

ACPA Consumer Guide to Pain Medication & Treatment

2010 Edition

American Chronic Pain Association

P.O. Box 850

Rocklin, CA 95677

Tel 800-533-3231

Fax 916- 632-3208

E-mail ACPA@pacbell.net

www.theacpa.org

Copyright 2010 American Chronic Pain Association, Inc.
All rights reserved. No portion of this book may be reproduced without permission of the
American Chronic Pain Association, Inc.

Table of Contents

INTRODUCTION.....	5
PART I: PAIN TYPES & CHRONIC PAIN CLASSIFICATION	7
PAIN IN CHILDREN	7
PAIN IN OLDER PERSONS	8
CLINICAL TRIALS	8
PART II: MEDICATIONS AND CHRONIC PAIN.....	9
HOW MEDICATIONS CAN HELP & HARM	9
ADVICE FROM THE ACPA.....	10
WARNING FROM THE ACPA ABOUT PURCHASING MEDICINES OVER THE INTERNET	11
MEDICATION PICTURES	12
MEDICATION SIDE EFFECTS, DRUG ALLERGIES & DRUG INTERACTIONS.....	12
OFF-LABEL MEDICATION USE.....	13
PART III - OVER-THE-COUNTER (OTC) PAIN RELIEVERS.....	15
THE SAFETY OF OTC MEDICATIONS	16
ACETAMINOPHEN SPECIAL COMMENTS.....	17
PART IV - PRESCRIPTION MEDICATIONS FOR CHRONIC PAIN.....	19
NON-OPIOID ANALGESIC PAIN RELIEVERS (NON-NARCOTIC).....	19
GI PROTECTIVE MEDICATIONS.....	21
NON-OPIOID ANALGESIC DRUGS AND THEIR USES	22
OPIOID ANALGESICS	23
OPIOID ADVERSE SIDE EFFECTS	28
DEFINITION OF TERMS	31
OPIOID USE CONSENSUS STATEMENT	34
OPIOIDS AND THE GOALS OF PAIN MANAGEMENT	36
EVALUATING OPIOID USE	36
OPIOID TREATMENT AGREEMENT	39
ANTIDEPRESSANTS.....	40
HOW ANTIDEPRESSANTS MAY HELP	40
ANTIDEPRESSANT SIDE EFFECTS	41
BENEFITS OF ANTIDEPRESSANTS IN CHRONIC PAIN	41
ANTIDEPRESSANTS COMMONLY USED FOR CHRONIC PAIN	42
TRICYCLIC ANTIDEPRESSANTS (TCAs)	42
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs).....	43
SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)	44
ANTICONSULSANT (ANTIEPILEPTIC) DRUGS.....	47
SODIUM CHANNEL BLOCKING & ORAL ANTI-ARRHYTHMIC AGENTS	49
TOPICAL PAIN RELIEVERS.....	50
COMPOUNDED MEDICATIONS	53
SEDATIVES, ANTI-ANXIETY MEDICATIONS, & TRANQUILIZERS	53
MUSCLE RELAXANTS.....	56
ANTI-PSYCHOTIC MEDICATIONS	57
ANTI-HYPERTENSIVE MEDICATIONS	57
BOTULINUM TOXIN.....	58
NMDA INHIBITORS	58
ADRENERGIC DRUGS, BISPHTHONATES, THALIDOMIDE & CALCITONIN.....	59
ACTIVATING MEDICATIONS (CENTRAL NERVOUS SYSTEM STIMULANTS).....	60
MIGRAINE HEADACHE TREATMENT.....	61
PART V - HERBAL MEDICINES, SUPPLEMENTS, & VITAMINS.....	63
POSSIBLE BENEFIT REGARDING THE USE OF HERBAL MEDICATIONS	63
CONCERNS REGARDING THE USE OF HERBAL PREPARATIONS, SUPPLEMENTS & VITAMINS.....	64
PART VI – ALCOHOL, MARIJUANA AND ILLICIT SUBSTANCES.....	66
ALCOHOL & CHRONIC PAIN	66



ILLEGAL DRUGS & MARIJUANA	67
PART VII - INVASIVE INTERVENTIONS	68
VISCOSUPPLEMENTATION.....	68
SPINAL CORD STIMULATION (SCS)	68
IMPLANTED INTRATHECAL DRUG DELIVERY SYSTEMS (“PAIN PUMPS”).....	70
EPIDURALS, NERVE & FACET BLOCKS & RADIOFREQUENCY ABLATION (RHIZOTOMY)	72
PART VIII – COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM).....	74
PART IX – PASSIVE NON-INVASIVE INTERVENTIONS	75
HYPERBARIC OXYGEN	75
ACUPUNCTURE.....	75
PASSIVE THERAPIES AND PHYSICAL MODALITIES	75
MANIPULATION & MOBILIZATION	76
MAGNET THERAPY	76
ELECTRICAL STIMULATION DEVICES (EXTERNAL)	76
TRIGGER POINT INJECTIONS	76
PROLOTHERAPY (SCLEROTHERAPY)	76
SURGERY	77
PART X – ACTIVE INTERVENTIONS	78
EXERCISE (ACTIVE THERAPY).....	78
PSYCHOLOGICAL AND BEHAVIORAL APPROACHES.....	79
MIND-BODY INTERVENTIONS.....	79
EDUCATION	80
FUNCTIONAL RESTORATION PROGRAMS & APPROACHES	80
CONCLUSION	81
LINKS TO CHRONIC PAIN SITES AND RESOURCES	82
REFERENCES ON THE INTERNET	82



Authors and Contributors

Written, reviewed & updated yearly by Senior Author Steven Feinberg, M.D., with Co-author David Provenzano, M.D., and with special thanks to April Fong, Pharm.D.

Dr. Feinberg (<http://www.StevenFeinbergMD.com>) is a practicing pain medicine physician in Palo Alto, California, and is an Adjunct Clinical Professor at Stanford University School of Medicine. He is a former Board member and Past President of the American Academy of Pain Medicine. He is a member of the ACPA Board of Directors. He is an Associate Editor of the Academy of Occupational and Environmental Medicine (ACOEM) Chronic Pain Guidelines 2008 Chapter update and a Medical Advisor to the Occupational Disability Guidelines (ODG).

Dr. David Provenzano is the Executive Director of the Institute for Pain Diagnostics and Care at Ohio Valley General Hospital in Pittsburgh, PA (<http://www.ohiovalleyhospital.org/pain/>), an ACPA Board Member, and Adjunct Assistant Professor of the Department of Pharmacology, Duquense University.

April Fong, Pharm.D., is a pharmacist at Stanford Hospital & Clinics.



INTRODUCTION

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

The ACPA Consumer Guide to Pain Medication & Treatment is updated yearly 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 doctor (in this document the word “doctor” or “physician” includes physician extenders such as prescribing nurse practitioners or physician assistants).

This ACPA Consumer Guide to Pain Medication & Treatment primarily covers medications but also various other treatments. The topics covered are not exhaustive and because something is not mentioned does not have any relevance to its possible usefulness. If you would like to see a topic covered in this ACPA Consumer Guide to 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 Consumer Guide to Pain Medication & Treatment is not unique or original and parts are borrowed, paraphrased, restructured and simplified from multiple sources too numerous to list. Where possible, Internet links are provided for reference. Any errors are those of the authors and recommendations for corrections, additions or deletions are welcomed at <http://www.theacpa.org/contact.asp>.

