/Extra Strength Acetaminophen PM Caplets or Gelatin Caplets/Infant's Acetaminophen Drops
- **Excedrin<sup>®</sup>** Aspirin-Free Tension Headache/ Quicktabs Fast Dissolving Pain Reliever Tablets
- **FeverAll<sup>®</sup>** Infants' or Children's Acetaminophen Suppositories
- **HealthLine<sup>™</sup>** Acetaminophen Caplets Extra Strength
- **Inholtra<sup>®</sup>** Caplets With Acetaminophen
- **Legatrin<sup>®</sup>** Advanced Formula PM Pain Reliever-Sleep Aid Caplets
- **Pamprin<sup>®</sup>** Cramp Caplets/Multi-Symptom Caplets Maximum Strength
- **Percogesic<sup>®</sup>** Analgesic Acetaminophen Caplets Extra Strength/Analgesic Acetaminophen Tablets/ Aspirin-Free, Pain Reliever, Fever Reducer Tablets
- **Premysyn<sup>®</sup>** PMS Maximum Strength Premenstrual Syndrome Relief with Acetaminophen
- **Rite Aid<sup>®</sup>** Children's Acetaminophen, Non Aspirin, Oral Suspension Liquid/Complete Allergy-Sinus-Headache Caplets/Extra Strength Acetaminophen/Extra Strength Acetaminophen PM/ Infants' Acetaminophen, Non Aspirin, Suspension Drops/Non-Aspirin, Non-Drowsy Sinus Formula Geltabs Pain Reliever Nasal Decongestant
- **Sudafed<sup>®</sup>** Sinus & Cold Liquid Capsules
- **Theraflu<sup>®</sup>** Packets Severe Cold
- **Triaminic<sup>®</sup>** Cold, Cough and Fever
- **Tylenol<sup>®</sup>** 8 Hour Extended Relief/Allergy Sinus - Day or Night; Caplets, Gelcaps or Geltabs/Arthritis Pain Caplets/Chewable Tablets/Children's Cold Plus Cough Liquid/Children's Soft-Chews/Cold - Day or Night; Caplets or Gelcaps/Extended Release Caplets or Geltabs/Flu Gelcaps Day and Night/Infant Cold Drops/Junior Strength Soft-Chews or Chewable Tablets/Nighttime Liquid Severe Cold and Flu/PM Extra Strength/Severe Allergy Sinus - Day or Night/Sore Throat Maximum Strength Adult Acetaminophen Liquid
- **Vicks<sup>®</sup>** DayQuil LiquiCaps Non-Drowsy/DayQuil LiquiCaps or Liquid/NyQuil LiquiCaps or Liquid
- **Walgreens<sup>®</sup>** Arthritis Pain Relief Extended-Release Caplets/Extra Strength Acetaminophen Caplets, Tablets, Gelcaps or Geltabs/Extra Strength PM Gelcaps or Caplets/Regular Strength Acetaminophen Tablets



## NON-OPIOID PAIN RELIEVERS (NON-NARCOTIC)

Aspirin, NSAIDs, and acetaminophen are the most widely used medications for most pain conditions. But these drugs are not without risk. Unlike opioids, these medications have an analgesic “ceiling effect.” This means that after a certain dose, additional quantities do not provide added pain relief.

NSAIDs can cause gastric distress with ulceration and bleeding, while acetaminophen can cause liver toxicity, particularly when taken in excess. Fortunately, non-opioids do not produce physical or psychological dependence. There is some evidence suggesting that long-term use of common analgesics, such as aspirin, acetaminophen, or NSAIDs, appears to increase the risk for hypertension.

Aspirin and acetaminophen are available OTC while NSAIDs are available both by prescription and some by non-prescription OTC purchase. Additionally aspirin, acetaminophen and NSAIDs were available in combination with opioids by prescription.

These non-opioid analgesic pain relievers are effective for pain and fever. Aspirin and the NSAIDs are also indicated for pain that involves inflammation, whereas acetaminophen does not have anti-inflammatory activity.

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

The cyclooxygenase-2 (COX-2) inhibitors are NSAIDs that have a lower risk of gastrointestinal (GI) side effects with short-term use. Currently available in the United States is celecoxib (Celebrex<sup>®</sup>), which is more expensive than some other NSAIDs and does not provide any better pain relief. Although celecoxib is associated with a lower risk for developing a stomach ulcer when taken for less than 6 months, serious stomach ulceration can still occur without warning with this drug. As with other NSAIDs, individuals who take celecoxib should be monitored for this serious side effect. There is no evidence that some of the NSAIDs with similar COX-2 selectivity as celecoxib, such as meloxicam (Mobic<sup>®</sup>), etodolac (Lodine<sup>®</sup>, Lodine<sup>®</sup> XL), and nabumetone (Relafen<sup>®</sup>), have fewer GI side effects. NSAIDs additionally are associated with potential kidney effects and heart (cardiovascular) complications, especially when taken for prolonged periods. Remember also that when acetaminophen (Tylenol<sup>®</sup>) is used in combination with NSAIDs, there is an increased risk of developing kidney problems. This effect is usually only seen with long-term use.

While the increased risk of cardiovascular events, such as stroke and myocardial infarction, associated with COX-2 inhibitors has been well established, data are emerging that demonstrate similar risk increases associated with NSAIDs that are not selective for COX-2. Currently, data show that Celecoxib 200 mg or less per day does not seem to increase the risk of cardiovascular events any more than the risk associated with traditional NSAIDs. You are advised to discuss the risk-benefit ratio of NSAIDs with your health care professional. The risk of experiencing adverse



events or side effects with NSAIDs increases with the duration of use and the dose. Therefore, it is often recommended that you use these medications for the shortest period and at the lowest dose required to achieve therapeutic improvement. Individuals taking aspirin for its ability to protect the heart should consult with their health care professional prior to utilizing NSAIDs on a long-term basis. The regular use of NSAIDs inhibits aspirin's ability to protect the heart.

In order to improve the side effect profile of NSAIDs, topical NSAIDs have been developed and approved by the FDA.

Diclofenac Products\*: Diclofenac Gel (Voltaren® 1% Gel) has been approved for the treatment of chronic pain associated with osteoarthritis in joints close to the skin surface (e.g., hands, knees, and ankles). In 2007, a topical NSAID patch containing diclofenac (Flector®) was approved by the FDA for the treatment of acute pain due to minor strains, sprains, and contusions. In 2009, the FDA issued an advisory that transdermal and topical patches that contain metal, which includes Flector®, need to be removed prior to MRI procedures. In 2009, a topical solution of diclofenac sodium (Pennsaid®) was approved by the FDA for the treatment of signs and symptoms of knee osteoarthritis.

**\*Warning:** All Diclofenac products are not recommended as first line due to increased risk profile for cardiovascular events (heart attack and stroke) and for increased risk of liver dysfunction (use has resulted in liver failure and death). With the lack of data to support superiority of diclofenac over other NSAIDs and the possible increased hepatic and cardiovascular risk associated with its use, alternative analgesics and/or non-pharmacological therapy should be considered.

Intravenous (IV) formulations of the NSAIDs ibuprofen (Caldolor®) and ketorolac (Toradol®) are given most often in the inpatient setting to manage moderate to severe pain in adults; ketorolac may also be given intramuscularly (IM). In November 2010, IV acetaminophen (Ofirmev®) was FDA approved for the management of mild to moderate pain, severe pain with adjunctive opioid analgesics, and reduction of fever in adults and children 2 or more years old. Similar to the IV NSAIDs, IV acetaminophen is administered in an inpatient setting and helps reduce the amount of opioid medication needed to manage pain. Unlike, oral acetaminophen, IV acetaminophen has been approved for dosages of up to 4 gms per day per the FDA approval and the fact that it is for short-term inpatient therapy. The side effect profile for IV acetaminophen is the same as other acetaminophen dosage forms: headache, agitation, nausea, vomiting, and constipation. Injection site reactions such as redness and swelling may occur with any of the IV non-opioids.



## GASTROINTESTINAL (GI) PROTECTIVE MEDICATIONS

As has been mentioned earlier, the NSAID medications can increase your risk of ulcers and other problems with your stomach and digestion. Often people are prescribed an additional medication to help protect their GI system, sometimes called cytoprotective medications, which are medications that protect cells from noxious chemicals or other harmful stimuli.

There are four commonly used cytoprotective classes of drugs:

1. Misoprostol (Cytotec<sup>®</sup>) - often combined with diclofenac and distributed as Arthrotec<sup>®</sup>
2. Sucralfate (Carafate<sup>®</sup>)
3. Histamine type 2 (H<sub>2</sub>) receptor blockers: famotidine (Pepcid<sup>®</sup>), nizatidine (Axid<sup>®</sup>), ranitidine (Zantac<sup>®</sup>), cimetidine (Tagamet<sup>®</sup>), etc.
4. Proton pump inhibitors (PPIs): esomeprazole (Nexium<sup>®</sup>), lansoprazole (Prevacid<sup>®</sup>), omeprazole (Prilosec<sup>®</sup>), pantoprazole (Protonix<sup>®</sup>), rabeprazole (Aciphex<sup>®</sup>).

Taking cytoprotective agents along with your NSAID pain medication is recommended for individuals who will benefit from an NSAID but also have a high GI risk factor profile. Individuals considered being at elevated risk include those with a history of prior GI bleed/uncomplicated ulcer or *H. pylori* infection, the elderly, diabetics, cigarette smokers and those with concurrent use of aspirin (including low dose), corticosteroids or anticoagulants (blood thinners). Long-term NSAID treatment increases the risk among those most susceptible, although any patient can potentially develop an adverse effect at any time.

PPIs have been shown to reduce the risk of GI ulcers and are recommended by the American College of Gastroenterology in individuals with moderate to high GI risk and are taking an NSAID. A study published in 2006 raised concerns because the chronic use of PPIs might have a significant impact on the rate of hip fractures. The authors think that acid-suppressive therapy may increase the risk of hip fractures by decreasing calcium absorption. Thus, as with all medications, PPIs must be used with caution, and the disadvantages must be weighed against the benefits.

Misoprostol (Cytotec<sup>®</sup>) mimics naturally occurring prostaglandins in the body. Prostaglandins play many roles, which include regulating blood pressure, the amount of stomach acid secretion, body temperature, and platelet aggregation; controlling inflammation; and affecting the action of certain hormones. Misoprostol inhibits gastric acid secretion via direct interaction on stomach cells called parietal cells. Misoprostol also exhibits mucosal protective effects which enables it to be a positive treatment for stomach ulcers. Prostaglandins increase the contraction ability in the uterus, so females should not take misoprostol if pregnant or planning to become pregnant.

Sucralfate (Carafate<sup>®</sup>) works via interactions with hydrochloric acid found in the stomach. The combination forms a paste-like substance, which forms a protective coating that acts locally to protect the stomach lining.



Treatment with antacids, such as TUMS<sup>®</sup>, and H<sub>2</sub> blockers offers little if any protection against duodenal and gastric ulcers. Many of the studies on H<sub>2</sub> blockers show that they have no value in the protection of the gastric mucosa.



## NON-OPIOID ANALGESIC DRUGS & THEIR USES

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

Medications (Generic) and Brand Names*	May Be Useful for	Pros	Cons	Comments
<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> choline salicylate Arthropan® Choline magnesium trisalicylate Trilisate®	Pain, osteoarthritis, and rheumatoid arthritis.	Fewer GI side effects than other NSAIDs.	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 than NSAIDs; safer for children. Does not promote bleeding (or protect against heart attack, stroke).	Does not reduce inflammation; may be less effective than aspirin for soft tissue pain.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily. May increase bleeding time in individuals receiving anticoagulation therapy.
<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. Cardiovascular risks.	May be harmful for people with kidney or liver disease, asthma, bleeding disorders, or those who drink alcohol heavily.
<b>Ketoprofen</b> Orudis® 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. Cardiovascular risks.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily. Not recommended for children without a health care professional'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. Cardiovascular risks.	Not recommended for children without a health care professional'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. Cardiovascular risks.	Generally well-tolerated but still need to be concerned about GI side effects.
<b>COX-2 Inhibitors</b> Celebrex®	Muscle aches, joint pain, arthritis, pain and inflammation.	Helps reduce inflammation; less stomach irritation than other NSAIDs.	Still a risk for stomach irritation. Tends to cost more. Cardiovascular risks.	Generally well-tolerated but still need to be concerned about GI side effects. No effect on bleeding time. 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) – see comments below
- Diflunisal (Dolobid<sup>®</sup>)
- Etodolac (Lodine<sup>®</sup>, Lodine<sup>®</sup> XL)
- Fenoprofen (Nalfon<sup>®</sup>)
- Flurbiprofen (Ansaid<sup>®</sup>)
- Ibuprofen (Caldolor<sup>™</sup>) - NSAID available intravenous for acute pain and fever
- Indomethacin (Indocin<sup>®</sup>, Indocin<sup>®</sup> SR)
- Ketorolac (Toradol<sup>®</sup>, others) – NSAID injectable formulation (intramuscular and intravenous)
- 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 medication's manufacturer.

**Diclofenac Warning: All diclofenac products are not recommended as first line due to increased risk profile for cardiovascular events (heart attack and stroke) and for increased risk of liver dysfunction (use has resulted in liver failure and death). With the lack of data to support superiority of diclofenac over other NSAIDs and the possible increased hepatic and cardiovascular risk associated with its use, alternative analgesics (pain medications) and/or non-medication therapy should be considered.**



# OPIOID ANALGESIC PAIN RELIEVERS

## THE OPIOID DILEMMA

Considerable controversy exists about the use of opioids for the treatment of chronic pain of non-cancer origin. Many health care professionals think 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 along with increasing side-effects in some 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 an increase in the person's level of functioning, a reduction or elimination of pain complaints, a more positive and hopeful attitude, and when side effects are minimal or controllable.

Opioids are not harmless drugs. The dilemma with the long-term use of opioids is that while opioid treatment may be prescribed to reduce pain and improve function, the treatment may actually result at times in just the opposite.

It is well known that in the opioid naïve (someone new to opioid use) patient, the use of opioids may heighten the risk of accidental death from respiratory (breathing) depression.

It is well known that prolonged use of opioids may result in problems including tolerance, hyperalgesia (increased pain sensitivity), hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses, etc.), depression, impaired sleep patterns, and suppression of the immune system. The long-term use of opioids may also impair functional improvement in an individual's recovery from surgery or with long-standing musculoskeletal disorders.

Research shows that long-term 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.

Fifty-one percent of all patients taking oral opioids experience at least one adverse event/effect. Approximately 20% of all patients taking oral opioids discontinue their use because of an adverse event or an associated side effect.

While tolerance may develop and the individual may be prescribed higher doses of opioids over time, there is still increased risk of death as the dose of opioids increases.



In an article published by the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, titled Increase in Fatal Poisonings Involving Opioid Analgesics in the United States, 1999–2006, opioid poisoning was noted to be the second leading cause of injury death overall and the leading cause of injury death for people ages 35–54 years, surpassing both firearm- related and motor vehicle-related deaths in this age group. The number of poisoning deaths and the percentage of these deaths involving opioid analgesics increased each year from 1999 through 2006.

Due to the seriousness of this problem, the FDA is now requiring that special safety procedures called REMS (Risk Evaluation and Mitigation Strategies) be put into place to protect people. One of the components of REMS requires that patients who receive opioids must be given an informational brochure called a Medication Guide for the specific drug they receive each time they get a new prescription. The Medication Guide is designed to inform patients about the serious risks associated with the drug. It should be read each time a new prescription is received, even if the specific opioid being used has not changed, since there may be important new information added. The FDA is also working in cooperation with other governmental agencies, state professional licensing boards, and societies of healthcare professionals to increase prescribers' knowledge about appropriate prescribing and safe use of opioids. There is renewed emphasis on home storage and safe disposal of unused medication to help patients protect their families and the continued availability of opioids to patients.

## WHAT ARE OPIOIDS?

### OPIOID AGONISTS

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 naturally occurring (opiate), synthetic (opioid), and semisynthetic forms.

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.

Examples of opioid agonists include morphine, hydromorphone, fentanyl, and oxycodone. There are a number of opioid receptors in the body that mediate analgesia. In 1975, it was discovered that the body generates its own (internal or endogenous) opioids (called endorphins, enkephalins, and dynorphins).

There are numerous opioids available by prescription (see chart below). 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.

There are both short- and long-acting opioid formulations. Some opioids are used around-the-clock in scheduled doses, while others are used as needed for intermittent or breakthrough pain.



## OPIOID MIXED AGONISTS/ANTAGONISTS

There are a number of opioid analgesics (pain relievers) that are partial agonists and mixed agonists/antagonists. The mixed agonists/antagonists are characterized as having an analgesic “ceiling” effect in which the analgesic benefit plateaus, and no further benefit is obtained by increasing the dose.

Given their antagonist nature, these medications can reverse the effects (analgesia and side effects) of full agonist opioids, such as morphine, fentanyl, hydromorphone, and oxycodone, and therefore should be used with caution in those taking a full agonist opioid. A partial agonist/antagonist is occasionally initiated in a person already taking an agonist opioid. The doses should be adjusted gradually to avoid symptoms of opioid withdrawal. In most cases, these two types of agents should not be used together.

Symptoms of withdrawal include sweating, gooseflesh or goose bumps (a temporary local change in the skin when it becomes rougher due to erection of little muscles, as from cold, fear, or excitement), runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your health care professional or pharmacist if you have these or other side effects.

## OPIOID DELIVERY

Opioids are available orally (by mouth), intravenously, by intramuscular injection (although not recommended), via nasal spray, transdermally (through the skin), oral transmucosally (absorbed under the tongue and the inside of the cheek), buccally (absorbed via the inside of the cheek), sublingually (absorbed under the tongue), via suppository, an epidural (injection of an anesthetic into the lumbar area of the spine in the space between the spinal cord and the covering dura), and intrathecal drug delivery (injection into the sheath surrounding the spinal cord – also see discussion on Implanted Intrathecal Drug Delivery Systems - “Pain Pumps”).

## SHORT-ACTING AND LONG-ACTING OPIOID AGONISTS

Short-acting oral opioids, also called immediate-release (IR) opioids, often contain an opioid as the only active ingredient (e.g., morphine, hydromorphone, oxycodone, and oxymorphone), while others contain a combination of an opioid and a non-opioid such as acetaminophen or ibuprofen.

Examples of short-acting opioid combination products include:

- oxycodone with acetaminophen (Percocet<sup>®</sup>)
- oxycodone with aspirin (Percodan<sup>®</sup>)
- oxycodone with ibuprofen (Combunox<sup>®</sup>)
- hydrocodone with acetaminophen (Lorcet<sup>®</sup>, Lortab<sup>®</sup>, Vicodin<sup>®</sup>, Norco<sup>®</sup>)



- hydrocodone with ibuprofen (Vicoprofen®)
- tramadol hydrochloride with acetaminophen (Ultracet®)

Short-acting oral opioids, true to their description, exert a rapid-onset but short-lived therapeutic effect. These agents typically start working 15–30 minutes after administration, with peak analgesic effect within 1–2 hours. Sustained pain relief is maintained for only about 4 hours. They are a potent option for treating acute pain (e.g., from a serious athletic injury or after a root canal) and are usually prescribed for pain that is anticipated to last only a few days.

Because of their short half-life and rapid clearance from the body, short-acting opioids must be taken every 3–4 hours. Therefore, these drugs are not ideal for long-term therapy of chronic pain. Short-acting opioids may be effective, however, as an initial “trial” therapy in patients with moderate or severe chronic pain who have not previously received opioid treatment. In this case, short-acting agents are used to establish an individual patient’s response and tolerance to opioid therapy and lay the groundwork for long-term dosing of long-acting opioid therapy.

In addition to their importance in managing acute pain and initiating therapy for chronic pain, short-acting agents can be used with a long-acting agent during long-term therapy as “rescue medication.” Rescue medication may be necessary for addressing breakthrough pain that occurs despite ongoing, long-term analgesic treatment.

Long-acting (sometimes called slow-release) medications are the opioid treatment of choice for patients with continuous moderate to severe chronic pain. They have a more lasting therapeutic effect than short-acting agents. Long-acting formulations are described as having sustained, extended, or controlled release of drug and are abbreviated as SR, ER, or CR, respectively.

Examples of long-acting opioids include:

- morphine (oral sustained release, e.g., MS Contin®, Avinza®, Kadian®)
- oxycodone (oral controlled release, e.g., OxyContin®)
- oxymorphone (oral extended release Opana® ER)
- hydromorphone (oral extended release EXALGO®)
- methadone (oral) (e.g., Dolophine®, Methadose®)
- fentanyl transdermal system (Duragesic®)

The prolonged effects of these agents are due to their long half-lives or slow delivery into the body via controlled-release opioid preparations. Because of the slower release of active drug, long-acting opioids can provide prolonged, steady pain relief for 8–12 hours. Long-acting drug preparations are given at regularly scheduled times, such as every 12 hours. Hydromorphone EXALGO® is a once-daily medication with reported sustained blood levels for 18-24 hours.

**Slow-release tablets should be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed slow-release pills can lead to rapid release and absorption of a potentially fatal dose of the drug.**



<b>Examples of Medical Opioid Agonists*</b>	
<b>Codeine</b> (with acetaminophen -Tylenol <sup>®</sup> with codeine No. 2, No. 3, No. 4)	Codeine is metabolized by the liver to morphine. Some individuals do not have the enzyme required to convert codeine to morphine, and therefore the medication is ineffective. Even though they do not receive benefit, they are still at risk for the associated side effects. Codeine often is associated with higher levels of nausea and vomiting and constipation compared to other opioids.
<b>Dihydrocodeine bitartrate, Aspirin, Caffeine</b> (Synalgos-DC <sup>®</sup> )	This combination drug of dihydrocodeine, aspirin and caffeine is rarely prescribed in chronic pain states.
<b>Fentanyl</b> (Actiq <sup>®</sup> lozenge, Fentora <sup>®</sup> buccal tablet and ONSOLIS <sup>™</sup> buccal film, Abstral <sup>®</sup> buccal film, Duragesic <sup>®</sup> transdermal patch, Lazanda <sup>®</sup> nasal spray)	<p>There have been reports of death and other serious side effects from overdoses while on fentanyl transdermal patches. Furthermore, patients that have not been on opioids (opioid naïve) should not be initially started on the fentanyl transdermal patch because of the inherent inaccuracies in dosing which can lead to an overdose. Exposure to heat (hot bath, heating pad, hot sun, etc.) can increase the speed of fentanyl release. The directions for using the fentanyl skin patch must be followed exactly to prevent death or other serious side effects from overdose. Do not cut fentanyl patches.</p> <p>Oral transmucosal fentanyl is available in multiple formulations for the treatment of breakthrough pain in cancer patients receiving opioid treatment and who have become tolerant to it. The FDA warns that serious adverse events, including deaths, can occur in patients treated with oral fentanyl. The deaths that have occurred were due to respiratory depression as a result of improper patient selection, improper dosing, and/or improper product substitution.</p> <p>Actiq<sup>®</sup> (oral transmucosal fentanyl lozenge on a plastic stick) is absorbed by swabbing the drug-containing lozenge over and under the tongue and between the cheeks and gums. It is contraindicated for acute postoperative pain and migraine headache.</p>
<b>Hydrocodone</b> <ul style="list-style-type: none"> <li>• With <b>acetaminophen</b> – Anexsia<sup>®</sup>, Lorcet<sup>®</sup>, Lortab<sup>®</sup>, Norco<sup>®</sup>, Vicodin<sup>®</sup>, Hycet<sup>®</sup>, Xodol<sup>®</sup>, Co-Gesic<sup>®</sup>, Zydone<sup>®</sup></li> <li>• With <b>ibuprofen</b> – Reprexain<sup>™</sup>, Vicoprofen<sup>®</sup></li> <li>• With <b>aspirin</b> – Azdone, Lortab ASA, Panasal</li> </ul>	Hydrocodone is a short-acting opioid available only in combination with other ingredients, and different combination products are prescribed for different uses. Some hydrocodone products are used to relieve moderate to severe pain. Other hydrocodone products are used to relieve cough.
<b>Hydromorphone</b> (Dilaudid <sup>®</sup> , Dilaudid-5 <sup>®</sup> , EXALGO <sup>®</sup> )*	EXALGO <sup>®</sup> tablets are an extended-release oral formulation.
<b>Levorphanol</b> (Levo-Dromoran <sup>®</sup> )	Levorphanol has the same properties as morphine with respect to the potential for habituation, tolerance, physical dependence and withdrawal syndrome. It is 4 to 8 times as potent as morphine and has a longer half-life.
<b>Meperidine</b> (Demerol <sup>®</sup> )	Due to its low potency, short duration of action, and unique toxicity (i.e., seizures, delirium, and other neuropsychological effects) relative to other available opioid analgesics, meperidine has fallen out of favor and is not recommended or typically used in chronic pain states.



### Examples of Medical Opioid Agonists\*

<p><b>Methadone</b> (Dolophine®, Methadose®)</p>	<p>Although methadone possesses analgesic properties, it must be used carefully and with a great deal of caution. It has a long half-life and can accumulate in the body which can lead to an overdose. It interacts with a large number of other medications, including OTC drugs. It is strongly recommended that the individual on methadone not use any OTC or herbal medications without clearing them with the prescribing health care professional. The addition of other commonly used pain medications (e.g., antidepressants, anticonvulsants, and NSAIDs) can increase the likelihood of methadone negatively influencing the heart's ability to conduct electrical signals properly. Prior to starting methadone, patients should undergo an electrocardiogram to check for any pre-existing heart abnormalities that may contraindicate its use. Methadone can also be associated with the development of central sleep apnea. Benzodiazepines should be utilized with extreme caution by individuals on methadone secondary to the synergistic negative respiratory and cardiac effects.</p>
<p><b>Morphine</b> (Avinza™, Duramorph®, Kadian®, MS-Contin®, Oramorph SR®)*</p>	<p>Morphine is considered to be the prototypical opioid and is available in many formulations.</p>
<p><b>Oxycodone</b> (OxyContin®, OxyIR®, Roxicodone™, Oxecta®)</p> <ul style="list-style-type: none"> <li>• Combunox® (containing ibuprofen, oxycodone)</li> <li>• Endocet® (containing acetaminophen, oxycodone)</li> <li>• Endodan® (containing aspirin, oxycodone)</li> <li>• Lynox® (containing acetaminophen, oxycodone)</li> <li>• Magnacet® (containing acetaminophen, oxycodone)</li> <li>• Narvox® (containing acetaminophen, oxycodone)</li> <li>• Percocet® (containing acetaminophen, oxycodone)</li> <li>• Percodan® (containing aspirin, oxycodone)</li> <li>• Perlox® (containing acetaminophen, oxycodone)</li> <li>• Primlev® (containing acetaminophen, oxycodone)</li> <li>• Roxicet® (containing acetaminophen, oxycodone)</li> <li>• Roxiprin® (containing aspirin, oxycodone)</li> <li>• Taxadone® (containing acetaminophen, oxycodone)</li> <li>• Tylox® (containing acetaminophen, oxycodone)</li> <li>• Xolox® (containing acetaminophen, oxycodone)</li> </ul>	<p>Recently, the manufacturer of OxyContin® reformulated its product. The previous OxyContin® product contained an immediate-release component (38%) as well as an extended-release component (62%). The reformulated OxyContin® is 100% extended-release. The reformulated OxyContin® is harder to crush or chew and therefore serves as a better deterrent for abuse. The previous OxyContin® had an imprint of "OC" on the tablet, whereas the reformulated OxyContin® has an imprint of "OP." There is currently no generic for the reformulated OxyContin®, which is the only form available in the United States. With the older formulation, many patients experienced euphoria, which was essentially due to the initial high levels of the oxycodone in the blood. Often times the euphoria feeling has been equated with better pain control, although research has not shown this to be the case. The new tablet formulation takes longer to reach peak levels, which can be incorrectly associated with inadequate pain control.</p>
<p><b>Oxymorphone</b> (Numorphan®, Opana® and Opana® ER)*</p>	<p>Opana® ER is an extended-release crush resistant oral formulation of oxymorphone.</p>
<p><b>Tapentadol</b> (Nucynta®, Nucynta® ER)*</p>	<p>Tapentadol is an opioid with both opioid and nonopioid activity. The drug binds to opioid receptors and also inhibits the reuptake of the neurotransmitter norepinephrine. The dual mechanism of action inhibits the transmission of pain signals in both the ascending and descending pathways. In pre-clinical studies, this drug has a lower affinity than morphine for the opioid receptor. The short-acting formulation is approved for acute pain treatment, and the extended-release formulation is approved for continuous moderate to severe chronic pain. Tapentadol may have an improved GI side effect profile in comparison with other opioids.</p>



### Examples of Medical Opioid Agonists\*

**Tramadol (Ultram<sup>®</sup>, Ultram<sup>®</sup> ER)\* and Tramadol combined with acetaminophen (Ultracet<sup>™</sup>)** considered a “weak” opioid

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. While a weak opioid, tramadol is not completely free of this risk and may trigger addiction even in those without a history of drug abuse or previous addiction. Tramadol reduces the respiratory rate to a lesser extent than opioids in overdoses and does not cause the sort of GI 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 such as certain antidepressants. Since tramadol is a centrally acting synthetic analgesic, not an 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). Tramadol should be used cautiously, if at all, in patients with underlying liver and kidney disease.

**\* Slow-release (e.g., extended-release, controlled-release, and sustained-release) oral opioid formulations should be swallowed whole and are not to be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed slow-release pills can lead to rapid release and absorption of a potentially fatal dose of the drug.**



<b>Examples of Medical Opioid Mixed Agonists/Antagonists</b>	
<b>Buprenorphine</b> (Buprenex <sup>®</sup> , Butrans <sup>™</sup> Transdermal, Subutex <sup>®</sup> ) - also used for the treatment of opioid dependence	In addition to its use for the treatment of chronic pain, buprenorphine is used to help alleviate unpleasant withdrawal symptoms associated with opioid detoxification. Buprenorphine exhibits a ceiling effect, which means increasing the dose of buprenorphine beyond a certain point results in no additional pain control. Doses greater than 32 mg / day are ineffective. The ceiling effect demonstrated with buprenorphine offers advantages when compared to other medications used to manage addiction because there is a lower abuse potential, lower level of both physical dependence and withdrawal, and there is a decreased incidence of dose related side effects.
<b>Buprenorphine/naloxone</b> (Suboxone <sup>®</sup> ) - also used for the treatment of opioid dependence	Buprenorphine/naloxone (Suboxone <sup>®</sup> ) is a combination drug. Naloxone is a pure opioid antagonist, meaning it blocks the effects that opioid drugs have on the receptors. When given sublingually, naloxone has no significant effects on buprenorphine. However if Suboxone <sup>®</sup> is crushed or injected, naloxone will block the effects of buprenorphine. This characteristic discourages misuse. If Suboxone <sup>®</sup> is swallowed instead of dissolved under the tongue, the patient may experience no effect due to the poor bioavailability and first pass metabolism. Naloxone inhibits respiratory depression, hypotension, sedation, and analgesia.
<b>Butorphanol</b> (Stadol <sup>®</sup> )	Available in injection or nasal spray formulations but not typically used for chronic pain treatment.
<b>Nalbuphine</b> (Nubain <sup>®</sup> )	Administered subcutaneously, intramuscularly or intravenously but not used for chronic pain treatment.
<b>Pentazocine</b> (Talwin <sup>®</sup> ; with acetaminophen-Talacen <sup>®</sup> ; with aspirin-Talwin <sup>®</sup> Compound)	Side effects are similar to those of morphine, but pentazocine may be more likely to cause hallucinations and other psychosis-like effects. Not used for chronic pain treatment.
<b>Pentazocine/naloxone</b> (Talwin <sup>®</sup> NX)	Talwin <sup>®</sup> NX is a combination of pentazocine and naloxone, an opioid antagonist. This oral formulation was developed to prevent tampering and reduce abuse. The goal of this drug design is to reduce the possible misuse of this medication when it is tampered with by crushing, chewing, or injecting. If the drug is taken as directed, the naloxone will not release and will pass through the body with no effect.



## **ALERT: PROPOXYPHENE (DARVON®, DARVOCET®) – DISCONTINUED FOR SALE IN THE USA**

In December 2010, propoxyphene, the active ingredient found in Darvocet® and Darvon®, a mild opioid analgesic structurally related to methadone, was discontinued for sale in the United States by the manufacturer. Propoxyphene is an opioid pain reliever that was used for many years for treatment of mild to moderate pain. Even when used at therapeutic doses, propoxyphene can lead to heart problems better known as arrhythmias, although the risk of this goes away when the medication is discontinued. Furthermore, propoxyphene has not been shown to alleviate pain any better than acetaminophen. If you have been previously prescribed propoxyphene, contact your health care professional as soon as possible to be switched to another medication to adequately manage pain. Do not abruptly stop taking this medication. It is best to titrate down to avoid withdrawal symptoms such as anxiety, diarrhea, nausea, and shaking. The health care professional may recommend switching to an NSAID, tramadol, tapentadol, or opioid therapy to best accommodate you. Propoxyphene tablets must be properly disposed. Unused propoxyphene should be disposed of in the following manner set forth by the Federal Drug Disposal Guidelines. Before throwing propoxyphene in the trash, take it out of the original container and mix it with coffee grounds or cat litter. By doing so, the drug becomes unattractive for any interested party, including children and pets. Finally, place the unused medication (with the coffee grounds or cat litter) in a zip lock bag or empty can and place it into the garbage bag.



## GENERAL 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 can usually be treated with dose adjustments, wane over time (with the exception of constipation), or can be offset by other alternate medications. Psychostimulants (see below) can be useful in selected patients to treat mild sedation.

Approximately 40% of individuals taking opioid therapy for non-cancer pain experience constipation (less than three bowel movements per week) secondary to opioid treatment. Most individuals taking opioid medications will not develop tolerance to the side effect/adverse effect of constipation. Therefore, an effective preventive bowel regimen including diet changes and a stimulant laxative plus a stool softener will have to be maintained throughout the course of opioid treatment. Even individuals that utilize appropriate laxative therapy often still experience constipation that may impede the appropriate use of opioid pain medication and thus result in higher levels of pain, so attention to and prevention of this side effect is essential.