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 – see page 78) 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.



PART I: PAIN TYPES & CHRONIC PAIN CLASSIFICATION

Many pain specialists recommend that the term “chronic pain” is better described as “persistent pain” – a condition which can be continuous or recurrent and of sufficient duration and intensity to adversely affect a patient’s well being, level of function, and quality of life. 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**.

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

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

PAIN IN CHILDREN

Chronic pain is a significant problem in the pediatric population. Children and their families experience significant emotional and social consequences as a result of pain and disability. The financial costs of childhood pain also may be significant in terms of healthcare utilization as well as other indirect costs, such as lost wages due to time off work to care for the child.

In addition, the physical and psychological sequelae associated with chronic pain may have an impact on overall health and may predispose for the development of adult chronic pain (from Pediatric Chronic Pain - A Position Statement from the American Pain Society at <http://www.ampainsoc.org/advocacy/pediatric.htm>).



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>) Clinical Practice Guideline (2002): The Management of Persistent Pain in Older Persons at the following Internet Web site: <http://www.americangeriatrics.org/products/positionpapers/JGS5071.pdf>.

There is a more recent American Geriatric Society article entitled Pharmacological Management of Persistent Pain in Older Persons (2009). The Executive Summary can be found at the following Internet Web site: http://www.americangeriatrics.org/education/executive_summary.shtml.

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

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.

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

Clinical Trials of interest are listed on the ACPA Web Site at <http://www.theacpa.org/people/clinicalTrials.asp>.



PART II: 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, 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 worsen their condition 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. Although opioid pain medications can be a useful tool in the treatment of pain, the misuse of opioid (narcotic) pain medications has become a national issue. 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 medications for pain is rarely worrisome, although side-effects are most problematic while initiating treatment and tend to reduce with prolonged use. On the other hand, in some cases, prolonged use 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.

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 benefit, cost, potential side effects, and the person’s other medical problems.

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

HOW MEDICATIONS CAN HELP & HARM

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

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

All prescription medications, over-the-counter medications, or nutritional and herbal supplements should be used carefully and appropriately because they can interact with each other and can cause side effects.



Even the most potent medications used for pain do not always completely eliminate pain but rather may reduce the severity of pain. As such, medications may not be adequate treatments themselves but should be considered as part of a comprehensive approach to pain management and functional improvements.

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

It is strongly advised that you take all of your current medications and other items you are taking with you to any doctor appointments and be honest and forthcoming about any other substances (even if they are not legal) you are using. Some drugs may cause serious side effects if they are combined with other medications. Even over-the-counter and herbal medications have possible side effects and the potential to have serious interactions with your prescription medications and each other.

A Guide to Safe Use of Pain Medicine from the FDA is available at:

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

and 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>

ADVICE FROM THE ACPA

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

If you are a person with chronic pain, you may be on medications, and you should know 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 what medications you are on, how much and how often you need to take them, and whether to take the medication before, with, or after meals or at bedtime. The dose you need depends on your medical condition, body size, age, and any other medications you take. 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.



The label may show a brand name or the generic name. It is often less expensive to buy your prescription by its generic name than by the brand name. Although the color or shape of the pill may be different, there is no difference in quality between generic and brand name drugs. Some people believe that generic drugs do not work as well as brand name medications, but there is no scientific evidence to support this claim.

You can ask your doctor to prescribe generic drugs if they are available. Follow the dose and directions written on the prescription label. Do not change your dose without consulting your health care provider, and never use medication prescribed for someone else.

WARNING FROM THE ACPA ABOUT PURCHASING MEDICINES OVER THE INTERNET

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

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.
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. 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 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(s), please contact or visit your pharmacist who should be able to help you identify your medication(s).

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 doctor of any side effects from the medications you are taking.

When you're taking any medicine, it's important to be aware of any change in your body. Tell your doctor 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 doctor when your symptoms started and whether they are different from other symptoms you have had from an illness. Be sure to remind your doctor of all the medicines you are taking. The following are some adverse drug reactions that you might notice:

- Skin rash or itching (pruritus)
- Headache
- Dry mouth
- Easy bruising or bleeding
- Edema (swelling)
- Stomach distress including pain, nausea and vomiting
- Diarrhea or constipation
- Drowsiness
- Confusion or other mental / behavioral changes
- Breathing difficulties
- Abnormal heartbeat
- Increased blood pressure
- Urinary retention



DRUG ALLERGIES

If you have a drug allergy, your immune system mistakes a medication for a disease-causing agent. A reaction to aspirin results in allergy-like symptoms but doesn't 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.

Many allergic reactions to drugs occur within a few days or as much as three weeks after drug treatment is started. If you're 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.

You should notify your doctor 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 physician to use a medication “off-label,” but your insurer, health plan, or pharmacist may question its use as recommended by your doctor.

A drug is used off-label when the doctor prescribes that drug for a medical use other than the one that received Food and Drug Administration (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, doctors frequently prescribe FDA-approved anticonvulsant medications for persons who do not have seizures, but who need a mood stabilizer. When your doctor prescribes an anticonvulsant medication for use as a mood stabilizer that is 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



physician recommends such a drug does not mean that the doctor thinks 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 physician has made a diagnosis of depression.

The Food and Drug Administration (<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, they can be used “off-label” for any condition in which there is evidence of effectiveness without the drug company proving to the FDA that the drug can treat the new “off-label” condition. The process of getting approval for another use of the medication can cost millions, so a company might not fund research studies to prove all the uses for a drug. This is especially true if the medication is no longer protected by a patent, and other companies can sell it.

Off-label prescribing is legal, and it is an accepted medical practice to use drugs in this way. However, a drug cannot be *advertised* for any condition unless the manufacturer goes to the expense of proving to the FDA that it is safe and effective for that condition. This is important because many of the drugs used for chronic pain have not been approved by the FDA for pain even though they may be useful for it. Indeed, drugs that have been FDA approved for a specific type of pain (e.g., diabetic nerve pain or post-herpetic 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 doctor to explain to the authorizing party that the medication is being prescribed off-label and for what reason.



PART III - 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 FDA has an article, **Over-the-Counter Medicines: What's Right for You?** which can be found at <http://tinyurl.com/OTC-Meds>.

There are basically two types of OTC pain relievers: 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, cough suppressants, and cold medications.

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

The traditional OTC pain group currently includes aspirin (Bayer[®]), acetaminophen (Tylenol[®]), naproxen sodium (Aleve[®]), ibuprofen (Advil[®], Motrin[®]), 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 understanding what you are taking and how much of it. You need to read the medication's ingredients to know what you are taking. Be sure 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 doctor any OTC medications you use or are considering using, especially if you also take a prescription medication. The pharmacist can be very helpful as well.



You can find further information about over-the-counter (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.

Acetaminophen (the ingredient in Tylenol[®] and a number of other OTC pain and cold remedies) can be toxic to the liver, especially with heavy alcohol use or those with liver problems, even at fairly low doses. The maximum recommended dose for acetaminophen is 4 grams or 8 extra-strength (500 mg) tablets in 24 hours. Patients can have elevations in liver enzymes (although often asymptomatic) at 2000 mg, and some physicians encourage patients to stay well below the 4000 mg cut off.