Non-pharmacological interventions that can be taken to assist with constipation include: 1) increasing dietary fiber intake, 2) increasing fluid intake, 3) increasing physical activity, and 4) encouraging daily bowel movements at the same time, often after a meal. Pharmacological treatments that can be utilized include stool softeners and stimulant laxatives. In cases that do not respond, other forms of laxative treatment can be considered. Bulk forming laxatives, such as psyllium, are often not useful and can actually worsen opioid-induced constipation by producing colon obstruction. New approaches to treating opioid-induced constipation are being developed. Currently, these new medications have only been FDA approved for the postoperative period and the treatment of opioid-induced constipation in patients with advanced illness.

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 is also common with opioid therapy. It can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be appropriate.

A side effect of long-term opioid use is a decrease in certain hormones, particularly sex hormones. This reduction may cause you to lose your 'sex drive', sometimes called libido. This tends to be associated with using these medications regularly for many years.

A serious side effect, particularly in opioid-naïve individuals (those who have not been taking opioids regularly), is respiratory depression (slowed rate of breathing or loss of urge to breathe). Tolerance to respiratory depression occurs with regular opioid use.

A genuine allergy to opioids is very rare. If an allergy does occur, opioids from another class should be chosen. For example, morphine, hydromorphone, oxycodone, and oxymorphone belong to the same class of opioid. Fentanyl and meperidine belong to a different class.



## Summary of Possible Opioid Side Effects

- Central nervous system
  - A sense of emotional well-being and euphoria.
  - Drowsiness, sedation, and sleep disturbance.
  - Hallucinations.
  - Potential for diminished psychomotor performance.
  - Dysphoria and agitation.
  - Dizziness and seizures.
  - Aberrant behavior (see addiction definition below).
  - Hyperalgesia (see definition below).
  
- Respiratory system
  - Respiratory depression is rare but the most serious adverse effect and may result from toxicity.
  - Diminution of pain or pain relief by other modalities may exacerbate respiratory depression.
  
- Ocular system
  - Constriction of the pupil of the eye.
  
- Gastrointestinal system
  - Constipation, nausea and vomiting.
  - Delayed gastric emptying.
  
- Genitourinary
  - Urinary retention.
  
- Endocrine
  - Hormonal and sexual dysfunction.
  
- Cardiovascular
  - Decreased blood pressure.
  - Slowed heart rate.
  - Peripheral edema (swelling).
  
- Musculoskeletal system
  - Muscle rigidity and contractions.
  - Osteoporosis.
  
- Skin system
  - Itching is common and not an allergic reaction.



- Immune system
  - There are data suggesting that long term administration of opioids suppresses the immune system. Research is being conducted to determine its clinical significance.
  
- Pregnancy & Breast Feeding
  - All opioids cross the placenta.
  - No teratogenic effects have been observed.
  - Neonatal central nervous system depression can occur if opioids are used during labor; attention to peak times is essential.
  - Use with caution in breast feeding; appropriate timing of opioid dose administration is important for safe opioid use during breast feeding.
  
- Analgesic Tolerance
  - Decreased duration of analgesia and then decreased effectiveness.
  
- Withdrawal Syndrome
  - Withdrawal symptoms may occur with abrupt opioid cessation and can include runny nose, shivering, “gooseflesh,” diarrhea, and dilation of the pupil of the eye.



## DEFINITION OF TERMS REGARDING OPIOIDS

**Opioid-responsiveness** is the ability to achieve pain relief with evidence of improved function without the development of unmanageable or intolerable side effects.

**Opioid-induced Hyperalgesia** is a controversial concept that continued opioid use can cause increased sensitivity to painful stimuli, worsening pain despite increasing doses of opioids, and pain that becomes more diffuse, extending beyond the distribution of pre-existing pain. This syndrome may reduce the clinical usefulness of opioids in treating chronic pain and require a reduction in dose or detoxification.

**Addiction** is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. 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.

**Addiction** should be distinguished from **physical dependence** (see below). *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,
- ❑ Inability to consistently **C**ontrol the quantity used,
- ❑ **C**raving the psychological 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 health care professionals/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.

An example of 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 and driving despite convictions for driving under the influence, or using analgesics and tranquilizers despite their having an adverse effect on the 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.

People sometimes worry that they may become addicted to their opioid pain medications. Factors which may increase your risk are if you or someone in your family have or have had a problem with drugs or alcohol in the past or you have a serious problem with anxiety, depression or other emotional health problem. People with a past history of adverse childhood experiences (including sexual abuse) during childhood or adolescence are also at risk; talk to your health care professional.

Let your health care professional know if you have ever had a problem with drugs or alcohol in the past or are currently using drugs or alcohol, or if many family members have this problem, as these are important in determining if opioid pain medications are right for you.

Similarly, let your health care professional know if you are concerned about becoming addicted to your opioid pain medications. Signs to be aware of include taking more medication than prescribed without checking with your health care professional first, loss of control over the medication, feelings of craving the medication or taking the medication for the euphoric (mental) effects rather than for pain relief.

**Pseudo-addiction** describes a syndrome of poorly or under-treated pain, which in certain patients may be inaccurately labeled as having substance abuse or addiction. Patients develop feelings of anger and isolation, which lead to acting-out behavior. Inadequate pain management often leads to pseudo-addiction. It commonly involves an ineffective medication or inadequate medication prescribing either by excessive intervals between allowed doses or inadequate doses. Pseudo-addiction may come about because the healthcare provider may be inadequately educated about pain management or have an excessive fear of causing addiction.

**Chemical Copers:** Some individuals demonstrate inappropriate medication use but not to the level of addiction and are not likely to display a severity that rises to the level of compulsivity or loss of control. In addition, they are not likely to display behaviors indicative of drug cravings, which would convince a clinician to diagnose addiction. Simply put, chemical copers occasionally use their medications in non-prescribed ways to cope with stress. One example is using pain



medications to fall asleep. A major hallmark of chemical coping is the overly central place in the person's life that is occupied by obtaining drugs for pain and a corresponding inflexibility about nondrug components of care. The use of medications becomes central in the chemical copers' life while other interests become less important. As a result, they often fail to move forward with psychosocial goals and are usually uninterested in treating pain non-pharmacologically; that is, they do not take advantage of other treatment options provided (i.e., functional restoration), such as exploring recommendations to see psychologists or physical therapists. Further, they remain on the fringe of appropriate use of their medication but are able to comply with their health care professional's opioid agreement enough to avoid being removed from treatment. Chemical copers often self-escalate their medication dosage when they are faced with stress and need to have their prescriptions refilled early.

**Physical Dependence** is a state of adaptation that is manifested by a withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. In the management of acute pain, physical dependence usually does not develop because of the limited duration of opioid use. *Physical dependence is not addiction.*

**Withdrawal** involves developing signs of illness/discomfort when intake of the substance is abruptly stopped. *Withdrawal is not addiction.* Many people who have taken opioids or sedatives 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 health care professional or pharmacist if you have these or other side effects. Obtaining refills on time will prevent withdrawal.

**Opioid Tolerance** is a phenomenon or adaptation of the body over a period of time 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 continued use, a person 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 to the different side effects does not develop at the same rate. With opioids, for example, one rapidly becomes tolerant to the sedating effects of the drugs. It has been shown that cancer patients who take large



but stable doses of morphine show little or no sedation. They do, however, continue to experience constipation if untreated, 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. Older patients may not become tolerant as quickly to the analgesic effects of opioids as younger patients.

**Pseudo-tolerance** is the need to increase medications such as opioids for pain when other factors are present such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interactions, addiction, and/or deviant behavior.

**Functional Impairment** and physical inactivity are additional concerns that make health care professionals 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.

**Drug Misuse** refers to the intentional or unintentional incorrect use of opioids in a manner other than that prescribed.

**Opioid Abuse** is the intentional incorrect use of opioids in a manner other than that prescribed. Another definition of abuse is any use of an illicit drug with the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness, e.g., getting high. A licit (legal) substance such as alcohol can be abused. It is a federal crime to take a controlled substance that has not been prescribed for oneself.

**Diversion** is allowing others to have access to your prescribed opioids. Diversion can be as simple as sharing one's medications with family members or friends on an occasional basis or can represent a conscious decision to distribute or sell them to others. Another definition of diversion is the intentional removal of a medication from legitimate distribution and dispensing channels for illicit sale or distribution. It is a federal crime to divert opioids from the person for whom they have been prescribed.



## THE EVIDENCE FOR OPIOID USE

The American Pain Society (<http://www.ampainsoc.org>) and the American Academy of Pain Medicine (<http://www.painmed.org>) issued the following document: Evidence Review: APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain which can be found at [http://www.ampainsoc.org/pub/pdf/Opioid\\_Final\\_Evidence\\_Report.pdf](http://www.ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf).

This document notes that “Several published guidelines and consensus statements recommend judicious use of opioids in appropriately selected patients with chronic noncancer pain who have not responded to other treatments and analgesic medications. Nonetheless, there remains uncertainty about the optimal use of opioids for chronic noncancer pain. Some patients do not experience significant improvements in pain or function even on high doses of opioids. In addition, opioids are associated with a variety of potentially serious adverse events, as well as aberrant drug-related behaviors (see glossary), including abuse (see glossary), addiction, and diversion.”

The actual American Pain Society and the American Academy of Pain Medicine Opioid Treatment Guidelines: Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain can be found at

<http://download.journals.elsevierhealth.com/pdfs/journals/1526-5900/PIIS1526590008008316.pdf>

The abstract of the article is as follows:

Abstract: Use of chronic opioid therapy for chronic noncancer pain has increased substantially. The American Pain Society and the American Academy of Pain Medicine commissioned a systematic review of the evidence on chronic opioid therapy for chronic noncancer pain and convened a multidisciplinary expert panel to review the evidence and formulate recommendations. Although evidence is limited, the expert panel concluded that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain. However, opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. The recommendations presented in this document provide guidance on patient selection and risk stratification; informed consent and opioid management plans; initiation and titration of chronic opioid therapy; use of methadone; monitoring of patients on chronic opioid therapy; dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy; prevention and management of opioid-related adverse effects; driving and work safety; identifying a medical home and when to obtain consultation; management of breakthrough pain; chronic opioid therapy in pregnancy; and opioid-related polices. Perspective: Safe and effective chronic opioid therapy for chronic noncancer pain requires clinical skills and knowledge in both the principles of opioid prescribing and on the assessment and management of risks associated with opioid abuse, addiction, and diversion. Although evidence is limited in many areas related to use of opioids for chronic noncancer pain, this guideline provides recommendations developed by a multidisciplinary expert panel after a systematic review of the evidence.



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.

The exact relationship between higher opioid dosage and risk is not yet clear, but a troubling pattern of increased deaths associated with prescription opioid use has emerged during the same period that average doses significantly increased.

The fact that opioids reduce the natural drive to breathe is a serious concern. In addition, opioids become particularly dangerous when used in conjunction with other medications that can also depress respiration — sedative-hypnotics, benzodiazepines, antidepressants, and muscle relaxants — or with alcohol.

The FDA has implemented a risk evaluation and mitigation strategy (REMS) for extended release and long-acting opioids as part of a federal initiative to address prescription drug abuse, misuse, and overdose. The REMS requires manufacturers to provide prescriber and patient education on the safe use of these drugs. Affected opioid drugs, which include brand name and generic products, are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Further information can be found at:

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

or <http://www.er-la-opioidrems.com/IwgUI/rems/home.action>

## KEY STEPS TO USE OPIOIDS SAFELY

1. **Keep your doctor informed.** Inform your health care professional about any past history of substance abuse. All patients treated with opioids for pain require careful monitoring by their health care professional for signs of abuse and addiction, and to determine when these analgesics are no longer needed.
2. **Follow directions carefully.** Opioids are associated with significant side effects, including drowsiness, constipation, and depressed breathing depending on the amount taken. Taking more than is prescribed could cause severe respiratory depression or death. Even if you are taking what the doctor prescribed, side effects should be reported. Do not crush, break, or dissolve pills. This can alter the rate at which the medication is absorbed and lead to overdose and death.
3. **Reduce the risk of drug interactions.** Do not mix opioids with alcohol, antihistamines, barbiturates, or benzodiazepines. All of these substances slow breathing, and their combined effects could lead to life-threatening respiratory depression.



4. Prevent theft and diversion. Do not store your opioids in the medicine cabinet or where others have access to the medications. The best strategy is to store your medications in a locked box.
5. Keep track of when refills are needed to prevent going without medications, leading to withdrawal. Discuss refill strategies with your prescriber ahead of time. Some pain clinics will not fill prescriptions without a visit to the clinic. Other clinics will not fill prescriptions on Friday afternoons or weekends/evenings.

## OPIOIDS & 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 pain 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 put forth by Federal and State authorities.



## MONITORING YOUR MEDICATION USE

Healthcare professionals who prescribe opioids are required to monitor for pain and any unusual drug-related behaviors as part of caring for their patients. .

The most relevant areas for monitoring have been termed the Four A's:

- 1) Analgesia (pain relief – often measured by a 10-point rating scale).
- 2) Activities of daily living (physical, psychological, and social functioning).
- 3) Adverse or side effects.
- 4) Aberrant or abnormal drug-related behaviors.

Some of the following questions may help clarify how appropriately opioid pain medications are being used, and whether they are helping or harming the person's well-being:

- ❑ *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. Often, patients with a previous history of substance abuse disorders are not ideal candidates for consideration for opioid treatment for pain management.
- ❑ *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 health care professional 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 often 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. Patients should not have the expectation of prolonged opioid use without concomitant benefits.

## **OPIOID TREATMENT AGREEMENT**

Patients have an important responsibility with respect to opioids to ensure that both they, as well as others, will be able to have access to opioids in the future. When opioids are prescribed, patients are usually requested to formally communicate their agreement with the written therapeutic plan (Opioid Treatment Agreement – sometimes termed an Opioid Contract or Opioid Therapy Plan), and, in particular, their understanding that the goal of opioid therapy is not the elimination of pain but, rather, its reduction to the point where measurable and meaningful increases in function are apparent. This would also include agreeing that they will



obtain opioids only from one pharmacy and one medical provider, abstain from using other sedatives without express permission from the health care professional prescribing the opioids, and not engage in activities that would be interpreted as representing misuse or diversion of their medication.

The majority of persons who abuse opioids obtain the drug from friends or family members, often without the knowledge of the person for whom the medication is prescribed. Opioids used in this way, or sold or purchased illicitly, are unacceptable and would constitute misuse and abuse that would void the opioid treatment agreement, resulting in loss of prescribed opioids. Further, it is important to take the opioid exactly as prescribed by the health care professional with respect to dose and to timing between doses.

The discussion of safe storage and disposal not only helps to prevent theft and subsequent abuse but also prevents accidental overdose by children and cognitively impaired family members. Patients should always be aware of how many refills and how many pills remain in their prescription.

Part of an opioid treatment agreement also includes random urine drug testing.

A sample Opioid Treatment Agreement is available at the following location <http://www.lni.wa.gov/ClaimsIns/Files/OMD/agreement.pdf> (Washington State Department of Labor and Industries Medical Treatment Guidelines).

A sample informed consent agreement form is available from the American Academy of Pain Medicine: **Long-term Controlled Substances Therapy for Chronic Pain SAMPLE AGREEMENT** at <http://www.partnersagainstpain.com/printouts/A7012CT6.pdf>.

## **URINE DRUG TESTING (UDT) / URINE DRUG SCREENING (UDS)**

Urine drug testing (UDT) or urine drug screening (UDS) is often ordered by the physician prior to starting opioids and at random intervals during treatment. UDT is used to check that the medications prescribed are being taken and that non-prescribed and/or illicit drugs are not used. Typically, urine tests include screening for prescription opioids, benzodiazepines, cocaine, heroin, amphetamines, and marijuana.



## ANTI-DEPRESSANTS

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.

There has long been a known association between depression and chronic pain. Not surprisingly, the chemicals (neurotransmitters such as serotonin and norepinephrine) in your brain and nervous system that play a key role in depression are also involved in chronic 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 acute musculoskeletal sports-type injuries.
- 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.

### 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.

The antidepressants that increase norepinephrine seem to have better pain relieving capabilities than those that increase serotonin. This helps to explain why the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac<sup>®</sup>) and paroxetine (Paxil<sup>®</sup>), work well for depression but do not have the same ability to control pain.

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, urinary retention, weight gain, 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, such as amitriptyline (Elavil<sup>®</sup>), nortriptyline (Pamelor<sup>®</sup>), and desipramine (Norpramin<sup>®</sup>), can be fatal in overdose and should only be available and prescribed in limited supply.

Tricyclic antidepressants (TCAs) can have significant anticholinergic effects which can include confusion, blurred vision, constipation, dry mouth, light-headedness, and difficulty with urination or loss of bladder control. In older patients with decreased cognitive abilities, the use of a tricyclic antidepressant can lead to significant confusion. Patients with Alzheimer's Disease should not be started on TCAs.

Also, patients with cardiovascular disease (CVD) should avoid the use of tricyclic antidepressants or be followed closely by a health care professional for cardiac abnormalities that can worsen with their use. In a study published online in December 2010 in the *European Heart Journal*, the authors assessed the association between antidepressant medication use and future risk for CVD. The study suggested TCAs are associated with a 35% increased risk for CVD, which is not explained by existing psychiatric illness. However, researchers found no increased cardiac risk associated with SSRIs.



## **BENEFITS OF ANTIDEPRESSANTS IN CHRONIC PAIN**

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

- ❑ They do not have the potential to cause stomach inflammation and bleeding, as do the anti-inflammatory drugs. The use of antidepressants (e.g., SSRIs) with NSAIDs should occur with caution secondary to a higher risk of GI bleeding.
- ❑ 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
Chronic musculoskeletal pain	Low back pain with radiculopathy



## ANTIDEPRESSANTS COMMONLY USED FOR CHRONIC PAIN

There are three main classes of antidepressant medications used in the management of chronic pain.

### TRICYCLIC ANTIDEPRESSANTS (TCAs)

The first class is the tricyclic antidepressants (TCAs) and includes the antidepressants amitriptyline (Elavil<sup>®</sup>), doxepin (Sinequan<sup>®</sup>), imipramine (Tofranil<sup>®</sup>), desipramine (Norpramin<sup>®</sup>), nortriptyline (Aventyl<sup>®</sup>, Pamelor<sup>®</sup>), protriptyline (Vivactil<sup>®</sup>), trimipramine (Surmontil<sup>®</sup>), and clomipramine (Anafranil<sup>®</sup>). Also included are maprotiline (Ludomil<sup>®</sup>) and mirtazapine (Remeron<sup>®</sup>), which are tetracyclic antidepressants.

The TCAs have been used to treat depression for a long time. 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. These antidepressants have been proven to have pain-relieving effects, typically at lower doses than required to treat depression.

The different tricyclic drugs have varied side effects which may sometimes be used to the patient's 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. Desipramine is considered to have the lowest side effects profile of the TCAs. For others with poor sleep hygiene, the sedating properties of certain TCAs, such as amitriptyline or doxepin, may be helpful.

Common side effects caused by the 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 TCA toxicity:

<http://www.emedicine.com/emerg/topic616.htm>

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



## SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

The second main class of drugs, the selective serotonin reuptake inhibitors (SSRIs), includes fluoxetine (Prozac<sup>®</sup>), sertraline (Zoloft<sup>®</sup>), paroxetine (Paxil<sup>®</sup>), fluvoxamine (Luvox<sup>®</sup>), citalopram (Celexa<sup>™</sup>), escitalopram (Lexapro<sup>®</sup>), and vilazodone (Viibryd<sup>®</sup>).

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

SSRIs have been disappointing for neuropathic pain. Most studies of the serotonin-selective type (non-tricyclic) antidepressants have shown little or no pain relief.

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 GI 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).

## SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS)

The third class includes a number of drugs that are mixed serotonin and norepinephrine reuptake inhibitors or SNRIs.

Duloxetine (Cymbalta<sup>®</sup>), venlafaxine (Effexor<sup>®</sup>), milnacipran (Savella<sup>™</sup>), and bupropion (Wellbutrin<sup>®</sup>) are the SNRIs that are most commonly encountered in association with pain management.

Duloxetine has been approved for management of painful diabetic peripheral neuropathy, fibromyalgia, anxiety disorder, depression, and in 2010 for chronic musculoskeletal pain including osteoarthritis and chronic low back pain.



Milnacipran has been approved for the management of fibromyalgia. Milnacipran more potently inhibits the reuptake of norepinephrine than duloxetine and venlafaxine.

These medications have no cholinergic inhibition and, thus, they are associated with fewer side effects.

Venlafaxine has been shown to have therapeutic benefit in the treatment of neuropathic pain. Venlafaxine is available in an extended-release formulation which has a better tolerability profile than the immediate-release formulation. Blood pressure should be monitored in these patients because venlafaxine can increase systolic blood pressure.

Although marketed for different indications, Wellbutrin<sup>®</sup> (antidepressant) and Zyban<sup>®</sup> (smoking cessation) contain the same active ingredient and therefore should not be taken concurrently without close health care professional supervision.

Side effects of SNRIs can include nausea, vomiting, dizziness, sleepiness, trouble sleeping, abnormal dreams, constipation, sweating, dry mouth, yawning, tremor, gas, anxiety, agitation, abnormal vision such as blurred vision or double vision, headache, and sexual dysfunction.

## OTHER ANTIDEPRESSANTS

Trazodone is a serotonin-2 receptor antagonist. Some of the most common side effects of trazodone 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) are generally not used to treat chronic pain. Those such as 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. They also have many drug-drug and drug-food interactions.

Antidepressants have significant implications for drug-drug interactions when used in conjunction with many other medications. For example, tramadol and the antidepressants have shared mechanisms on serotonin reuptake and may need to be used together with caution.



## **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.*

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, sertraline, paroxetine, escitalopram (Lexapro<sup>®</sup>), duloxetine, milnacipran, and venlafaxine. 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, they 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<sup>®</sup>), paroxetine (Paxil<sup>®</sup>), sertraline (Zoloft<sup>®</sup>), citalopram (Celexa<sup>®</sup>), escitalopram (Lexapro<sup>®</sup>), trazodone (Desyrel<sup>®</sup>), venlafaxine (Effexor<sup>®</sup>), desvenlafaxine (Pristiq<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 (Ionamin<sup>®</sup>).

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

Certain drugs for nausea, specifically ondansetron (Zofran<sup>®</sup>), dolasetron (Anzemet<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, Delsym<sup>®</sup>) or the antibiotic linezolid (Zyvox<sup>™</sup>).



## ANTICONVULSANT (ANTIPILEPTIC) DRUGS

Anticonvulsant medications have been found to be widely effective in various neuropathic pain conditions.

Several drugs that were developed for the prevention of epileptic seizures (convulsions) have been found to help certain pain conditions. For example, carbamazepine (Carbatrol<sup>®</sup>, Tegretol<sup>®</sup>) is approved by the FDA for relieving the pain of trigeminal neuralgia. Gabapentin (Neurontin<sup>®</sup>) is approved for the management of postherpetic neuralgia (PHN - pain that lasts one to three months after shingles has healed). Pregabalin (Lyrica<sup>®</sup>) is approved for PHN, painful diabetic neuropathic pain, and fibromyalgia. 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 health care professional. Common side effects are drowsiness, peripheral edema (lower extremity swelling), 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. Decreased mental alertness or awareness is possible at higher doses (e.g., 3600 mg/day) but this is variable and is person specific. Generic gabapentin is now available. In January 2011 Gralise<sup>®</sup> a once-a-day gabapentin was approved by the FDA.

A similar drug to gabapentin, pregabalin (Lyrica<sup>®</sup>), has been found effective in postherpetic neuralgia, fibromyalgia, and diabetic neuropathy. Its primary advantage over gabapentin is thought to be pregabalin’s longer duration of action, allowing a twice daily dosing and improved absorption; 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 to 600 mg/day). 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 being the most common. Other adverse effects include dry mouth, peripheral edema, blurred vision, weight gain, and concentration or attention difficulties. Often, gabapentin and pregabalin require a period of time before their effectiveness in treating a patient’s pain is seen because the medications need to be titrated to the appropriate dose. Recently, the FDA has issued a warning on the use of anticonvulsants and the risks of suicidal thoughts and suicide. Patients utilizing anticonvulsants for pain control should be monitored for any signs and symptoms of suicidal thoughts.



### ANTICONVULSANTS POSSIBLY USEFUL IN CHRONIC PAIN

\*Only gabapentin and pregabalin are approved by the FDA and for which there is solid evidence of efficacy in general neuropathic pain.

<b>Gabapentin*</b> (Neurontin <sup>®</sup> )	Has proven to be effective in some people for nerve injury or neuropathic pain. Seems safer, easier to use. Some mental fuzziness possible at higher doses.
<b>Pregabalin*</b> (Lyrica <sup>®</sup> )	Found effective in postherpetic neuralgia and diabetic neuropathy. Some advantage over gabapentin. It is generally well tolerated.
Carbamazepine (Tegretol <sup>®</sup> )	Interacts with some other drugs, can affect the liver and white blood cells. Used for trigeminal neuralgia.
Valproic acid (Depakote <sup>®</sup> )	Used in headache or nerve pain. May affect platelets as an adverse effect.
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. Not FDA approved and clinically not recommended for neuropathic 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. Possibly useful in treating neuropathic pain. Most common side effects include nonspecific dizziness, drowsiness, and difficulty with concentration. Has been associated with new onset seizures and status epilepticus in patients without epilepsy.
Lacosamide (Vimpat <sup>®</sup> )	Lacosamide is being studied as an anticonvulsant with potential for reducing diabetic neuropathic pain.
Topiramate (Topamax <sup>®</sup> , Topiragen <sup>TM</sup> )	Generally well tolerated but sometimes causes confusion, dizziness, fatigue, and problems with coordination and concentration. Minimally 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. May cause secondary angle closure glaucoma and, if left untreated, may lead to permanent vision loss. It may also cause dose-related weight loss, and cause or predispose to kidney stones.
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. Possibly useful in treating neuropathic pain. Probably useful for trigeminal neuralgia.
Zonisamide (Zonegran <sup>®</sup> )	Indicated for use as adjunctive therapy for treatment of partial seizures (or <i>focal seizures</i> ) in adults with epilepsy. Possibly useful in 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 use 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 anti-arrhythmics with local anesthetic properties are occasionally used in refractory or difficult to treat 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. This leads to less firing of the nerve, and hence less capability of the nerve to trigger pain.

Due to safety concerns, the only anti-arrhythmics that are used 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 (CRPS) or reflex sympathetic dystrophy (RSD), 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. Consult a health care professional if you are pregnant, have a history of heart attack, are a smoker, or take any of the following medications: amiodarone, fluvoxamine, dofetilide (Tikosyn<sup>®</sup>), bupropion, or sodium bicarbonate. It should be taken three times daily 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 overdose including seizures, convulsions, chest pain, shortness of breath, irregular or fast heartbeat, and cardiac arrest.

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, they can be catastrophic. An EKG is recommended before treatment is started. This drug should probably not be used for pain management in patients with a history of cardiovascular disease or heart. Inform your health care professional if you have kidney or liver problems because this may require monitoring of drug levels or a dosage reduction. Flecainide interacts with amiodarone, several antipsychotic and anti-arrhythmic medications, and ranolazine (Ranexa<sup>®</sup>). Common side effects, which usually occur within the first two to four weeks of therapy, are nausea or vomiting, constipation, headache, dizziness, visual disturbances, edema, and tremor.



## 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. Whereas topical agents work locally and must be applied directly over the painful area, transdermal drugs have effects throughout the body and work when applied away from the area of pain (currently available transdermal drugs include fentanyl, buprenorphine, lidocaine with or without tetracaine, and clonidine). Transdermal medication in a patch is absorbed through the skin by the bloodstream over a period of time. (In general, you should never cut a transdermal patch into smaller pieces, but topical lidocaine patches may be cut into smaller sizes with scissors as noted on the packaging.)

Some of the OTC 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. Large amounts can be absorbed and lead to similar adverse effects as when given orally.

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.

Counterirritants come in various forms such as balms, creams, gels, and patches under several brands such as BenGay<sup>®</sup>, Icy Hot<sup>®</sup>, Salonpas<sup>®</sup>, and Thera-Gesic<sup>®</sup> for ease of application. The balms, creams, and gels can be applied to the painful area(s) three to four times a day (usually for up to one week). When using the BenGay<sup>®</sup> patch product, one patch can be applied for up to 8 to 12 hours; if pain is still present, a second patch may be applied for up to 8 to 12 hours (maximum: 2 patches in 24 hours for no longer than 3 days of consecutive use). The Salonpas<sup>®</sup> Pain Relief Patch<sup>®</sup> (10% methyl salicylate and 3 % menthol) is currently the only FDA-approved OTC topical analgesic patch and can be applied up to 3 to 4 times/day for 7 days; the patch may remain in place for up to 8 hours. It is approved for temporary relief of mild to moderate aches and pains of muscles and joints associated with strains, sprains, simple backache, arthritis, and bruises.

Even though these products are sold without a prescription, they still carry some risk of adverse effects (mostly skin irritation). Topical products containing NSAIDs (methyl salicylate) carry



less risk of side effects versus the oral NSAIDs (e.g., ibuprofen), but they still apply. Also, these products should not be applied on wounds, damaged skin, or the face. Lastly, after application, be sure to wash your hands thoroughly to avoid getting these products in sensitive areas such as your eyes. When removing and discarding used patches, fold the used patches so that the adhesive side sticks to itself. Safely discard used patches where children and pets cannot get to them.

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

Aspirin in chloroform or diethyl ether, capsaicin (Zostrix<sup>®</sup>, Zostrix<sup>®</sup>-HP, Qutenza<sup>™</sup>), EMLA<sup>®</sup> (eutectic mixture of local anesthetics; contains lidocaine and prilocaine) 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 5% and capsaicin patch are the only FDA-approved treatments for neuropathic pain, and they require a prescription. 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 which produces a characteristic heat sensation when applied to the skin (dermal drug delivery). Several studies have suggested that capsaicin (cap-SAY-sin) can be an effective analgesic in at least some types of neuropathic pain and arthritic conditions (osteoarthritis and rheumatoid arthritis). 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.

In late 2009, the FDA approved Qutenza<sup>™</sup> (capsaicin) 8% patch for the management of neuropathic pain attributed to PHN that may occur after an episode of [herpes zoster](#) (shingles). The Qutenza<sup>™</sup> patch releases a synthetic form of capsaicin through a dermal delivery system at a much stronger dosage than capsaicin creams available over the counter. Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza<sup>™</sup>. Qutenza<sup>™</sup> is applied for 60 minutes and may be repeated every 3 months or as warranted by the return of pain (not more frequently than every three months). Before patch application, a physician must identify and mark the painful area, including areas of hypersensitivity. A topical anesthetic is applied before Qutenza<sup>™</sup> application as it can create significant pain during application. In clinical trials, the most common adverse reactions were application site redness, pain, itching, and bumps. The majority of these reactions were transient and self-limited. Among patients treated with Qutenza<sup>™</sup>, 1% discontinued treatment prematurely due to an adverse event.



Serious adverse reactions included application-site pain and increased blood pressure. Information can be found at [http://www.qutenza.com/docs/qutenza\\_full\\_PI.pdf](http://www.qutenza.com/docs/qutenza_full_PI.pdf).

Topical anesthetics, such as EMLA<sup>®</sup> (Eutectic Mixture of Local Anesthetic; contains lidocaine and prilocaine) cream and L.M.X.4 (contains lidocaine 4%), are used primarily prior to painful procedures such as blood draws, 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. Pain relief 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. Side effects to EMLA<sup>®</sup> cream include skin blanching, redness, and swelling. In younger individuals or in cases in which too much has been applied, negative effects can occur to hemoglobin (red blood cells). Therefore, EMLA<sup>®</sup> cream should be avoided in individuals less than one month old and in patients with a predisposition to methemoglobinemia (a problem with the red cell). EMLA<sup>®</sup> cream should also not be applied to broken skin or mucous membranes (e.g., mouth).

L.M.X.4<sup>®</sup> contains 4% lidocaine and is available without a prescription. It has a shorter application time (30 minutes) and a shorter duration of action (30 minutes) than EMLA. It has not been shown to be effective for chronic pain most likely because of its short duration.

Lidoderm<sup>®</sup> 5% (lidocaine) patches can be cut to fit over the area of pain. The 5% lidocaine patch is FDA approved for the treatment of a neuropathic pain condition, specifically PHN. It measures 10 cm x 14 cm and has a clear plastic backing that must be removed before application of the patch to the skin. The manufacturer states that 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 usually minimal and include localized skin irritation and swelling that generally disappear within two to three hours after the local anesthetic is removed from the skin. As a rule, blood concentrations of topical local anesthetics are well below toxic levels.

Potential hazards still exist, however. In 2007, the FDA issued a public health advisory to notify consumers and health care professionals of potential life-threatening side effects associated with the use of topical anesthetics, particularly before cosmetic procedures. At risk are consumers,



especially those without the supervision of a health care professional. They may apply large amounts of anesthetics or cover large areas of the skin, leave these products on for long periods of time, or use materials, wraps, or dressings to cover the skin after anesthetic application. Application to areas of skin irritation, rash, or broken skin may also increase the risk of systemic absorption. The FDA recommends that if topical anesthetics are needed prior to medical or cosmetic procedures, consumers ask their healthcare provider for instructions on the safe use of these products, use only FDA-approved products, and use products with the lowest amount of anesthetic while applying the least amount possible to relieve pain.

## COMPOUNDED MEDICATIONS

Compounded medications are not commercially available; rather, they are prescribed by a health care professional and prepared by a pharmacist to meet an individual's unique needs. These compounded medications do not go through the same FDA approval process that is required for commercially available prescription drugs. Therefore, trials may or may not be conducted to determine safety and efficacy. Such studies are not a legal requirement for compounded medications.

The most common compounded medications are topical gels. They typically contain ingredients such as lidocaine, amitriptyline, gabapentin, or ketoprofen. Most of them use PLO (Pluronic Lecithin Organogel) as a vehicle to help deliver the active ingredients through the skin. The benefit to this type of delivery system is that medication is localized to the area of pain. Studies show less systemic absorption for ingredients like lidocaine and amitriptyline when used in PLO gels. Lidocaine 5% in PLO gel has been shown in studies to be effective in relieving pain with a minimal enough amount of systemic absorption to alleviate fears of approaching toxic levels. Studies regarding the efficacy of amitriptyline in PLO gels have been more ambiguous; more research needs to be conducted to determine its role in compounded topical pain medications.