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’s in the medicines you’re prescribed *before* you take them.

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

When acetaminophen (Tylenol[®]) is used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) there is an increased risk of developing kidney abnormalities. This side effect is often only seen with long-term use.

The nonsteroidal anti-inflammatory drugs or NSAIDs (aspirin, ibuprofen, and others) cause an increase in stomach acid. They also reduce the stomach’s protective mucous layer. Thus, they are associated with gastric bleeding, and such risk increases with dose and duration of use. They also may cause kidney failure in people with damaged kidneys, liver disease, and certain other conditions. Use with diuretics can increase this danger. 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 cardiovascular disease. Individuals with any of these conditions should check with their doctor before taking any NSAID medication.

The American Heart Association (AHA) recommends doctors change their approach to prescribing pain relievers for patients with or at risk for heart disease.

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

ACETAMINOPHEN SPECIAL COMMENTS

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.

OTC Drugs with Acetaminophen

- **Backaid**[®] Maximum Strength Back Relief
- **Benadryl**[®] Allergy and Sinus Headache Caplets
- **Contac**[®] Day or Night Cold/Flu Caplets
- **CVS**[®] 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**[®] 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**[®] Aspirin-Free Tension Headache/ Quicktabs Fast Dissolving Pain Reliever Tablets
- **FeverAll**[®] Infants' or Children's Acetaminophen Suppositories
- **HealthLine**[™] Acetaminophen Caplets Extra Strength
- **Inholtra**[®] Caplets With Acetaminophen
- **Legatrin**[®] Advanced Formula PM Pain Reliever-Sleep Aid Caplets
- **Pamprin**[®] Cramp Caplets/Multi-Symptom Caplets Maximum Strength
- **Percogesic**[®] Analgesic Acetaminophen Caplets Extra Strength/Analgesic Acetaminophen Tablets/ Aspirin-Free, Pain Reliever, Fever Reducer Tablets
- **Premysyn**[®] PMS Maximum Strength Premenstrual Syndrome Relief with Acetaminophen
- **Rite Aid**[®] 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**[®] Sinus & Cold Liquid Capsules
- **Theraflu** Packets Severe Cold
- **Triaminic**[®] Cold, Cough and Fever
- **Tylenol**[®] 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**[®] DayQuil LiquiCaps Non-Drowsy/DayQuil LiquiCaps or Liquid/NyQuil LiquiCaps or Liquid
- **Walgreens**[®] Arthritis Pain Relief Extended-Release Caplets/Extra Strength Acetaminophen Caplets, Tablets, Gelcaps or Geltabs/Extra Strength PM Gelcaps or Caplets/Regular Strength Acetaminophen Tablets



Prescription Drugs with Acetaminophen

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



PART IV - PRESCRIPTION MEDICATIONS FOR CHRONIC PAIN

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

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

1. **Non-opioids:** Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.
2. **Opioids** (also called narcotics – but this term should be avoided as it suggests illicit drug use to some).
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.

NON-OPIOID ANALGESIC PAIN RELIEVERS (NON-NARCOTIC)

Nonsteroidal anti-inflammatory drugs (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, they do not produce physical or psychological dependence. There is some evidence suggesting that regular use of common analgesics, such as aspirin, acetaminophen, or NSAIDs, appears to increase the risk for hypertension.

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

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 (COX)-2 inhibitors are NSAIDs that have a lower risk of gastrointestinal side effects with short term use. Currently available is celecoxib (Celebrex[®]); however, serious stomach ulceration can still occur without warning with this drug. As with other NSAIDs, patients should be monitored during long-term use. There is no evidence that somewhat COX-2



selective NSAIDs such as meloxicam (Mobic[®]), etodolac (Lodine[®], Lodine[®] XL), and nabumetone (Relafen[®]) have less gastrointestinal side effects. NSAIDs additionally have potential kidney effects and heart (cardiovascular) complications, especially when taken for prolonged periods.

The COX-2 inhibitor celecoxib (Celebrex[®]) is more expensive than some other NSAIDs and does not provide any better pain relief, but it does seem to be less risky for developing an ulcer when taken for less than 6 months.

While the increased risk of vascular events associated with cyclooxygenase-2 (COX-2) inhibitors has been well established, data are emerging that demonstrate similar risk increases associated with non-steroidal anti-inflammatory drugs (NSAIDs) that are not selective for COX-2. You are advised to discuss the risk-benefit ratio of NSAIDs with your physician. Currently, it appears that doses of celecoxib (Celebrex[®]) 200 mg or less per day do not seem to increase the risk of a cardiovascular event any more than the risk associated with traditional NSAIDs. 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 physician prior to utilizing NSAIDs chronically. 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 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). By applying the drug topically to the joint, one is able to receive the pain relieving benefits of the medication while at the same time having lower levels of the drug in the body. Therefore, the risk of experiencing systemic side effects from the medication is theoretically reduced. However, in December 2009, the FDA issued a new warning about the potential for liver damage during treatment with all diclofenac products, including the gel. The smallest effective amount should be applied for the shortest time possible to minimize the potential for an adverse liver-related event. After applying the gel, the area should not be covered for at least 10 minutes, and showering and bathing should be avoided for at least one hour after application. Skin irritation (e.g. rash, dry skin) may occur with topical diclofenac administration.

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. The Flector[®] patch has not been approved for the treatment of chronic pain from osteoarthritis. In 2009, the FDA issued an advisory that transdermal patches that contain metal, which includes Flector[®], need to be removed prior to MRI procedures.

Remember also that when acetaminophen (Tylenol[®]) is used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs), there is an increased risk of developing kidney problems. This effect is often only seen with long-term use.



GI PROTECTIVE MEDICATIONS

There are four commonly used cytoprotective (protecting cells from noxious chemicals or other stimuli) classes of drugs:

1. Misoprostol (Cytotec[®]) - (often combined with diclofenac and distributed as Arthrotec[®])
2. Sucralfate (Carafate[®])
3. Histamine type 2 (H₂) receptor blockers: famotidine (Pepcid[®]), nizatidine (Axid[®]), ranitidine (Zantac[®]), cimetidine (Tagamet[®]), etc.
4. Proton pump inhibitors (PPIs): esomeprazole (Nexium[®]), lansoprazole (Prevacid[®]), omeprazole (Prilosec[®]), pantoprazole (Protonix[®]), rabeprazole (Aciphex[®]).

Concomitant use of cytoprotective agents is recommended for individuals with a high risk factor profile who also have indications for NSAIDs. Individuals considered being at elevated risk include those with a history of prior gastrointestinal bleed, the elderly, diabetics, and cigarette smokers. Longer term treatment increases the risk among those most susceptible, although any patient can potentially develop an adverse effect. Treatment with antacids and H₂ blockers offer little if any protection against duodenal and gastric ulcers. Many of the studies on H₂ blockers show that they have no value in the protection of the gastric mucosa.

PPIs have been shown to reduce the risk of gastrointestinal ulcers. 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 be increasing 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.



NON-OPIOID ANALGESIC DRUGS AND 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 and Their Common Brand Names*	May Be Useful for	Pros	Cons	Comments
Aspirin 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.
Salicylate Salts Salicylate Trisalicylate	Pain, osteoarthritis and rheumatoid arthritis.	Fewer gastrointestinal side effects.	May irritate stomach.	Do not affect bleeding time or platelet aggregation.
Acetaminophen FeverALL® Tylenol®	Headache, muscle ache, backache, fever, and arthritis pain (especially osteoarthritis).	More gentle to the stomach; safer for children. Does not promote bleeding (or protect against heart attack, stroke).	Does not reduce inflammation; less effective than aspirin for soft tissue pain.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily.
Ibuprofen Advil® Motrin®	Headache, muscle ache, fever, sprains, menstrual cramps, backache, and arthritis pain.	Stronger and generally longer lasting than aspirin.	May irritate stomach.	May be harmful for people with kidney or liver disease, asthma, bleeding disorders, or those who drink alcohol heavily.
Ketoprofen 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.	May be harmful for people with kidney or liver disease or those who drink alcohol heavily. Not recommended for children without doctor's supervision.
Naproxen Sodium Aleve® (OTC) Anaprox® Naprelan® Naprosyn®	Headache, muscle ache, fever, menstrual cramps, backache, arthritis pain and inflammation.	Stronger and generally longer lasting than aspirin for menstrual cramps, toothache, and inflammation.	May irritate stomach; tends to be higher in cost.	Not recommended for children without doctor's supervision.
Meloxicam Mobic®	Arthritis pain	Associated with less risk of ulcers than other NSAIDs.	Still a risk for stomach irritation. Tends to cost more.	Generally well-tolerated but still need to be concerned about gastrointestinal side effects.
COX-2 Inhibitors Celebrex®	Muscle aches, joint pain, arthritis, pain and inflammation.	Helps reduce inflammation; less stomach irritation.	Still a risk for stomach irritation. Tends to cost more.	Generally well-tolerated but still need to be concerned about gastrointestinal side effects. 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[®], Voltaren[®], others)
- Diflunisal (Dolobid[®])
- Etodolac (Lodine[®], Lodine[®] XL)
- Fenoprofen (Nalfon[®])
- Flurbiprofen (Ansaid[®])
- Indomethacin (Indocin[®], Indocin[®] SR)
- Mefenamic acid (Ponstel[®])
- Nabumetone (Relafen[®])
- Oxaprozin (Daypro[®])
- Piroxicam (Feldene[®])
- Sulindac (Clinoril[®])
- Tolmetin (Tolectin[®])
- Ketorolac (Toradol[®], others) – NSAID injectable formulation (intramuscular and intravenous)
- Ibuprofen (Caldolor[™]) - NSAID available intravenous for acute pain and fever

* Brand names are the trademarked property of the medication's manufacturer.

OPIOID ANALGESICS

The Opioid Dilemma

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

The dilemma with the long term use of opioids is that while there is a role for opioids in chronic, non-cancer pain, it is well known that prolonged use of opioids may result in problems including tolerance, hyperalgesia (increased pain sensitivity), hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses), depression, impaired sleep patterns and suppression of the immune system. The chronic utilization of opioids may also impair functional recovery in an individual's recovery from surgery or with long-standing musculoskeletal disorders. Fifty one percent of all patients taking oral opioids experience at least one adverse event/effect. Approximately 20% of all patients taking oral opioids will discontinue their use because of an adverse event or an associated side effect. While opioid treatment may be



prescribed to reduce pain and improve function, the treatment may actually result at times in just the opposite.

Opioids are not benign drugs. 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 aged 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.

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

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

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

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.

These agents include buprenorphine (Buprenex[®], Subutex[®]), butorphanol (Stadol[®]), nalbuphine (Nubain[®]), and pentazocine (Talwin[®]). Combination products include Talwin NX (pentazocine/naloxone) and Suboxone (buprenorphine/naloxone). Some are also used for the treatment of opioid dependence.



Given their agonist/antagonist nature, these medications should be used with caution in those taking agonist opioids. 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 withdrawal. If possible, these two types of agents should not be used together.

Symptoms of withdrawal to monitor for 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 doctor or pharmacist if you have these or other side effects.

Opioid Delivery

Opioids are available orally (by mouth), intravenously, by injection, transdermally (through the skin), buccally (absorbed via the inside of the cheek), via suppository, and intrathecally (see discussion on Implanted Intrathecal Drug Delivery Systems - “Pain Pumps”).

Short- and Long-acting Opioids

Short-acting opioids, also called immediate-release (IR) opioids, often contain an opioid as the only active ingredient, 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[®])
- oxycodone with aspirin (Percodan[®])
- oxycodone with ibuprofen (Combunox[®])
- hydrocodone with acetaminophen (Lorcet[®], Lortab[®], Vicodin[®])
- hydrocodone with ibuprofen (Vicoprofen[®])

Short-acting 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 to 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 also 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 medications are the opioid treatment of choice for patients with 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 and are abbreviated as SR, ER, or CR, respectively.

Examples of oral and transdermal long-acting opioids include:

- morphine sustained release (e.g., MS Contin[®], Avinza[®], Kadian[®], Embeda[™])
- oxycodone sustained release (e.g., OxyContin[®])
- fentanyl transdermal system (Duragesic[®])
- methadone (e.g., Dolophine[®], Methadose[®])
- oxymorphone (Opana ER[®])

The prolonged effects of these agents are due to their long half-lives or slow discharge into the body via controlled-release preparations of a short-acting agent. 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.

These are examples of medical opioids:

Hydrocodone (with acetaminophen – Anexsia [®] , Lorcet [®] , Lortab [®] , Norco [®] , Vicodin [®] , Xodol [®] , Zydone [®] ; with ibuprofen – Reprexain [™] , Vicoprofen [®] ; with aspirin—Azdone, Lortab ASA, Panasal)	Oxycodone (OxyContin [®] , OxyIR [®] , Roxicodone [™] ; with acetaminophen - Endocet [®] , Percocet [®] , Roxicet [™] , Tylox [®] ; with aspirin – Endodan [®] , Percodan [®] , with ibuprofen - Combunox [™])
Codeine (with acetaminophen -Tylenol [®] with codeine No. 2, No. 3, No. 4)	Levorphanol (Levo-Dromoran [®])
Dihydrocodeine bitartrate, Aspirin, Caffeine (Synalgos-DC [®])	Methadone (Dolophine [®] , Methadose [®])
Hydromorphone (Dilaudid [®])	Fentanyl (Actiq [®] lozenge, Fentora [®] and ONSOLIS [™] buccal tablets, Duragesic [®] patch) – FDA warning below (see opioid adverse side effects)
Morphine (Avinza [™] , Duramorph [®] , Kadian [®] , MS-Contin [®] , Oramorph SR [®] , Roxanol [™] , Embeda [™])	Butorphanol (Stadol [®])
Meperidine (Demerol [®])	Oxymorphone (Numorphan [®] , Opana [®] and Opana ER [®])



Pentazocine (Talwin [®] ; with acetaminophen-Talacen [®] ; with aspirin-Talwin [®] Compound)	Buprenorphine (Buprenex [®] , Subutex [®]) and Buprenorphine and Naloxone (Suboxone [®])
--	---

The FDA recently approved the combination of morphine sulfate and naltrexone hydrochloride (Embeda[™]) for the treatment of moderate to severe chronic pain. Embeda[™] is a unique combination of morphine, an opioid agonist, and naltrexone, an opioid antagonist. This formulation was developed to reduce abuse. If the drug pellets in the capsule are crushed or chewed, the naltrexone will release and diminish the effects of the morphine. The goal of this drug design is to reduce the possible misuse of this medication when it is tampered with by crushing or chewing. If the capsule is taken as directed, the naltrexone will not release and it passes through the body with no effect.