Topical medications, such as the combination of ketamine and amitriptyline (a tricyclic antidepressant) have been proposed as an alternative treatment for neuropathic disorders including complex regional pain syndrome (CRPS). These types of topical medications are so far unproven and their use should be limited to patients with clinical evidence of neuropathic type pain. Continued use of these agents beyond the initial prescription requires documentation of effectiveness, including functional improvement, and/or decreased use of other pain medications.

Other compounded agents include those injected into the epidural and spinal canal. A recent outbreak of meningitis secondary to epidural steroids that were compounded has produced much more scrutiny of compounding pharmacies (ref on 01/13/2013:



[http://en.wikipedia.org/wiki/New\\_England\\_Compounding\\_Center\\_meningitis\\_outbreak](http://en.wikipedia.org/wiki/New_England_Compounding_Center_meningitis_outbreak)). Many intraspinal or intrathecal analgesics need to be compounded for improved pain relief and delivered via intraspinal drug delivery systems or pumps. The best recommendation is to work with a compounding pharmacy that has a history of quality care and can answer questions about stability and sterility of their compounding techniques.



## SEDATIVES AND ANTI-ANXIETY MEDICATIONS

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 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, 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 sleep aid, 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 medications, 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.

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 8 mg 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.

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 ACPA Resource Guide to Chronic Pain Medication & Treatment.



## BENZODIAZEPINES

Most people experience anxiety at one time or another in their lives. Anxiety can present as nervousness or sweaty palms, 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.

One of these benzodiazepines, diazepam (Valium<sup>®</sup>), is recognized for causing depression and physical dependence when used for long periods.

Most benzodiazepines are not recommended for chronic pain, but clonazepam (Klonopin<sup>®</sup>) is an anticonvulsant that appears to have some use with neuropathic pain.

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. Another major side-effect is respiratory depression, particularly when combined with long-acting opioids. Caution should be used when prescribing both classes of medications: opioids and benzodiazepines.

Because of withdrawal symptoms, these drugs should be discontinued slowly under a health care professional'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.



## 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. They should be used in caution with opioids. Sedation is a concern for those who drive, operate machinery, or otherwise are engaged in safety sensitive jobs. Some also have analgesic (pain reducing) properties. Cyclobenzaprine (Flexeril<sup>®</sup>, Amrix<sup>®</sup> – extended release) 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. There are no studies to support the long-term use of muscle relaxants, especially for low back pain. Also, the long-term use of muscle relaxants for low back pain does not improve functional recovery and can also hinder recovery.

### 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. Use in chronic pain should be avoided.
Cyclobenzaprine (Flexeril <sup>®</sup> , Amrix <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 regular 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> - oral and injectable), Gablofen <sup>®</sup> - injectable)	Reduces spasticity after neurological illness or injury. Withdrawal should not be abrupt and can be life-threatening (mainly with intrathecal therapy). 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. This drug may increase liver enzyme levels. Tizanidine interacts with blood pressure medications and causes low blood pressure.
Diazepam (Valium <sup>®</sup> )	Other benzodiazepines also have muscle-relaxant properties. Most pain specialists 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 <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.

Clonidine 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 TOXINS

Botulinum toxins, Botox<sup>®</sup> (onabotulinumtoxinA), Dysport<sup>®</sup> (abobotulinumtoxinA), Xeomin<sup>®</sup> (incobotulinumtoxinA) and Myobloc<sup>®</sup> (rimabotulinumtoxinB) have been found to be effective in decreasing tone in overactive (hypertonic) muscles, which may be present in a number of chronic pain conditions. A recent review article regarding the treatment of refractory pain by Dr. Jabbari summarizes that botulinum toxins have “established efficacy” to control pain of cervical dystonia, chronic migraine, and chronic lateral epicondylitis – tennis elbow. The review also found a lower level of evidence and classified botulinum toxin as “probably effective and recommended” for post-herpetic neuralgia, post-traumatic neuralgia, pain of plantar fasciitis, piriformis syndrome, and pain in total knee arthroplasty; “possibly effective, may be used at discretion of clinician” for allodynia of diabetic neuropathy, chronic low back pain, painful knee osteoarthritis, anterior knee pain with vastus lateralis imbalance, pelvic pain, post-operative pain in children with cerebral palsy after adductor hip release surgery, post-operative pain after mastectomy, and sphincter spasms and pain after hemorrhoidectomy; “efficacy not proven due to diverse class I and II results” for myofascial pain syndrome and chronic daily headaches; and “negative” for episodic migraine and tension headaches (Pain Med 2011; 12:1594-1606). There appears to be additional pain relieving properties of botulinum toxin irrespective of muscle relaxation.

Botox<sup>®</sup>, Dysport<sup>®</sup>, Xeomin<sup>®</sup> and Myobloc<sup>®</sup> are FDA—approved for the treatment of the postural abnormalities and pain associated with cervical dystonia – also known as torticollis (head tilting, neck pain, and neck muscle spasms). Only one botulinum toxin (Botox<sup>®</sup>, onabotulinumtoxinA) is approved by the FDA for the treatment of chronic migraine headache and spasticity treatment in the upper limb in adults.

The efficacy of botulinum toxins in back, neck, and extremity muscle pain has been studied, as an off- label use, with mixed results. In some studies on myofascial pain, botulinum toxin has not been found to be more effective than traditional trigger point injections with local anesthetic or saline.

The dosage units for botulinum toxins are unique to each product and ~~they~~ are not interchangeable. In addition the FDA has specified nonproprietary names for each drug to help prevent medication errors. Many physicians are using botulinum toxins off-label for other painful conditions including types of headache other than chronic migraine treated with Botox<sup>®</sup> (onabotulinumtoxinA), osteoarthritis of the knee and shoulder, and various muscle pain syndromes (myofascial pain) although the evidence for such use is not conclusive.

For treatment of chronic pain conditions, when effective, botulinum toxins typically demonstrate efficacy within 3 to 5 days after intramuscular administration and lasts for an average of 12 weeks.



Side effects may occur after receiving botulinum toxin (see FDA warning box below). Muscle weakness is one of the most common side effects. Swallowing problems can develop when treating cervical muscle problems, especially with injections into the sternocleidomastoid muscle. Other adverse effects include dry mouth, pain at the injection site, neck pain, headache, and flu-like symptoms. Additionally, adverse effects may include local bruising, generalized fatigue, lethargy, dizziness, and difficulty speaking or hoarseness.

**FDA WARNING: DISTANT SPREAD OF BOTULINUM TOXIN EFFECT**

Postmarketing reports indicate that botulinum toxin may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.



## NMDA INHIBITORS

Numerous 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.

The utility of these agents has been limited by their significant dose-related side effect profile, which includes lightheadedness, dizziness, tiredness, headache, nervous floating sensation, bad dreams, and sensory changes.

Agents that have clinically relevant NMDA blocking properties include ketamine, amantadine (an anti-influenza medication), memantine (an Alzheimer drug; Namenda™), 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 they 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 central nervous system (CNS) side effects.

Some pain specialists have been prescribing NMDA inhibitors for chronic neuropathic pain, but further studies are needed to determine their effectiveness. Studies have not shown any functional improvements in patients with CRPS treated with ketamine infusions. Because their potential for harm outweighs evidence of limited short-term benefit in patients with CRPS, NMDA receptor antagonists are not recommended.



## ADRENERGIC DRUGS, BISPHOSPHONATES, THALIDOMIDE, & CALCITONIN

**Alpha adrenergic antagonists** (e.g., clonidine, 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 due to its side effect profile. It is more widely utilized in implantable intrathecal drug pumps for pain.

**Bisphosphonates** are a class of drugs used primarily to increase bone mass and reduce the risk of fractures in patients with osteoporosis. There are seven FDA-approved bisphosphonates: alendronate (Fosamax<sup>®</sup>, Fosamax Plus D<sup>TM</sup>), etidronate (Didronel<sup>®</sup>), ibandronate (Boniva<sup>®</sup>), pamidronate (Aredia<sup>®</sup>), risedronate (Actonel<sup>®</sup>, Actonel<sup>®</sup> with calcium), tiludronate (Skelid<sup>®</sup>), and zoledronic acid (Reclast<sup>®</sup>, Zometa<sup>®</sup>). They are more popularly known for treatment and prevention of osteoporosis. For chronic pain, they have been used 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. Adverse effects can include gastritis and erosive esophagitis (stomach and esophagus distress), and rarely, damage of the jaw bone (osteonecrosis). In October 2010, the FDA also issued a special alert on the association between the use of bisphosphonates and the risk of atypical fractures of the thigh. Patients are encouraged to consult their healthcare providers for new hip or thigh pain.

There has been interest in the use of **thalidomide** as a treatment for CRPS. This is based on the possible role played by natural chemicals found in the body called inflammatory cytokines, which thalidomide inhibits. There are no published clinical trials on thalidomide use in CRPS, only case reports demonstrating benefit. The drug is currently being studied in clinical trials. But because of its history of causing birth defects, women of childbearing age have been excluded, and extensive monitoring is required.

**Calcitonin** is the lesser known of the thyroid's two main hormones. It decreases bone resorption and has direct effects on the kidneys and gastrointestinal tract. It is also thought to have anti-pain effects. Recently, the salmon calcitonin formulation that is nasally inhaled has been more commonly used than injectable calcitonin due to ease of administration. Calcitonin has been used to treat the bone pain associated with compression and sacral insufficiency fractures.



## 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 health care professionals 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>), armodafinil (Nuvigil<sup>®</sup>), and combination products (Adderall<sup>®</sup>).

While these activating drugs may be appropriate for a few individuals, consideration for weaning of the offending pain medication that is causing the drowsiness is recommended.

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 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 (<http://www.nida.nih.gov/Infobox/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. There have been rare cases of serious or life threatening rash including Stevens-Johnson syndrome and toxic epidermal necrolysis reported in adults and children.



Armodafinil (Nuvigil<sup>®</sup>) is a wakefulness-promoting agent for oral administration. It is indicated to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, narcolepsy, and shift work sleep disorder. There is some suggestion that it is longer acting than modafinil (Provigil<sup>®</sup>) and may result in fewer headaches as a side effect.

## MIGRAINE HEADACHE TREATMENT

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, Sumavel<sup>®</sup> DosePro<sup>®</sup> – needle-free delivery), 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.

For patients who are diagnosed with Chronic Migraine, a neurological disorder characterized by patients who experience headaches on 15 or more days per month with headaches lasting four hours a day or longer, Botox<sup>®</sup> was granted approval in 2010 as a preventive treatment option.

Patients taking certain migraine and antidepressant medications together may be at risk for a dangerous chemical imbalance. Antidepressant medications included in this warning are duloxetine (Cymbalta<sup>®</sup>), escitalopram (Lexapro<sup>™</sup>), fluoxetine (Prozac<sup>®</sup>), paroxetine (Paxil<sup>®</sup>), sertraline (Zoloft<sup>®</sup>), and venlafaxine (Effexor<sup>®</sup>). Migraine drugs include almotriptan (Axert<sup>™</sup>), naratriptan (Amerge<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.



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 the discussion about antidepressant medications in this ACPA Resource Guide to Chronic Pain Medication & Treatment 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 Journal of Medicine in January 2003 at [www.ccjm.org/pdf/files/Mannix103.pdf](http://www.ccjm.org/pdf/files/Mannix103.pdf).

Treximet<sup>®</sup> is a product that was FDA-approved in August 2008 as a combination medication for migraine treatment that contains naproxen 500 mg and sumatriptan 85 mg. Treximet<sup>®</sup> works to relieve the pain of migraines in two ways; the sumatriptan portion works by increasing the amount of the hormone serotonin in the blood vessels and causing constriction of the arteries in the head, and the naproxen works to decrease inflammation and pain. The FDA issued black box warnings regarding the cardiovascular and gastrointestinal risks associated with Treximet<sup>®</sup>. This combination may cause an increased risk of serious cardiovascular complications including heart attack and stroke. Also, since this product contains naproxen (an NSAID), there is an increased risk of gastrointestinal adverse reactions including bleeding, ulceration, and perforation of stomach or intestines. Caution should be used in patients with a history of kidney or liver disease.



## HERBAL MEDICINES, SUPPLEMENTS, & VITAMINS

Herbal supplements come from plants and claim to have medicinal properties that can cure, treat, or prevent disease. Nutraceuticals are nutrient products such as fish oils and megavitamins.

Even though these products may be billed as “natural” on the label, this does not ensure their efficacy, purity, or safety. Manufacturers of dietary supplements can market their products without receiving approval from the FDA. However, the FDA can remove products from the market if they have been proven to pose serious or unreasonable risk to consumers.

While there are proven health benefits for some herbal and nutraceutical products, potentially harmful effects exist for others. Dietary supplements are not standardized, contrary to FDA approved prescription medications. The same ingredients can be found in different products in varying amounts, and this can lead to toxic levels that may cause harmful reactions in the body. Herbal remedies and medicinal agents undergo little oversight of safety, efficacy, sterility of production, bio-equivalency, or stability of product life.

It is important to tell your health care professional if you are taking any of these products as they can interact with other medications and can cause serious side effects.

You can check for certification symbols, such as a United States Pharmacopeia (USP) symbol, which verifies that the product contains the stated ingredients in amounts and strength, is pure, meets limits for contaminants, and disintegrates quickly. The NSF International verifies products for content and label accuracy, purity, contaminants, and manufacturing processes. ConsumerLab.com independently tests supplements for purity and active ingredients.

### POSSIBLE BENEFIT OF HERBAL MEDICATIONS FOR PAIN

There are some herbal remedies for which there is evidence with regards to the management of acute low back pain and osteoarthritis. White willow bark (*Salix*) extract has been studied in low back pain. A principal ingredient is salicin, with salicylic acid as the principal metabolite.

Extract of *Harpagophytum procumbens* (devil’s claw root) has been used in Europe to treat musculoskeletal symptoms with some evidence that it may relieve acute low back pain, acute episodes of chronic low back pain, and osteoarthritis. Mild gastrointestinal upset has been reported at higher doses.

There is evidence that the antioxidant alpha lipoic acid (ALA) significantly and rapidly reduces the frequency and severity of symptoms of the most common kind of diabetic neuropathy.



Symptoms decreased include burning and sharply cutting pain, prickling sensations, and numbness.

There is also evidence that acetyl-L-carnitine (ALC) not only improves the symptoms of diabetic neuropathy, but also helps regenerate nerve fibers and vibration perception.

Recently, much attention has been given to glucosamine and chondroitin sulfate. Early research suggested that glucosamine and chondroitin sulfate were effective in improving pain and decreasing functional impairment from symptomatic osteoarthritis. The more recent Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) implied that glucosamine and chondroitin sulfate did not reduce pain in individuals with knee osteoarthritis, although a small select group of patients with moderate to severe osteoarthritis may benefit from treatment. When using glucosamine and chondroitin sulfate, the recommended daily dose is 1500 mg per day. Currently, a majority of studies do not show medical benefit with this supplement. Glucosamine may also worsen insulin resistance.

## **CONCERNS REGARDING THE USE OF HERBAL PREPARATIONS, SUPPLEMENTS, & VITAMINS**

All of these OTC products have the potential for toxic side effects and cross reactivity with each other and with prescription medications. Unexpected toxicity or drug interaction from any product or medication may accrue due to many variables such as age, gender, nutritional status, other illnesses, and surgery.

The American Society of Anesthesiologists recommends that patients discontinue or taper off of herbal products 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, lower seizure threshold, elevated digoxin levels, central nervous system depression, skin sensitivity to light, chest pain, electrolyte alterations, low blood pressure, irregular heartbeat, kidney failure, carcinogenicity, and autoimmune effects. Herbal medicines can also affect the ability of blood to clot. Therefore, information on current use of herbal medicines should be provided to your physician prior to undergoing any interventional pain procedure.



Some of the undesirable effects of a few of the more commonly used herbals are shown below.

<b>Possible Herbal Medication Adverse Side Effects</b>	
Aloe vera	Nausea, vomiting, diarrhea.
Astragalus	Autoimmune disease.
Belladonna	Atropine effects.
Chaparral	Hepatitis.
Ephedra (also called ma huang)	High blood pressure, irregular heartbeat, nervousness, headaches, trouble falling asleep, or even a heart attack or a stroke.
Ginkgo biloba	Excess bleeding.
St. John's wort	Upset stomach, a tired feeling, dizziness, confusion or dry mouth. You may also get a sunburn more easily.
Kava products	Sleepiness, a rash, or strange movements of your mouth and tongue or other parts of your body.
Garlic	Increased bleeding risk.

The National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM) and the National Library of Medicine (NLM) have partnered to create *CAM on PubMed*, a subset of NLM's PubMed. [PubMed](#) provides access to citations from the MEDLINE database and additional life science journals. It also includes links to many full-text articles. More information on the National Center for Complementary and Alternative Medicine can be found at <http://nccam.nih.gov/>.

You can also find an article (Herbal Remedies: Adverse Effects and Drug Interactions at <http://www.aafp.org/afp/990301ap/1239.html>) and a patient handout (Herbal Health Products--What You Should Know at <http://www.aafp.org/afp/990301ap/990301e.html>) on the American Academy of Family Physicians web site.