Tapentadol (Nucynta[™]) is an oral opioid analgesic recently approved for the treatment of moderate to severe acute pain. Tapentadol has both opioid and nonopioid activity. The drug binds to opioid receptors and also inhibits the reuptake of the neurotransmitter norepinephrine. This 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. Tapentadol may have an improved gastrointestinal side effect profile in comparison to other opioids.

WEAK OPIOIDS: TRAMADOL & PROPOXYPHENE

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

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

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

In the past, tramadol reportedly caused fewer problems with drug addiction than other opioids, but this is being questioned. The rate of dependence and abuse with tramadol may be much higher than previously reported. Regardless, tramadol is not completely free of this risk and may trigger addiction even in those without a history of drug abuse or previous addiction. This appears more likely to occur when used with carisoprodol (Soma[®]). Soma[®] is metabolized to a compound (meprobamate), which is a federally scheduled drug that can cause both physical and psychological dependence.

Tramadol reduces the respiratory rate to a lesser extent than opioids in overdoses and does not cause the sort of gastrointestinal irritation produced by NSAIDs. Tramadol reduces the threshold



for seizures, which may occur in overdose. Seizures may also be provoked in those with a history of seizure disorders, head trauma, etc., or in those taking other drugs that reduce the seizure threshold. These include certain antidepressants such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs). They also include some antipsychotic medications (Thorazine[®], Compazine[®], etc.). Thus, caution is advised when tramadol is combined with these medications.

Since tramadol is a centrally acting synthetic analgesic, not a non-steroidal anti-inflammatory drug (NSAID), it has no anti-inflammatory activity. Also unlike NSAIDs, tramadol does not have the potential to compromise the efficacy of certain antihypertensive agents (diuretics and ACE-inhibitors). The tramadol dose should not exceed 400 mg (300 mg in the elderly) in divided doses a day. When combined with acetaminophen, the amount of acetaminophen should not exceed the maximum recommended daily dose. Tramadol should be used cautiously, if at all, in patients with underlying liver and kidney disease.

Propoxyphene is a mild opioid analgesic structurally related to methadone. The potency of propoxyphene is from two thirds to equal that of codeine. Darvocet-N[®] 50, Darvocet-N[®] 100, and Darvocet A500[™] tablets contain propoxyphene with acetaminophen. The combination of propoxyphene and acetaminophen produces greater analgesia than that produced by either drug alone. These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever. Propoxyphene has an active metabolite, norpropoxyphene, which can negatively affect the heart. Also, elderly patients taking propoxyphene can be at a higher risk for falls secondary to the side effects of the medication. This drug is not recommended for chronic pain management.

OPIOID ADVERSE SIDE EFFECTS

Common opioid side effects, particularly with higher doses, include nausea, vomiting, constipation, thought and memory impairment, and drowsiness. The majority of these side effects are easily treated with dose adjustments, wane over time, or can be offset by other alternate medications. Psychostimulants (see below) can be useful in selected patients to treat mild sedation. Constipation should be anticipated with a preventative bowel regimen including diet changes and a stimulant laxative, plus a stool softener. Most individuals taking opioid medications will not develop tolerance to the side effect/adverse effect of constipation. Therefore, an effective bowel regimen will have to be maintained throughout the time course of the opioid pain medication. Approximately 40% of individuals taking opioid therapy for non-cancer pain experience constipation (less than three bowel movements per week) secondary to opioid treatment. Furthermore, 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. 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 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 in the treatment of opioid induced constipation. 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 can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be appropriate.

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 compared to other opioids. Certain opioids (e.g. morphine, meperidine, and propoxyphene) should be avoided in patients with kidney disease because of the possibility of the accumulation of active toxic compounds.

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

In July 2005, the Food and Drug Administration (FDA) issued a public health advisory to alert people of reports of death and other serious side effects from overdoses while on fentanyl transdermal patches. Deaths and overdoses have occurred in patients using both the brand name Duragesic[®] and the generic product. Some patients and health care providers may not be fully aware of the dangers of this drug. Improper patient selection is one concern. 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.

Fentora[®] (a fentanyl buccal tablet), a potent opioid pain medication, is recommended only for the treatment of breakthrough pain in cancer patients receiving opioid treatment and who have become tolerant to it. Fentora[®] is contraindicated for migraine and acute postoperative pain. In September 2007, the FDA issued a product safety alert to pain management specialists and health-care professionals that serious adverse events, including deaths, have occurred in patients treated with Fentora[®]. The deaths occurred due to respiratory depression as a result of improper patient selection, improper dosing, and/or improper product substitution.

ONSOLIS[™] (a fentanyl buccal soluble film) is an opioid analgesic indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The same concerns as noted for Fentora[®] are relevant for ONSOLIS[™].

Methadone, a potent opioid, has also been mentioned recently in FDA reports because of the increasing number of adverse events associated with its use. In November 2006, the FDA sent a letter to health-care workers to alert them of the increase in adverse events associated with methadone. Although methadone possesses analgesic properties, it must be used carefully and



with a great deal of caution. It can accumulate in the body and 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 it with the prescribing physician. 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.

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, sleep disturbance, or hallucinations
 - Potential for diminished psychomotor performance
 - Dysphoria, agitation, dizziness and seizures
 - Aberrant behavior (see addiction below)
 - Hyperalgesia (see definition below)
- Respiratory system
 - Respiratory depression is the major adverse effect and may result from toxicity
 - Diminution of pain or pain relief by other modalities may exacerbate respiratory depression
- Ocular system
 - 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
 - Not an allergic reaction
- Immune system
 - There is 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
 - Neonatal depression can occur if opioids are used during labor
 - No teratogenic effects have been observed
 - Use with caution in 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

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

Opioid-induced Hyperalgesia is a syndrome of 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,
- **I**nability 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 physicians/pharmacists to guarantee a supply, and spending scarce resources on the drug.

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



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

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

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. 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 coper’s 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 physician’s opioid agreement enough to avoid being removed from treatment. Physicians commonly see chemical copers 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 tranquilizers for more than a few doses will show some tolerance with use and withdrawal on abrupt drug cessation. In addition, numerous drugs can produce tolerance and withdrawal, yet do not produce addiction (e.g., epilepsy medications, some blood pressure drugs). Symptoms of withdrawal to monitor for include sweating, goose flesh, runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell your doctor or pharmacist if you have these or other side effects.

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 physicians reluctant to provide chronic opioids. It is well known that a sedentary life decreases blood flow, impedes healing, decreases muscle tone, and contributes to depression, bone loss, and fatigue.



Clearly, some people become inactive and passive on opioids, while others become more active. It may be that some are able to obtain good analgesia without taking enough to produce intoxication, while others are not able to do so.

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.

OPIOID USE CONSENSUS STATEMENT

The American Pain Society (<http://www.ampainsoc.org>) and the American Academy of Pain Medicine (<http://www.painmed.org>) issued a joint consensus statement in 1997 entitled, "The Use of Opioids for the Treatment of Chronic Pain" (<http://www.painmed.org/pdf/opioids.pdf>), supporting the cautious use of chronic opioid analgesics (pain medications) for some people with persistent pain problems. Cautious use requires careful examination, discussion of risks and benefits with patients, thorough documentation, and sufficiently careful follow-up for the physician to be able to determine whether the drugs are actually improving the person's overall status.

Taking opioids may or may not be in one's best interest. The literature does not provide simple, clear guidelines for those who must face day-to-day pain.

It is well known that in the opioid naïve patient, use of opioids may heighten the risk of accidental death from respiratory depression. The dilemma with the long term use of opioids is that it may also result in problems including tolerance, hyperalgesia (abnormal pain sensitivity), hormonal effects (decreased testosterone levels, decreased sex drive and irregular menses), and suppression of the immune system.



Research shows that chronic use of large quantities of opioids may interfere with the body's natural pain relievers, the endorphins. Since physical activity is thought to promote release of endorphins, it is also possible that opioids could inhibit the body's own mechanism of reducing pain by causing a person to be less active. Additionally, long-term opioid use may cause depression in some patients, which may impede their ability to recover.

Although opioid treatment may be prescribed to reduce pain and hopefully improve function, the treatment may actually result at times in just the opposite.

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.

Respiratory depression with opioid use is a serious concern. In addition, opioids become particularly dangerous when used in conjunction with other medications — sedative-hypnotics, benzodiazepines, antidepressants, and muscle relaxants — or with alcohol.

The FDA has notified makers of certain opioid drugs that these products will need to have a Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits continue to outweigh the risks. 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://tinyurl.com/OpioidREMS>.

FDA 3 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 or break 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.** Don't 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.



OPIOIDS AND THE GOALS OF PAIN MANAGEMENT

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

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

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

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

EVALUATING OPIOID USE

Monitoring for pain and aberrant drug-related behaviors by the prescribing physician, nurse practitioner or physician assistant is an ongoing aspect of patient care. The most relevant areas for monitoring have been termed the 4 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; and 4) aberrant or abnormal drug-related behaviors.

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

- ❑ *Is the person’s day centered around taking medication?* If so, consultation with the health care professional may clarify long-term risks and benefits of the medication and identify other treatment options.
- ❑ *Does the person take pain medication only on occasion, perhaps three or four times per week?* If this is the case, then the likelihood of addiction is low.



- ❑ *Have there been any other chemical (alcohol or drug) abuse problems in the person's life?* If so, then it is important to inform the health care professional, who will need to take that into consideration when prescribing. 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 physician for a graduated exercise program.
- ❑ *Is the person in pain able to function (work, household chores, and play) with pain medication in a way that is clearly better than without?* Chances are that the pain medication is contributing to wellness. Most people who are addicted to pain medications or other substances (excluding nicotine) do not function well. They are 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 in order 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), 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 and tranquilizers without express permission from the physician 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 obtained the drug from friends or family members. Opioids used in this way or purchased illicitly are unacceptable and would constitute misuse and abuse and would void the opioid treatment agreement and result in loss of prescribed opioids. Further, it is important to take the opioid exactly as prescribed by the doctor with respect to dose and to timing between doses.

The discussion of important 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).



ANTIDEPRESSANTS

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

There has long been a known association between depression and chronic pain. Not surprisingly, the chemicals (neurotransmitters) in your brain and nervous system (serotonin and norepinephrine) 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. The selective serotonin reuptake inhibitors 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[®]), nortriptyline (Pamelor[®]), and desipramine (Norpramin[®]), can be fatal in overdose and should only be available and prescribed in limited supply. Tricyclic antidepressants 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 tricyclic antidepressants. Also, patients with cardiac disease should avoid the use of tricyclic antidepressants or be followed closely by a physician for cardiac abnormalities that can worsen with their use.

BENEFITS OF ANTIDEPRESSANTS IN CHRONIC PAIN

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

- ❑ They do not have the potential to cause stomach inflammation and bleeding, as do the anti-inflammatory drugs. The use of antidepressants (i.e. SSRIs) with NSAIDs should occur with caution secondary to a higher risk of gastrointestinal 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

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[®]), doxepin (Sinequan[®]), imipramine (Tofranil[®]), desipramine (Norpramin[®]), nortriptyline (Aventyl[®], Pamelor[®]), protriptyline (Vivactil[®]), trimipramine (Surmontil[®]), and clomipramine (Anafranil[®]). Also included are maprotiline (Ludiomil[®]) and mirtazapine (Remeron[®]), which are tetracyclic antidepressants.

The tricyclic antidepressants have been used to treat depression for a long time. Tricyclic antidepressants (TCAs) and related drugs can be roughly divided into those with additional sedative and relaxing properties and those that are less so. Agitated and anxious patients tend to respond best to antidepressants with sedative properties whereas withdrawn individuals and those with less energy will often obtain the most benefit from less sedating antidepressants. These antidepressants have been proven to have pain-relieving effects.



The different tricyclic drugs have varied side effects and may sometimes be used to the patients' advantage. For the overweight patient with lethargy and tiredness, the clinician may choose a TCA with more noradrenergic selectivity (e.g., desipramine), which may be activating and can cause some anorexia. 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, 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 tricyclic antidepressant toxicity:

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

Mirtazapine (Remeron[®]) 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[®]), sertraline (Zoloft[®]), paroxetine (Paxil[®]), fluvoxamine (Luvox[®]), citalopram (Celexa[™]), and escitalopram (Lexapro[®]).

The selective serotonin reuptake inhibitors 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.

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

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

SSRIs should be used with caution in patients with epilepsy, history of mania, cardiac disease, diabetes, angle-closure glaucoma, concomitant use of drugs that increase risk of bleeding, history of bleeding disorders (especially gastrointestinal bleeding), disorders of the liver and kidneys,



pregnancy and breast-feeding. SSRIs, particularly paroxetine, may also impair performance of skilled tasks (e.g., driving) by causing drowsiness. Use within 14 days of an MAO inhibitor should be avoided.

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

While trazodone (Desyrel[®]), venlafaxine (Effexor[®]), bupropion (Wellbutrin[®], Zyban[®]) and duloxetine (Cymbalta[®]) are often placed into this class of drugs, trazodone is a serotonin-2 receptor antagonist, while venlafaxine, bupropion and duloxetine are mixed norepinephrine and serotonin inhibitors (SNRIs).

SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

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

Duloxetine (Cymbalta[®]), venlafaxine (Effexor[®]), milnacipran (Savella[™]) and bupropion (Wellbutrin[®], Zyban[®]) 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 and depression.

Milnacipran (Savella[™]) 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 (Effexor[®]) 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 (Effexor[®]) can increase systolic blood pressure.

Although marketed for different indications, Wellbutrin[®] and Zyban[®] contain the same active ingredient and therefore should not be taken concurrently without close physician 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 (Desyre[®]) 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[®]), tranylcypromine (Parnate[®]), isocarboxazid (Marplan[®]), and selegiline (Eldepryl[®]) 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.