A Guide to Herbal Supplements can also be found on the SparkPeople at the following address: [http://www.sparkpeople.com/resource/articles\\_print.asp?id=506](http://www.sparkpeople.com/resource/articles_print.asp?id=506)



## TOBACCO, ALCOHOL, MARIJUANA, AND ILLICIT SUBSTANCES

### THE EFFECTS OF CIGARETTE SMOKE ON PAIN

Smoking causes blood vessels to become constricted; this restricts the amount of oxygen rich blood flowing to areas of pain. Smoking not only reduces blood flow to your heart but also to other structure such as the skin, bones, and discs. Due to this, you may get accelerated aging leading to degenerative conditions. The lack of blood supply caused by cigarette smoke is also responsible for increased healing time after surgery. After back fusion surgery, smoking cigarettes can increase the risk of your fusion not healing properly. Smoking should be avoided both before and after spine surgery. Cigarette smoke triggers the release of pro-inflammatory cytokines, increasing inflammation and intensifying pain. Smoking makes the bones weak and increases the prevalence of osteoporosis, spinal degenerative disease, and impaired bone and wound healing. Symptoms of depression are more commonly seen among smokers. Below are some tips to help you become smoke free.

Assess your readiness to quit smoking and ask your health care professional or pharmacist for help. They will make recommendations, modifications, and develop a treatment plan to optimize success. Even one less cigarette a day is a step in the right direction. There is nicotine replacement therapy available such as lozenges, gum, or patches. There is also pharmaceutical intervention available to help decrease not only the number of cravings and urges but also the severity.

Keep a Smoker's Log:

Cigarettes per day	
Time of each cigarette	
What triggered the craving?	
What were you doing while smoking?	
How did you feel while smoking?	

Keeping a log can help you pinpoint when and why you are smoking. Knowing these triggers can help you replace smoking a cigarette with other less toxic habits.

There are some medications which can help with the craving of cigarettes that many people experience when they are trying to quit. These medications work by affecting dopamine. Dopamine is a neurotransmitter, a chemical messenger, which plays a prominent role in addiction. Dopamine plays a role in movement control, emotional response, and pleasure / pain. It is responsible for the reward pathway and the “feel good” phenomenon experienced when smoking. Nicotine triggers dopamine release in the brain.



Norepinephrine is also a neurotransmitter that sends signals from one neuron to the next. Norepinephrine is similar to adrenaline and is responsible for constricting and narrowing the blood vessels. It can therefore increase blood pressure. It can also increase blood sugar levels. Norepinephrine can affect both mood and behavior.

Varenicline (Chantix®) mimics nicotine at the receptors in order to aid in smoking cessation. Varenicline is similar in structure to cytosine, a natural compound that has aided in smoking cessation since the 1960s. Varenicline works via two different mechanisms. First, varenicline is effective because it provides partial nicotine effects to help with nicotine withdrawal symptoms. Second, varenicline also binds to nicotine receptors to block nicotine's effect if one is to relapse. Duration of therapy is normally 12 weeks. Patients who respond to treatment may receive another 12 weeks of therapy to increase their success rate. There is an FDA black box warning for neuropsychiatric symptoms such as change in behavior and mood, agitation, and risk of suicide. Common side effects include the following: nausea, vomiting, insomnia, headache, and abnormal dreams.

Bupropion (Zyban®) is an antidepressant; however, it is also used in the smoking cessation process. Bupropion inhibits the reuptake of both dopamine and norepinephrine, increasing their concentrations within the brain. By increasing dopamine, the frequency and severity of nicotine cravings and urges are reduced. Norepinephrine plays a role in alleviating symptoms associated with withdrawal. Bupropion effects are not fully seen until one week of treatment is complete. Therefore, it is important for patients to start this medication one to two weeks prior to their "quit-date." Bupropion is associated with several FDA black box warnings; there is an increased risk of suicide, and neuropsychiatric symptoms may be exhibited. These symptoms include behavior changes, hostility, agitation, and depression. Seizures may occur; however they are dose dependent. Less severe, more common side effects include dry mouth, headache, nausea, dizziness, sweating, and insomnia.



## 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 effects 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 mixture of alcohol and opioids or other respiratory depressants can cause death.

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, and poor performance of any brain or muscle function. Signs of severe alcohol intoxication include stupor or coma with slow, noisy breathing, cold and clammy skin, and an increased heartbeat.

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.



## ILLEGAL DRUGS & MARIJUANA

Health care professionals will not prescribe opioids and other medications to individuals who are known to use illegal “street” drugs (heroin, methamphetamines, cocaine, etc.) or to be irresponsible with prescription pain medication.

The use of marijuana for pain is controversial. It is allowed by some states for “medicinal” purposes but overall it is banned for distribution by the United States federal government.

Some physicians will prescribe marijuana, some will not prescribe it but not object to its use with other pain medicines, and some will refuse to prescribe medications (especially opioids) if the patient is using marijuana. Some physicians take a “don’t ask, don’t tell” philosophy and don’t check for marijuana when doing urine drug testing.

The active ingredient found in marijuana (THC) can help pain, but can also lead to dependence and addiction in certain individuals.

Some states allow the legal use of marijuana for health purposes, including pain, although there is no high-level scientific research supporting the long-term use of marijuana for chronic pain. In fact, there is good evidence that excessive smoking of marijuana can be harmful. The use of any substances should be discussed openly between you and your health care professional.

Despite some states allowing medicinal marijuana, it is a federal crime for a health care professional to prescribe a scheduled drug to a patient known to be using illegal drugs, including marijuana. It is also important to remember, if you travel through a state where medicinal marijuana is not allowed, you could be charged with possession of an illegal substance, even if you have the proper documentation from your home state. Additionally, you can be denied employment or fired if your employer or prospective employer conducts drug screenings as a part of the hiring process or has a ‘no-drug tolerance’ policy. Also you can be charged with driving under the influence (DUI) if your driving is impaired and you test positive for marijuana, even in states where medicinal marijuana is allowed.

People who are self-medicating with marijuana for various complaints may not recognize the reality of marijuana withdrawal symptoms. Marijuana withdrawal symptoms, which can start as early as hours after smoking marijuana and last for up to a month, include sleep disturbances, substantial anxiety (which can worsen pain), discomfort, lack of appetite, and commonly trigger marijuana-seeking.

There are risks associated with chronic marijuana use. More frequent marijuana use is associated with increased risk of severe respiratory illnesses, especially chronic bronchitis. Use also leads to



reduced workplace productivity, as well as impaired judgment even hours after use. Marijuana intoxication impairs cognitive and psychomotor performance with complex, demanding tasks. Individuals who have used marijuana over long periods of time demonstrate impaired performance on a variety of neuropsychological tests (e.g., attention, memory, and processing complex information) even when not acutely intoxicated. A recent review of the existing medical literature concluded that the early use increased the risk of schizophrenia or a schizophrenia-like psychotic illness by approximately three-fold. Emerging evidence suggests a link between more frequent, or severe, marijuana use and anxiety symptoms and disorders.



## **INVASIVE INTERVENTIONS**

### **INTRA-ARTICULAR STEROID INJECTIONS**

Invasive therapeutic interventions for osteoarthritis include steroid injections into the joint. Intra-articular steroids are effective for short-term (1 to 3 weeks) pain relief but do not seem to improve function or to provide pain relief for longer time periods. The number of steroid injections should be limited secondary to associated side effects including fat necrosis, loss of skin pigmentation, skin atrophy, avascular necrosis of the femoral head, Cushing's disease, and in some cases acceleration of joint degeneration. Following a steroid injection, the treated joint should be rested (limit its use) for a minimum of 24 hours in order to prolong and to improve effects on function and pain control.

### **VISCOSUPPLEMENTATION**

Viscosupplementation may also be used for osteoarthritis (OA) of the knee. Viscosupplementation involves injecting lubricating substances (hyaluronic and hylan derivatives) into the knee joint in order to restore the lubrication of the joint and, therefore, decrease pain and improve mobility. Although viscosupplementation may be effective short term treatment for osteoarthritis of the knee, the improvements in pain and function are relatively small. Viscosupplementation seems to have a more prolonged pain relieving effect than intra-articular steroids.

There are currently five available products on the market; Orthovisc<sup>®</sup>, Synvisc<sup>®</sup>, Hyalgan<sup>®</sup>, Supartz<sup>™</sup>, and Euflexxa<sup>™</sup>. In 2009, Synvisc-One<sup>™</sup> (hylan G-F 20) was approved as a single-injection viscosupplement for the treatment of OA knee pain in the United States.

### **SPINAL CORD STIMULATION (SCS)**

Neurostimulation therapy is delivered with a small device implanted under the skin, typically in the abdomen or buttock area. The neurostimulator generates mild electrical signals, which are delivered to an area near the spine. The impulses travel from the device to this spinal area over thin insulated wires called leads.

Medical researchers are still investigating how SCS exactly controls pain and are considering multiple theories. One is the gate control theory, which was the originally proposed mechanism of action of SCS. This theory states that by providing a pleasant vibratory and touch sensation



via the SCS system, pain signals that reach the brain are decreased. It has been discovered that spinal cord stimulation modifies the chemical makeup of the spinal cord.

The current SCS devices are programmable via a remote control, which allows the patient to adjust the therapy within certain limits to help them receive the best pain relief each day, depending on their activity level or changes in pain during the day. It is not uncommon for patients being considered for a SCS to have a psychological evaluation as a part of the overall evaluation process. The purpose of this psychological evaluation is to see if there are any emotional or other difficulties in your life that may adversely affect the surgery or your recovery. During the psychological evaluation, you can expect to be asked questions about how the pain is currently affecting your sleep, mood, relationships and your work, household and recreational activities. You may also be asked to complete some paper-and-pencil tests as well. The results of this evaluation should be shared with you and with your doctor who will consider all the information to determine if you are a good candidate for a SCS.

Two stages are involved in SCS implantation. In both stages, a physician, guided by an x-ray, places a lead into the epidural space located within the bony spinal canal. The first stage is the trial phase, which provides information to predict the success of permanent implantation.

During the trial phase, one or two leads are placed via an epidural needle in the appropriate position. This is an outpatient procedure done under light sedation. Once the lead is in position, it is tested to see if the patient's painful area is covered with a tingling sensation (paresthesia). It is important that the patient is alert during the insertion and testing of the lead so they can inform the healthcare provider if the lead is in the appropriate position.

The lead is programmed with a computer. The patient then goes home for three to five days. He or she has an external power source and remote control that allows him or her to control the amount of stimulation being received. During the trial, the patient should keep an activity record to determine if the treatment is helpful in relieving pain and improving function. At the end of the trial, the patient returns to the physician's office to discuss the results and have the lead removed.

Together, the healthcare provider and the patient decide whether or not to advance to permanent implantation. In this stage, the lead is again placed and implanted underneath the skin with a power source the size of a pacemaker battery. Either a rechargeable or non-rechargeable power source is implanted. For the non-rechargeable systems, the battery cannot be recharged and needs replacement every several years with a minor surgical procedure. The rechargeable system needs recharging when the power source runs low. While it typically lasts longer (up to nine years) than a conventional system, eventually it will need to be replaced with a minor surgical procedure when it can no longer be recharged in a reasonable period of time. The SCS recipient goes home with a remote-control and battery charger (if they have a rechargeable battery). The



patient is instructed to limit activity for about 12 weeks to allow for healing.

The reader should understand that this discussion of SCS systems is limited. These devices are expensive, and their use is limited to selected individuals as a treatment alternative for specific conditions, after consideration of the risks, after failure of a reasonable trial of less invasive methods, and following a successful temporary trial. A psychological evaluation is recommended prior to implantation.

When utilized, spinal cord stimulation should be part of an overall rehabilitation treatment strategy combining behavioral and physical medicine approaches to pain management. Effectively treating pain by implanting an SCS system requires a responsive, long-term relationship between the person with pain and his or her healthcare provider. A significant advantage of a SCS system is that it is a reversible and nondestructive treatment option. Occasional re-programming will be needed to optimize coverage of the painful area.

Furthermore, it is important for the patient and healthcare provider to have realistic expectations regarding treatment, with the goal being pain reduction and control rather than complete elimination. As with most treatments for chronic pain, it is important for people with SCS to involve themselves in a multidisciplinary treatment plan if they are to get the best results. In appropriately selected individuals, SCS treatment can be an important tool in a treatment plan and significantly reduces pain and associated limitations.

In general terms, spinal cord stimulation is primarily suited to certain neuropathic and ischemic (loss of oxygenated blood flow) pain states. Currently, conditions that can respond favorably to SCS treatment include:

- Failed back surgery syndrome with radicular symptoms
- Complex regional pain syndrome (previously known as RSD and causalgia)
- Peripheral neuropathic pain
- Peripheral vascular disease
- Ischemic heart disease

SCS has been proven to be effective for many of these conditions with lasting results in terms of pain relief, pain medication reduction, and improvement in quality-of-life indices and satisfaction scores. Although SCS can also be quite effective in relieving ischemic pain due to peripheral vascular disease and even coronary artery disease, these are currently not FDA approved indications.

Potential complications that may occur include lead migration or fracture and infection. Lead migration after implantation may require revision surgery to regain appropriate coverage. An infection of any kind requires an immediate assessment by the physician. An unrecognized and



untreated infection around the hardware can progress to more serious complications such as an epidural abscess or meningitis.

## **IMPLANTED INTRATHECAL DRUG DELIVERY SYSTEMS (PAIN PUMPS)**

Unlike medications that circulate through your body and in your bloodstream, intrathecal drug delivery systems release medication directly into the fluid surrounding your spinal cord, which may lead to fewer or more tolerable side effects, and in some instances is the only route possible for certain drugs.

With Intrathecal Drug Delivery Therapy:

- Pain medication is delivered via a drug pump directly to the fluid around the spinal cord, in an area called the intrathecal space.
- The drug pump is connected to a thin, flexible tube called a catheter.
- Both the pump and the catheter are surgically implanted under the skin.

The reader should understand that this discussion of implanted drug delivery systems is limited.

These systems are expensive, and their use is limited to selected individuals as an end-stage treatment alternative for specific conditions, after consideration of the risks, after failure of a reasonable trial of less invasive methods, and following a successful temporary trial. It is not uncommon for patients being considered for an intrathecal pump to have a psychological evaluation as a part of the overall evaluation process. These are often done by psychologists or psychiatrists. The purpose of this evaluation is to see if there are any emotional or other difficulties in your life that may adversely affect the surgery or your recovery. During the psychological evaluation, you can expect to be asked questions about how the pain is currently affecting your sleep, mood, relationships and your work, household and recreational activities. You may also be asked to complete some paper-and-pencil tests as well. The results of this evaluation should be shared with you and with your doctor who will consider all the information to determine if you are a good candidate for an intrathecal pump.

A decision to proceed with an implanted drug delivery system should include:

- Failure of 6 months of other conservative treatment modalities (medication, surgical, psychological, or physical),
- Intractable pain secondary to a disease state with objective documentation of pathology;
- Documentation that further surgical intervention is not indicated,



- Psychological evaluation has been obtained, and evaluation states that the pain is not primarily psychological in origin and that benefit would occur with implantation despite any psychiatric comorbidity,
- No contraindications to implantation exist such as sepsis or coagulopathy;
- A life span of at least 3-6 months, and
- If the above criteria are met, a temporary trial of spinal (epidural or intrathecal) opiates has been successful prior to permanent implantation as defined by at least a 50% to 70% reduction in pain and documentation in the medical record of improved function and associated reduction in oral pain medication use.

Opioids (e.g., morphine) are the most common medications delivered by intraspinal infusion. Other medications (e.g., bupivacaine, clonidine, and baclofen) may be added to opioids, particularly in patients with nerve injury pain states (neuropathic pain). In patients with intraspinal infusions, monitoring is needed to check for the development of a mass at the tip of the catheter. Numerous case reports have recently been published demonstrating granulomas (an abnormal tissue growth) at the tip of these catheters which can compress the spinal cord or associated nerve roots. The doses of intraspinal opioids should be limited to the lowest dose possible required to achieve pain relief.

Constipation, urinary retention, nausea, vomiting, and pruritus are typical early adverse effects of intrathecal morphine and are readily managed symptomatically. Other potential adverse effects include amenorrhea, loss of libido, edema, respiratory depression, and technical issues with the intrathecal system. Granulomas and abscesses are possible complications.

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. The drug is delivered intrathecally by continuous infusion through a pump directly into the fluid surrounding the spinal cord. Common side effects include dizziness, nausea, vomiting, confusional states, and nystagmus (inability to control eye movements). Rarely, adverse events such as meningitis, psychosis, convulsions, and rhabdomyolysis (muscle breakdown) have been reported. Ziconotide should be titrated slowly to the appropriate therapeutic effect.

The only drugs that have been approved by the FDA for continuous intrathecal use with implanted intrathecal delivery devices include ziconotide, morphine, and baclofen.