Alert: Mixing Anti-migraine Agents and 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 (Prozac[®]), sertraline (Zoloft[®]), paroxetine (Paxil[®]), escitalopram (Lexapro[®]), duloxetine (Cymbalta[®]), milnacipran (Savella[™]), and venlafaxine (Effexor[®]). Migraine drugs include naratriptan (Amerge[®]), almotriptan (Axert[™]), sumatriptan (Imitrex[®]), and zolmitriptan (Zomig[®]).

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[®], Sarafem[®]), paroxetine (Paxil[®]), sertraline (Zoloft[®]), citalopram (Celexa[®]), escitalopram (Lexapro[®]), trazodone (Desyrel[®]), venlafaxine (Effexor[®]), desvenlafaxine (Pristiq[®]), duloxetine (Cymbalta[®]), clomipramine (Anafranil[®]), buspirone (BuSpar[®]), mirtazapine (Remeron[®]), lithium, St. John's Wort, phenelzine (Nardil[®]), tranylcypromine (Parnate[®]), or isocarboxazid (Marplan[®]).

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

Diet pills, specifically L-tryptophan (5-HTP), sibutramine (Meridia[®]), or phentermine (Ionamin[®]).

Certain pain medicines including tramadol (Ultram[®]), fentanyl (Duragesic[®] patch), pentazocine (Talwin[®]), duloxetine (Cymbalta[®]), or meperidine (Demerol[®]).

Certain drugs for nausea, specifically ondansetron (Zofran[®]), dolasetron (Anzemet[®]), granisetron (Kytril[®]), or metoclopramide (Reglan[®]).

Cough syrups or cold medicines if they contain the anti-cough ingredient dextromethorphan (DM, Delsym[®]) or the antibiotic linezolid (ZyvoxTM).



ANTICONVULSANT (ANTIEPILEPTIC) 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[®], Tegretol[®]), is approved by the FDA for relieving the pain of trigeminal neuralgia. Gabapentin (Neurontin[®]) is approved for the management of postherpetic neuralgia (PHN - pain that lasts one to three months after shingles has healed). Pregabalin (Lyrica[®]) is approved for PHN and painful diabetic neuropathic pain and more recently, 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 physician. 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[®]) 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. A similar but newer drug, pregabalin (Lyrica[®]), 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 (150-600 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 USED IN CHRONIC PAIN

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



SODIUM CHANNEL BLOCKING & ORAL ANTI-ARRHYTHMIC AGENTS

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

Those 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[®]) and flecainide (Tambocor[™]). They reduce pain in diabetic neuropathy, post stroke pain, complex regional pain syndrome or reflex sympathetic dystrophy, and traumatic nerve injury.

Mexiletine is chemically similar to lidocaine, an anesthetic frequently used by dentists. Common side effects of mexiletine include dizziness, anxiety, unsteadiness when walking, heartburn, nausea, and vomiting. Consult a physician if you are pregnant, have a history of heart attack, are a smoker, or take any of the following medications: amiodarone, fluvoxamine, Tikosyn, bupropion, or sodium bicarbonate. This may lead to an alteration in therapy. 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. Immediate discontinuation of the medication followed by emergency treatment is appropriate in these conditions.

Flecainide (Tambocor[™]) 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. Therefore an ECG is recommended before treatment is started, and this drug should probably not be used for pain management in patients with a history of cardiovascular disease, or heart failure because it may cause your heart rate to slow. Inform your doctor if you have kidney or liver problems, because this may lead to monitoring of drug levels or a dosage reduction. Flecainide interacts with amiodarone, several antipsychotic and anti-arrhythmic medications, and Ranexa. 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, but the drug may have effects throughout the body and work away from the area of pain (currently available transdermal drugs include fentanyl and clonidine). Transdermal medication in a patch is absorbed through the skin by the bloodstream over a period of time (you should never cut a transdermal patch into smaller pieces).

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

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

Counterirritants come in various forms such as balms, creams, gels, and patches under several brands such as BenGay®, Icy Hot®, Salonpas®, and Thera-Gesic® 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 a patch product, only one patch can be applied for up to 8 to 12 hours with a maximum of 2 patches in 24 hours for no longer than 3 days of consecutive use. The Salonpas® Pain Relief Patch® (10% methyl salicylate and 3 % menthol) is currently the only FDA-approved over-the-counter (OTC) topical analgesic patch. It is approved for temporary relief of mild to moderate aches & pains of muscles & 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 (i.e., 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.



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

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

Capsaicin is the active ingredient in hot peppers. Several studies have suggested that capsaicin (cap-SAY-sin) can be an effective analgesic in at least some types of neuropathic pain 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 US Food and Drug Administration approved Qutenza[™] (capsaicin) 8% patch for the management of neuropathic pain attributed to postherpetic neuralgia (PHN) that may occur after an episode of [herpes zoster](#) (shingles). The Qutenza[™] patch releases a synthetic form of *capsaicin*, a substance in chili peppers that gives them their heat sensation, through a dermal delivery system. Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza[™]. Qutenza[™] 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 and allodynia. A topical anesthetic is applied before Qutenza[™] application. In clinical trials, the most common adverse reactions were application site redness, pain, itching, and papules. The majority of these reactions were transient and self limited. Among patients treated with Qutenza[™], 1% discontinued 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.

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



EMLA[®] 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[®] cream is applied to intact skin and covered with an occlusive dressing. The minimal application time to obtain reliable superficial pain relief is one hour. However, the cream may be left on the skin for up to two hours, depending on the degree of the procedure performed. Analgesia can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. Side effects to EMLA[®] 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[®] 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[®] cream should also not be applied to broken skin or mucous membranes (e.g. mouth).

Lidoderm[®] 5% (lidocaine) patches can be cut to fit over the area of pain. The 5% lidocaine patch is the only topical anesthetic agent to receive FDA approval for the treatment of a neuropathic pain condition, specifically postherpetic neuralgia (PHN). It measures 10 cm x 14 cm and has a clear plastic backing that must be removed before application of the patch to the skin. 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(s) 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.

Topical DMSO (dimethyl sulfoxide) 50% and oral NAC (N-acetylcysteine) recently were shown to possibly have some benefit in CRPS, but there is no scientific evidence as yet to support its use.



COMPOUNDED MEDICATIONS

Compounded medications are prescriptions that are written by physicians and prepared by pharmacists for individual patients. They are not commercially available; rather, they are prescribed by a physician 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 compounding medications.

The most common compounded medications are topical gels. They typically contain ingredients such as lidocaine, amitriptyline, 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.

SEDATIVES, ANTI-ANXIETY MEDICATIONS, & TRANQUILIZERS

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

Zolpidem tartrate (Ambien[®]) 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[®], especially those taking serotonin-boosting antidepressants, have experienced unusual changes in their thinking and/or behavior. Ambien[®] 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[®] 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[®].



Another sleep aid, eszopiclone (Lunesta™), 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™) 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®) 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 Consumer Guide to 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®), lorazepam (Ativan®), clonazepam (Klonopin®), flurazepam (Dalmane®), triazolam (Halcion®), temazepam (Restoril®), and alprazolam (Xanax®). 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®), is recognized for causing depression and physical dependence when used for long periods.