## **EPIDURALS, NERVE & FACET BLOCKS, & RADIOFREQUENCY ABLATION (RHIZOTOMY)**

An epidural steroid injection involves the injection of steroid into the epidural space in the cervical spine (neck) or lumbar spine (low back). Sometimes, a local anesthetic (numbing medicine) may be injected with the steroid. The epidural space is located in the spine just outside of the sac containing the spinal fluid. Epidural steroid injections are often provided to individuals with herniated discs, degenerative disc disease, or spinal stenosis that have associated nerve pain in their arm or leg. The steroids are injected into the epidural space in order to reduce inflammation in and surrounding the spinal nerve roots and adjacent tissues. By reducing inflammation and compression, the level of pain may be decreased. Epidurals are most useful in patients with acute nerve pain from the above conditions. Since a majority of individuals (80 to 90%) with acute low back pain and associated nerve pain will recover spontaneously within three months, these injections should be viewed as a way to facilitate earlier pain relief and return to function. These injections have not been demonstrated to provide long-term successful pain relief for patients solely suffering from chronic (long-standing) back pain or chronic nerve pain. Epidurals rarely provide long lasting benefit but may be useful in these chronic pain conditions for a flare-up. Some patients who have residual pain after the first injection may receive a second epidural steroid injection. Patients who do not receive any relief from the first injection are unlikely to benefit from a second injection. Furthermore, the number of steroid injection per year should be limited in order to avoid side effects that may occur including osteoporosis (weakening of the bones) and avascular necrosis (bone cell death often seen in the hip). Diabetic patients receiving epidural steroids should monitor their blood sugars closely following the procedure since elevations can occur.

Nerve and facet blocks use a combination of local anesthetic and steroid for diagnostic purposes to identify pain generators. These blocks can also be used therapeutically to “block” a painful condition. Unfortunately, these procedures do not provide lasting benefit and are best used as part of an overall treatment plan to relieve discomfort temporarily while engaging in an active rehabilitation program.

Radiofrequency ablation (rhizotomy) or lesioning involves inserting a probe to destroy the nerve that supplies the facet joint. The facet joint, a small joint that connects the back portion of your spine, can become arthritic and cause neck or back pain. Facet joints allow you to bend and twist your back and neck. For an individual with facet joint disease, these movements can be very painful and may limit daily activities. Patients with lumbar (low back) facet joint syndrome often complain of hip and buttock pain, low back stiffness, and pain that is made worse by prolonged sitting or standing. Patients with cervical (neck) facet joint syndrome often complain of neck pain, headache, and/or shoulder pain. In addition, they will often have pain when they rotate or bend their neck.



In order to determine if facet joints are responsible for neck or back pain, medial branch blocks are performed. A medial branch block is a block that is performed under fluoroscopy (x-ray), and local anesthetic (numbing medicine) is injected on the nerves in the back or neck that supply the facet joint. Following the procedure, patients are asked to keep a pain diary to record any pain relief, the amount of pain relief, and for how long. Based on the response to this block, it can be determined if you are a candidate for medial branch radiofrequency ablation (rhizotomy). Patient selection is important to achieving successful results.

Following radiofrequency ablation, patients are often asked to resume physical therapy for flexibility and strengthening exercises. Radiofrequency usually blocks the signal for a prolonged period of time (six months to a year). Eventually, the nerve grows back and can allow the pain signal to be transmitted again. If this happens, the procedure can be repeated. This procedure often does not relieve all back pain, but it relieves the pain associated with facet joint arthritis.

With rhizotomies there is denervation of the spinal muscles with these procedures and thus repeated rhizotomies can cause atrophy of these muscles and thus lead to other untoward effects.

As with any procedure, there are certain risks involved which should be discussed with a treating physician. In order to achieve optimal results, it is important that these interventions be incorporated into a multidisciplinary treatment plan.



## COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Complementary and Alternative Medicine (CAM) includes a diverse group of healing systems, practices, and products that are not part of conventional medicine, although some have proven scientific validity and have become mainstream (acupuncture, meditation, hypnosis, yoga, certain herbal preparations, etc.). Other CAM approaches have strong followers, but their “proof” of value is really anecdotal rather than based on scientific fact.

In fact, what is considered to be CAM changes continually, as those therapies that are proven to be safe and effective become adopted into conventional health care and as new approaches to health care emerge.

Complementary medicine and alternative medicine are different from each other. Complementary medicine is used together with conventional medicine while alternative medicine is used in place of conventional medicine. Integrative or integrated medicine combines treatments from conventional medicine and CAM for which there is some high-quality evidence of safety and effectiveness.

The reader is referred to the following Internet web sites for further information.

The National Center for Complementary and Alternative Medicine (<http://nccam.nih.gov>) is part of the National Institutes of Health (NIH) and is the lead agency for scientific research on CAM.



## **PASSIVE THERAPIES & PHYSICAL MODALITIES**

Passive therapy (those treatment modalities that do not require energy expenditure on the part of the patient) can provide short term relief during chronic pain flare-ups and is directed at controlling symptoms such as pain, inflammation, and swelling. These therapies can include massage, ultrasound, iontophoresis, paraffin (wax) treatment, light therapy or traction. Passive therapies may be useful over the short term but have limited benefit in chronic pain conditions overall.

### **HYPERBARIC OXYGEN**

Hyperbaric oxygen (HBO) involves the administration of oxygen in a pressurized chamber to increase oxygen delivery to the tissues of the body. It has been used to treat a number of conditions with problematic microvascular blood supply, including diabetic foot ulcers and decubitus ulcers.

HBO therapy recently has shown promising results for some chronic pain syndromes, but its use is far from proven.

Several authors claim HBO is a reliable method of treatment and may be beneficial if appropriate persons are selected. Further research is required to identify the best treatment protocol, the cost/benefit ratio, and the safety of HBO in chronic pain management—and whether it actually works.

### **ACUPUNCTURE**

Acupuncture originated in China and is based in part on the theory that many diseases are manifestations of an imbalance between yin and yang as reflected by disruption of normal vital energy flow (Qi) in specific locations, referred to as meridians. Needling along one of the 361 classical acupuncture points on these meridians is believed to restore the balance. This stimulation is classically done with thin, solid, metallic needles, which are then manipulated (or turned) manually or stimulated electrically (electroacupuncture). Besides needling, acupuncture frequently involves moxibustion and cupping. Besides traditional Chinese acupuncture, there are many other types of acupuncture that have arisen, including accessing non-traditional acupuncture points.

Acupuncture has been utilized to treat many different disorders including smoking cessation, nausea and chronic pain. It has gained wide and increasing acceptance and is now covered by many insurance policies.



## **MANIPULATION & MOBILIZATION**

Spinal Manipulative Therapy (SMT) is a therapeutic intervention performed for what is described as “restricted joint(s)” in the spinal column.

Spinal manipulation is a historically recognized therapeutic intervention employed in various cultures for thousands of years. In modern time, the procedure is utilized by Doctors of Chiropractic (DCs), Doctors of Osteopathy (DOs) and physical therapists (PTs). Chiropractors prefer the term "adjustment" whereas physical therapists apply the word "mobilization." Adjustment is described as a more specific type of SMT, often provided to address a specifically identified biomechanical fault.

Manipulation and mobilization are two types of manual (hands-on) therapy that include a wide array of different techniques and schools of thought. Traditional manipulation involves high force, high velocity, and low amplitude action (HVLA) forces with a focus on moving a targeted, fixated or hypomobile joint(s). In general, mobilization involves assisted low force, low velocity movement often directed to one or more restricted vertebral segments and typically uses long lever arms to deliver the force. As commonly used, adjustment is generally a synonym for manipulation.

The effects of spinal manipulation include relief of acute and chronic back pain, improved spinal motion, and affecting the nervous system mostly at the local spinal level. There are research studies which supports the benefits of SMT.

Overall, studies have shown that spinal manipulation can provide relief from acute and chronic low back and neck pain. SMT can be as or more effective as conventional medical treatments. In 2007 Guidelines, the American College of Physicians and the American Pain Society include spinal manipulation as one of several treatment options for practitioners to consider using when pain does not improve with self-care. Research studies have shown that spinal manipulation can be a more effective treatment of chronic back pain than bed rest, traction, topical gels, or no treatment; some studies show superiority of SMT over acupuncture, physiotherapy, and back school for low back pain.

## **ELECTRICAL STIMULATION DEVICES (EXTERNAL)**

Electrotherapy represents the therapeutic use of electricity and is another modality that can be used in the treatment of pain. Transcutaneous electrotherapy is the most common form of electrotherapy in which electrical stimulation is applied to the surface of the skin. The earliest devices were referred to as TENS (transcutaneous electrical nerve stimulation) and are the most commonly used.



Interferential Current Stimulation (ICS) Interferential stimulation allows for deeper penetration of tissue, whereas TENS is predominantly a cutaneous or superficial stimulus. Interferential current is proposed to produce less impedance in the tissue and the intensity provided is supposed to be more comfortable. Because there is minimal skin resistance with the interferential current therapy, a maximum amount of energy goes deeper into the tissue. It also crisscrosses, as opposed to the linear application of the TENS. This crisscrossing is postulated to be more effective because it serves to confuse the nerve endings, preventing the treated area from adjusting to the current.

## **TRIGGER POINT INJECTIONS**

Trigger point injections are given to individuals with a myofascial pain syndrome, a regional painful muscle condition. These injections may provide short term benefit only.

The CA Chronic Pain Medical Treatment Guidelines reports the following: a trigger point is a discrete focal tenderness located in a palpable taut band of skeletal muscle, which produces a local twitch in response to stimulus to the band. Trigger points may be present in up to 33-50% of the adult population. Myofascial pain syndrome is a regional painful muscle condition with a direct relationship between a specific trigger point and its associated pain region. These injections may occasionally be necessary to maintain function in those with myofascial problems when myofascial trigger points are present on examination.



## **ACTIVE INTERVENTIONS - MONOTHERAPIES**

### **EDUCATION**

Education of the patient and family should be a primary emphasis in the treatment of chronic pain. Currently, many persons with chronic pain and their practitioners often think of education last, after medications, passive therapy, other invasive interventions and surgery. It is critical for all concerned to develop and implement effective strategies and skills to educate persons with chronic pain. No treatment plan is complete without addressing issues of individual and/or group patient education as a means of facilitating self-management of symptoms and prevention.

### **EXERCISE (ACTIVE THERAPY)**

The overwhelming theme in the treatment of most persons with chronic pain is to keep as physically active as possible. In fact, advancement of activity levels and education is recommended, as inactivity is detrimental despite the temporary relief of symptoms that often accompanies it.

There is strong evidence that exercise programs are beneficial for persons with chronic pain. After consultation with a physician and/or physical therapist, a therapeutic exercise program should be initiated at the start of any chronic pain treatment program. Such programs should emphasize education, independence, and the importance of an on-going self-directed exercise regimen.

Therapeutic exercise can be classified to include 1) Range-of-motion exercises; 2) Stretching; 3) Strength training; and 4) Cardiovascular conditioning.

Active therapy is based on the philosophy that therapeutic exercise and/or activity are beneficial for restoring flexibility, strength, endurance, function, range of motion, and can alleviate discomfort. Active therapy requires an internal effort by the individual to complete a specific exercise or task.

Aquatic therapy or exercise may be beneficial for individuals who have comorbidities that preclude participation in weight-bearing exercise or for those whose pain or weakness limits them from participating in even a low-level land program. Hydrostatic principals and buoyancy can provide decreased stress on weight-bearing joints. Once the individual gains strength and flexibility in the water, they should transition, at least in part, to a land based exercise program.



Persons with chronic pain can become discouraged when their pain temporarily increases due to therapeutic exercise, and they will sometimes terminate treatment too early before achieving maximal benefit. A flare-up of pain with exercise should be expected even with safe exercise, but can also be due to poor body mechanics, guarded or stiff movement, high levels of demand on an injured site, or compensatory movements. It is important to have a health care professional knowledgeable about treating chronic pain to assist not only with setting up a graded and careful exercise program, but also to assist with distinguishing new symptoms that may signify problems from the “good” discomfort that normally goes along with an increasing exercise program

## **TAI CHI**

Tai Chi is an ancient Chinese system of meditative movements practiced as exercises. Originally, Tai Chi was used as a form of combat. But today, it is a gentle form of exercise, popularized in the Western world in the 1980s and 1990s. Now, people of all ages use these movements to gain strength and flexibility.

As a low-impact exercise, Tai Chi is great for people with joint problems because it actually helps build connective tissue and improve circulation. Additionally, this form of exercise improves balance and posture by emphasizing correct form with each movement. Instead of developing bulky muscles and brute force, exercisers tackle tension and stress while improving body awareness.

Tai Chi is a series of soft, flowing movements choreographed into a slow routine. Each specific movement corresponds with either the inhalation or exhalation of a deep, gentle breath. This coordination of movement and breath is believed to free the flow of “chi”- a life-force energy that when blocked, purportedly can cause stress and illness. By improving the mind/body connection, Tai Chi brings the yin and yang of a person back into natural harmony, exercising emotions just as it does the muscles. Tai Chi revolves around a series of movements called “forms” which can last anywhere from five to 20 minutes. There are over 100 different stances to learn.

## **YOGA**

Yoga helps to manage chronic pain by stretching, strengthening and relaxing the body. It creates a greater sense of health and well-being by emphasizing mindful practice, breath awareness and proper body alignment. There are many different styles and schools of yoga. There are multiple poses (asanas) and different props can be used. People with chronic pain should begin with a gentle, slow-paced class. Benefits of yoga include improvements in sleep and the ability to handle stress and feeling more relaxed throughout the day.

These three styles of yoga are good for beginning students:



Iyengar Yoga utilizes straps, blocks and chairs as props to assist participants in the precise alignment of their poses. Because of this assistance, Iyengar is an ideal style of yoga for beginners or those suffering from chronic pain. Unlike 'flow yoga', Iyengar poses are held in order to focus on safe alignment and to build endurance.

Yin Yoga focuses on the body's connective tissue, ligaments and joints as opposed to the muscles. Yin Yoga is practiced on the floor and most poses are either sitting or reclining. To affect change in the connective tissue poses are held for time – sometimes up to ten minutes. Although challenging, Yin Yoga has a deeply soothing effect on the nervous system and for that reason is more relaxing than Iyengar Yoga.

In Restorative Yoga, the body is supported in the poses by a variety of props. This encourages passive stretching and deeper awareness of the breath. Because of their passive nature, restorative poses are often held for up to twenty minutes.

These styles of yoga require strength and endurance:

- Ashtanga Yoga is characterized by constant movement, or flow, from one posture to another. It is vigorous and fast-paced, earning it the nickname of Power Yoga. The focus is on deep breathing during each pose.
- Vinyasa is similar to Ashtanga Yoga in its emphasis on flowing through postures, particularly Surya Namaskar (Sun Salutation). The goal of Vinyasa is to improve coordination, strength and balance by following the sequence of active poses.
- Bikram or "hot" yoga literally refers to the fact that the practice studio is heated to 104 degrees Fahrenheit. The practice consists of 26 poses which are repeated twice. The intense sweat produced is thought to purify the body.
- Kundalini yoga focuses on purifying the emotions, the mind and the body while placing emphasis on the effects of breathing on each pose. Chanting mantras and meditation are common practices of Kundalini. The word Kundalini refers to an energy which is said to reside at the base of the spine. The intention of Kundalini practice is to release this energy.

## **GRADED MOTOR IMAGERY**

Research has shown that there are altered connections and reorganization of the brains of those who suffer from chronic pain; although it is not clear whether these changes are a consequence of the chronic pain or that they may have led to the pain becoming chronic. Treatment of chronic pain has started to include techniques called graded motor imagery which focus on brain re-training.

Graded motor imagery is a set of rehabilitation process used to treat pain and movement problems related to altered nervous systems. The three different treatment techniques include



limb laterality training, motor imagery exercises and mirror therapy. These techniques are delivered sequentially or individually. A leading group in this type of treatment is the noigroup.

People suffering from chronic pain often lose the ability to identify left or right images of their painful body parts. Limb laterality training includes viewing photographs of left or right body parts in a variety of postures, focused on improving speed and accuracy. Motor imagery involves thinking about a movement, but not actually performing that movement. By imagining movements, you use similar areas of the brain as you would when you perform the same movement. This technique is commonly used in competitive sports training. Mirror therapy involves movement of the limb inside a mirror-box such that visual feedback of the affected hand is replaced with that of the (reflected) unaffected hand. Mirror therapy is thought to reconnect motor output and sensory feedback and active pre-motor cortices. Mirror therapy has been found effective for CRPS and phantom limb pain in particular.



## PSYCHOLOGICAL & BEHAVIORAL APPROACHES

Psychological therapies are sometimes known as mental health treatment, psychotherapy, talk-therapy or counseling. The primary focus of these therapies is to help improve a sense of control over the pain. Pain can be stressful and strategies to reduce stress and improve coping can be directly beneficial.

Therapists help the person with chronic pain to identify the vicious cycle of pain. People who hurt tend to be inactive and to guard and hold muscle areas to prevent more pain. Over time they can become deconditioned, socially isolated, have recurrent worried thoughts, and have problems with sleep, often staying up at night and napping during the days. With time they can become depressed, alone and even more anxious, and this can have a tendency to make the pain worse.

A therapist can help to break this cycle by exploring ways for the individual to gradually improve function, reduce worried thoughts, and improve mood. Strategies that have been most helpful include monitoring daily activity and mood, using problem-solving techniques, challenging some of the recurrent worried thoughts, engaging in a gradual exercise program, watching body cues, maintaining a daily routine and schedule, learning to pace activities, watching diet and caloric intake, getting involved in distracting activities with others, sharing emotions associated with the pain, and contacting others for help when needed. Therapists can also be helpful in reviewing steps to prevent a relapse. With time the person with pain can become more “smart” about the pain in working toward better control, anticipating good and bad days, and not dwelling on those things that are out of the person’s control.

Therapists trained in behavioral medicine also often participate in relaxation training using various techniques that include diaphragmatic breathing, progressive muscle relaxation, autogenic relaxation, guided imagery, cue-controlled relaxation, and hypnosis. Some therapists use sensitive equipment to measure muscle tension, hand temperature or skin conductance known as a “biofeedback.” This form of treatment uses feedback from the equipment in order to help an individual learn to relax. With practice the individual can eventually relax without using equipment.

There are a number of mental health therapists who offer psychotherapy and behavioral therapy for persons with chronic pain and who are specially trained and licensed by the state in which they practice. This therapy can be provided by psychologists, social workers, and other counselors.

- Psychologists are doctors who have a Doctor of Philosophy (Ph.D.) or Doctor of Psychology (Psy.D.) and specialize in human behavior and emotional health. They have training in working with individuals, couples, and families and do so either in group or individual sessions. They can also administer and interpret psychological tests. They have expertise in



dealing with most emotional and behavioral problems. In some states, psychologists can prescribe medications for emotional problems.

- Social Workers have Masters Degrees (MA or MS) and are sometimes called Licensed Clinical Social Workers (LCSW). They receive specialized training in how people function in their environment and solve personal and family problems. Some also have experience in case management and can assist you in finding government and local resources in your community for your needs.
- Masters-Level Counselors have Masters Degrees (MA or MS) in either clinical or counseling psychology. They are sometimes called Licensed Marriage & Family Therapists or Licensed Professional Counselors. They have specialized training in dealing with individuals and families particularly in relationship problems.

It is important to remember that the goal of psychotherapy and behavioral therapy is not to ‘cure’ or get rid of your pain, and seeing a psychologist or other counselor does not mean that your pain is not real. Psychotherapy can help you cope or manage your pain to lessen its impact on you, your activities, relationships, and other aspects of your life.

There are many forms of psychotherapy; the ones with the greatest scientific support are cognitive-behavioral therapies (CBT), most typically delivered by psychologists. The central idea in CBT is that a person’s thoughts and beliefs, moods, and emotions influence pain and the behaviors that lead to activity engagement. For example, unhelpful thoughts can contribute to negative feelings, and negative feelings can increase sensitivity to pain and decrease engagement in activity. In CBT, you will work with your therapist to identify, evaluate and modify unhelpful thoughts, emotions, and behaviors that may influence pain and engagement in activities. CBT includes a range of strategies aimed at enhancing coping skills, increasing confidence and self-efficacy for managing pain, and changing how individuals behave in response to pain. Commonly, CBT incorporates interventions to address other present health problems and behaviors that can interfere with pain management such as sleep disturbances, smoking, and obesity. Remember the goal of these interventions is not to get rid of your pain, but to help you better cope with pain and lessen pain’s impact on your day-to-day activities and quality of life.

CBT is also effective for children and adolescents who are struggling with chronic pain. In treating children, therapists also work with parents to provide education and instruction in strategies to best support the young person in better coping with pain.

Another form of therapy designed to help persons with chronic pain is called Acceptance and Commitment Therapy or ACT. It is a psychological intervention that focuses on acceptance and uses mindfulness strategies to increase awareness and psychological flexibility. It differs from CBT by teaching individuals to passively notice, accept and embrace events rather than teaching



individuals to control their worries, thoughts and feelings. There is evidence that ACT can be very helpful for certain persons with chronic pain who struggle in trying to change what has happened to them.

Again, just because these psychotherapeutic techniques are effective in improving your ability to better manage your chronic pain, it does not mean that your pain was ‘all in your head’ or that your pain is not real.

## **MIND-BODY INTERVENTIONS**

There are numerous mind-body interventions including relaxation, meditation, imagery, biofeedback, and hypnosis. Many psychologists also use mind-body interventions as a part of the CBT.

Hypnosis is a state of deep relaxation that involves selective focusing, receptive concentration, and minimal motor functioning. A National Institutes of Health Technology Panel found strong support for the use of hypnosis for the reduction of pain. Individuals can be taught to use hypnosis themselves (self-hypnosis), and the use of self-hypnosis can provide pain relief for up to several hours at a time.

There are a variety of meditative practices, with the most studied one for chronic pain being mindfulness-based stress reduction (MBSR). It is a variant of meditation that has been applied to stress reduction.

Techniques, such as relaxation and biofeedback, are directed toward helping persons with chronic pain become aware of their ability to exert some control over physiologic processes of which they are not normally aware (e.g., muscle tension, heart rate, skin temperature, and respiration).

Relaxation, self-hypnosis, and meditation techniques are a form of physiologic self-management. They assist individuals with muscle relaxation and distraction away from pain perception.

Biofeedback uses feedback from a device or computer to give information about a person’s progress. This can be particularly useful in headaches and chronic pain in which pain tends to tense muscles, which often causes increased pain due to muscle fatigue.

## **ELECTRONIC PAIN-MANAGEMENT PROGRAMS**

There are a number of stand-alone and Internet-based programs to help in the management of pain. The American Chronic Pain Association website can be a great source of information



([www.theacpa.org](http://www.theacpa.org)). This and other pain management programs include ways to track daily pain and activity and can be a useful vehicle to easily summarize progress over time. They can be especially helpful when starting an exercise routine by tracking progress based on frequency and duration of the exercises. These programs can also suggest warm-up and cool-down stretching routines catered for each individual's pain problem. They also can be useful for monitoring medication use and giving helpful reminders throughout the day. A daily food diary can help in identifying healthy and unhealthy eating habits. In development are smart phone applications (apps) just for persons with chronic pain. These programs are useful in identifying important information about the pain, summarizing progress for your healthcare provider, and in offering daily tips and recommendations for improving pain management.



## **ACTIVE INTERVENTIONS- INTERDISCIPLINARY**

Although there are many different individual, helpful active interventions that will be described below, more and more the literature is supporting a “whole person” approach for those dealing with chronic pain. This is often described as a functional restoration approach. This approach encompasses many of the individual interventions, in a coordinated, goal-oriented manner.

### **FUNCTIONAL RESTORATION PROGRAMS & APPROACHES**

Functional restoration refers to a philosophy and approach to medical care that is unique and is based on a biopsychosocial model of medical diagnosis and care that focuses on not just the biology (injury/illness and associated pathology), but also on the individual as a whole person including psychological and social aspects.

Functional restoration involves multiple disciplines that work together in a coordinated fashion with shared treatment goals. Functional restoration approaches are focused on maximizing function, returning to pre-injury productivity (with sufficient functional capacity to avoid recurrent injuries), and preventing needless disability, unnecessary medical and surgical care, and healthcare related complications.

The biopsychosocial model of pain recognizes that pain is ultimately a sum of the individual’s biology, psychological history and state, belief system about pain, and interactions with the environment (workplace, home, disability system, and health care providers). All of these factors can strongly influence symptom severity and how quickly the individual can return to function.

Functional restoration can be defined as the process by which an individual acquires the skills, knowledge, and behavioral changes necessary to assume or re-assume primary responsibility for his/her physical and emotional well-being. Functional restoration thereby empowers the individual to achieve maximum functional independence, to have the capacity to regain or maximize activities of daily living, and to return to vocational and avocational activities.

Fundamental elements of a functional restoration approach include assessment of the person’s dynamic physical, functional, and psychosocial status. This is followed by a treatment plan that includes directed conditioning and exercise, cognitive behavioral therapy, patient and family education, and counseling; functional goal setting; ongoing assessment of participation, compliance, and complicating problems; and progress toward achievement of goals.

Functional restoration treatment team members act as educators, de-emphasizing passive and/or palliative therapies, while emphasizing independent self-management. There should be a shift of



health and well-being responsibility from the health care professionals and therapists to the person.

A functional restoration approach can include the limited/adjunctive use of medications and appropriate interventions for the specific purpose of supporting the individual's effort to reach and maintain maximum functional improvement; institution of preventive measures, expectation management, education for relapse prevention, proper activity and work pacing, ergonomic accommodation; and when appropriate, transitional return to gainful employment with as little disruption from the work site and coworkers as possible.

Functional restoration involves objective measures of physical performance that guide treatment progression. At the same time, physical and occupational therapists, psychologists, nurses, and case managers provide education on pain management, coping skills, return to work issues, and fear-avoidance beliefs. They often use a cognitive behavioral therapy (CBT) approach consistent with the biopsychosocial view of chronic pain/disability.

Ultimately, successful individuals with chronic pain take control of and re-engage in life activities and have achieved mastery over when and how to access the medical community in a way that is most beneficial for them. The goal is a mitigation of suffering and return to a productive life despite having a chronic/persistent pain problem.

These programs involve an integrated team of professionals providing intensive, coordinated care which may include pain specialist physicians, physical therapists, occupational therapists, psychologists, vocational counselors, nurses, and case managers providing individualized treatment in a structured setting.



## FINAL COMMENTS

An essential concept in pain management is that each person is different and will respond differently to situations, interventions, surgeries, 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 any particular treatment or medication. The best place to get advice about treatments and 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 provided a certain treatment or who is taking medication. Sometimes the person provided the treatment or taking the medication does not realize the changes that are produced. Family member observations will be helpful to the health care provider.

There is no question that there are many treatment approaches (tools) in the “tool chest” of the treating health care professional or therapist, but they should be used judiciously. Benefit should be based on less pain, more function, and return to everyday activities with the least, manageable side effects possible.

This ACPA Resource Guide to Chronic Pain Medication & Treatment only deals with certain treatments and medications, but it is important to understand that there are many other treatment approaches to chronic pain that may not be covered in this document. This document is a work in progress, and the ACPA welcomes your comments and recommendations.

The ACPA once again reminds you that this ACPA Resource Guide to Chronic Pain Medication & Treatment is not meant to serve as medical advice for your condition or regarding your treatment or medication needs. Remember that the best source of information about your health care regarding treatment and medication needs is from an open dialogue with your health care professional and therapist.



## REFERENCES: LINKS TO CHRONIC PAIN SITES & RESOURCES

Learning as much as you can about your health condition is part of being an informed consumer and an active partner on your care team. Go to the following ACPA website to find sites that can help you learn more and better manage your chronic pain:

<http://www.theacpa.org/28/Links.aspx>.

### MEDICATION RELATED

1. WebMD: Drugs & Medications A-Z - <http://www.webmd.com/drugs>
2. Drug InfoNet: - <http://www.druginfonet.com/drug.htm>
3. PDR.net: Drug Information - <http://www.pdr.net>
4. Medscape: Drugs - <http://www.medscape.com/druginfo>
5. FDA: Drugs - <http://www.fda.gov/cder/drug/default.htm>
6. MedLine Plus: Drugs, Herbals, and Supplements - <http://www.nlm.nih.gov/medlineplus/druginformation.html>
7. HealthSquare.com: Drugs and Medicines - <http://www.healthsquare.com/drugmain.htm>
8. Drugs.com: Drug Information Online - <http://www.drugs.com/>
9. RxList: The Internet Drug Index - <http://www.rxlist.com>
10. Popular Medications – And Drug Information You Should Know: <http://www.medicinenet.com/pdf/popularmedicationsguide.pdf>
11. Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act, A Joint Statement From 21 Health Organizations and the Drug Enforcement Administration: [http://aspmn.org/pdfs/A\\_JOINT\\_STATEMENT\\_FROM\\_21\\_HEALTH\\_ORGANIZATIONS.pdf](http://aspmn.org/pdfs/A_JOINT_STATEMENT_FROM_21_HEALTH_ORGANIZATIONS.pdf)
12. Drugs and Supplements: <http://www.mayoclinic.com/health/drug-information/DrugHerbIndex>
13. Nonsteroidal anti-inflammatory drugs (NSAIDs): [http://www.stoppain.org/pain\\_medicine/content/medication/nsaids.asp](http://www.stoppain.org/pain_medicine/content/medication/nsaids.asp)



14. Adjuvant Medications:

[http://www.stoppain.org/pain\\_medicine/content/medication/adjuvants.asp](http://www.stoppain.org/pain_medicine/content/medication/adjuvants.asp)

15. Opioid Analgesics: [http://www.stoppain.org/pain\\_medicine/content/medication/opioids.asp](http://www.stoppain.org/pain_medicine/content/medication/opioids.asp)

16. American Society of Health-System Pharmacists: <http://www.safemedication.com/>

17. eMedicineHealth: [http://www.emedicinehealth.com/pain\\_medications/article\\_em.htm](http://www.emedicinehealth.com/pain_medications/article_em.htm)

18. WebMD: <http://www.webmd.com/pain-management/guide/pain-relievers>

19. C.A.R.E.S. Alliance: <http://www.caresalliance.org/>

## OTHER REFERENCES

Agency for Healthcare Research and Quality (AHRQ). (2007). *Choosing Nonopioid Analgesics for Osteoarthritis: Clinician Summary Guide: Available at* <http://informahealthcare.com/doi/abs/10.3109/15360280903332237>

American Academy of Pain Medicine (AAPM), American Pain Society (APS), American Society of Addiction Medicine (ASAM). (2001). *Definitions related to the use of opioids for the treatment of pain*. Available at <http://www.painmed.org/Workarea/DownloadAsset.aspx?id=3204>

American Academy of Family Physicians (AAFP). Herbal health products. What you should know. Available at <http://www.aafp.org/afp/990301ap/990301e.html>

American Chronic Pain Association (ACPA). List of professional groups and pain initiatives available at <http://theacpa.org/58/ProfessionalGroups.aspx>

American College of Rheumatology (ACR) Subcommittee on Osteoarthritis Guidelines. (2000). Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 43(9):1905-1915. Available at <http://rheumatology.org/practice/clinical/guidelines/oa-mgmt.asp>

American Geriatrics Society (AGS) Panel on Persistent Pain in the Older Person. (2002). The management of persistent pain in older persons. *J Am Geriatr Soc*, 50(Suppl 6), S205-S224.



American Geriatrics Society (AGS). (2009). Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*, 57, 1331-1346. Available at [http://www.americangeriatrics.org/files/documents/2009\\_Guideline.pdf](http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf)

American Pain Society (APS). (2008). *Principles of analgesic use in the treatment of acute and cancer pain* (6<sup>th</sup> ed). Glenview, IL: APS. Available at <http://ampainsoc.org>

American Pain Society and American Academy of Pain Medicine (2009). *Evidence Review: APS-AAPM Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain*. Available at [http://ampainsoc.org/pub/pdf/Opioid\\_Final\\_Evidence\\_Report.pdf](http://ampainsoc.org/pub/pdf/Opioid_Final_Evidence_Report.pdf)

Argoff, C.E., Albrecht, P., Irving, G., et al. (2009). Multimodal analgesia for chronic pain: Rationale and future directions. *Pain Medicine*, 10(Suppl 2), S53-S66.

Bruckenthal, P. (2010). Integrating nonpharmacologic and alternative strategies into a comprehensive management approach for older adults with pain. *Pain Management Nursing*, 11(2), S23-S31.

Compton, P. (Aug. 20, 2008). The OIH paradox: Can opioids make pain worse? *Pain Treatment Topics*. Available at <http://pain-topics.org/pdf/Compton-OIH-Paradox.pdf>

Drug Information Online (Drugs.com). *Drug Interactions Checker*. Available at [http://www.drugs.com/drug\\_interactions.php](http://www.drugs.com/drug_interactions.php)

Dworkin, R.H., O'Connor, A.B., Audette, J.B., et al. (2010). Recommendations for pharmacological management of neuropathic pain. *Mayo Clinic Proceedings*, 85 (3 Suppl), S3-14.

Epocrates online. Available at <http://www.epocrates.com/online>

Familydoctor.org. Information about over-the-counter and prescription drugs. Available at <http://familydoctor.org/familydoctor/en/drugs-procedures-devices.html>

Feinberg Medical Group. List of references, professional organizations, and websites. Available at <http://www.feinbergmedicalgroup.com/#!reference/vstc2=internet-links>

Food and Drug Administration (FDA). Variety of drug safety information available at <http://www.fda.gov/Cder/drugSafety.htm>

Food and Drug Administration (FDA). *A Guide to Safe Use of Pain Medicine*. Available at <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm095742.pdf>



Food and Drug Administration (FDA). *Consumer Education: What You Need to Know to Use Medicine Safely*. Available at <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm101467.htm>

Food and Drug Administration (FDA). *Over-the-Counter Medicines: What's Right for You?* Available at <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/Choosingtherightover-the-countermedicineOTCs/UCM150312.pdf>

Food and Drug Administration (FDA). *Buying Prescription Medicine Online: A Consumer Safety Guide*. Available at <http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM133237.pdf>

National Center for Complementary and Alternative Medicine (NCCAM). (2010). What is CAM? Available at <http://www.nccam.nih.gov/health/whatiscam/>

Pain Treatment Topics. Available at <http://www.pain-topics.org/>

Pasero C, McCaffery M. (2011). *Pain Assessment and Pharmacologic Management*. St. Louis: Elsevier/Mosby.

Passik, S. (2005). *Managing Drug Abuse, Addiction, and Diversion in Chronic Pain: The 4 A's for Ongoing Monitoring*. Available at [http://www.medscape.org/viewarticle/510856\\_5](http://www.medscape.org/viewarticle/510856_5) (Must sign-up as a member).

Risk Evaluation and Mitigation Strategies (REMS). Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

SparkPeople. Guide to use of herbal supplements. Available at

[http://www.sparkpeople.com/resource/nutrition\\_articles.asp?id=506](http://www.sparkpeople.com/resource/nutrition_articles.asp?id=506)