Most benzodiazepines are not recommended for chronic pain, but clonazepam (Klonopin®) 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.



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



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. 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[®], Amrix[®] – 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 [®])	Converted by the body into meprobamate, a barbiturate-like drug. It may cause physical dependence. It should be avoided in kidney or liver disease. With prolonged use, it is associated with dependence. Long-term use in chronic pain should be avoided.
Cyclobenzaprine (Flexeril [®] , Amrix [®])	Skeletal muscle relaxant that is structurally similar to the TCAs. Side effects include dizziness, drowsiness, dry mouth, constipation, confusion, and loss of balance. Long-term use in chronic pain should be avoided.
Methocarbamol (Robaxin [®])	Skeletal muscle relaxant with sedative properties. Side effects include drowsiness and urine discoloration to brown, black, or green.
Metaxalone (Skelaxin [®])	Skeletal muscle relaxant. It should be used with caution in liver disease.
Chlorzoxazone (Parafon Forte [®] DSC)	Skeletal muscle relaxant with sedative properties. It should be used with caution in liver disease.
Baclofen (Lioresal [®])	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 [®])	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 [™])	A skeletal muscle relaxant with analgesic properties.
Tizanidine (Zanaflex [®])	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 [®])	Other benzodiazepines also have muscle-relaxant properties. Most pain physicians avoid prescribing diazepam for muscle spasm. Toxicity of benzodiazepines is discussed at www.emedicine.com/emerg/topic58.htm .



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[®]), aripiprazole (Abilify[™]), clozapine (Clozaril[®]), haloperidol (Haldol[®]), olanzapine (Zyprexa[®], Zydys[®]), quetiapine (Seroquel[®]), risperidone (Risperdal[®]), and ziprasidone (Geodon[®]).

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

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

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



BOTULINUM TOXIN

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

Botox[®] (Botulinum Toxin Type A) and Myobloc[®] (Botulinum Toxin Type B) are FDA approved for cervical dystonia – also known as torticollis (head tilting, neck pain, and neck muscle spasms). Many physicians are using botulinum toxin off-label for other conditions including headache, osteoarthritis of the knee and shoulder and various muscle pain syndromes (myofascial pain).

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

The occurrence of side effects after receiving botulinum toxin is not common (see warning box below). Muscle weakness may occur and is the most common side effect. Swallowing problems can develop when treating cervical muscle problems. Other possible adverse effects include dry mouth, pain at the injection site, swallowing problems, headache, and flu-like symptoms. Additionally, adverse effects may include local bruising, generalized fatigue, lethargy, dizziness, and difficulty speaking or hoarseness - but these side effects are extremely rare.

Prompted by reports of serious adverse events, the U.S. Food and Drug Administration announced on 4/30/09 that safety label changes, including a boxed warning, were necessary for all botulinum toxin products. The agency said it took the action because of reports that the effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism, including unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids.

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 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 CNS side effects.

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

ADRENERGIC DRUGS, BISPHOSPHONATES, THALIDOMIDE & CALCITONIN

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

Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk of fractures in patients with osteoporosis. There are 7 FDA-approved bisphosphonates: alendronate (Fosamax®, Fosamax Plus D™), etidronate (Didronel®), ibandronate (Boniva®), pamidronate (Aredia®), risedronate (Actonel®, Actonel® with calcium), tiludronate (Skelid®), and zoledronic acid (Reclast®, Zometa®). 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).

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 physicians will try to treat the side effect of sleepiness and lethargy by prescribing an "activating" medication such as methylphenidate (Ritalin[®], Concerta[®], and Metadate[®]), dextroamphetamine (Dexedrine[®]), modafinil (Provigil[®]), amodafinil (Nuvigil[®]) and combination products (Adderall[®]).

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



Dextroamphetamine (Dexedrine[®]) 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[®]) 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[®] 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.

Amodafinil (Nuvigil[®]) 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[®]) 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[®] – also available by injection or nasal spray), zolmitriptan (Zomig[®] – also available by nasal spray or as orally-disintegrating tablets), naratriptan (Amerge[®]), rizatriptan (Maxalt[®] – also available as orally-disintegrating tablets) and almotriptan (Axert[™]). More recently introduced triptans include frovatriptan (Frova[®]) and eletriptan (Relpax[®]).

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

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

Effective migraine treatment begins with the early recognition that an attack is pending followed by immediate treatment. Migraine sufferers are encouraged to take an active role in managing



their headaches by avoiding common triggers, making lifestyle changes, and taking their medication at the first sign of migraine pain.

Patients taking certain migraine and antidepressant medications together may be at risk for a dangerous chemical imbalance. Antidepressant medications included in this warning are Prozac[®], Zoloft[®], Paxil[®], Lexapro[™], Cymbalta[®] and Effexor[®]. Migraine drugs include Amerge[®], Axert[™], Imitrex[®], and Zomig[®]. 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 Consumer Guide to 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 Medical Journal in January 2003 at www.ccjm.org/pdffiles/Mannix103.pdf.



PART V - 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, that doesn’t ensure their efficacy, purity, or safety.

While there are proven health benefits for some herbal and nutraceutical products, potentially harmful effects exist for others. Because these supplements are not standardized as are 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 doctor if you are taking any of these products as they can interact with other medications causing 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.

There is some evidence though for a number of these products as being of benefit. These medicinal agents do have the potential to interfere and interact with other prescription medications.

POSSIBLE BENEFIT REGARDING THE USE OF HERBAL MEDICATIONS

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 most 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 over-the-counter products have the potential for toxic side effects and cross reactions 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, phototoxicity, myocardial ischemia, electrolyte alterations, hypotension, arrhythmias, renal 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.

Possible Herbal Medication Adverse Side Effects	
Aloe vera	Nausea, vomiting, diarrhea
Astragalus	Autoimmune disease
Belladonna	Atropine effects
Chaparral	Hepatitis
Ephedra (also called ma huang)	High blood pressure, cardiac arrhythmias, 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	Garlic can inhibit platelet aggregation and thus blood clotting for approximately seven days and cause an 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 at journal Web sites and other related Web resources. 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



PART VI – ALCOHOL, MARIJUANA AND ILLICIT SUBSTANCES

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

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

Alcohol and chronic pain medications do not mix.



ILLEGAL DRUGS & MARIJUANA

Many physicians will not prescribe opioids and other medications to individuals who are known to use illegal drugs or to be irresponsible with prescription pain medication. The use of marijuana for pain is controversial. The active ingredient found in marijuana (THC) can help pain, but can also lead to dependence and addiction in certain individuals. Some recent research indicates that THC may be helpful in pill form.

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 physician.

While sometimes ignored, it is a crime for a physician to prescribe a scheduled drug to a patient known to be using illegal drugs, including marijuana.



PART VII - 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, 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[®], Synvisc[®], Hyalgan[®], Supartz[™], and Euflexxa[™]. In 2009, Synvisc-One[™] (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. 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.

Two stages are involved in SCS. 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 determines 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.

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. Recently, it has been discovered that spinal cord stimulation modifies the chemical makeup of the spinal cord.

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
- 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”)

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

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. A psychological evaluation is recommended prior to implantation.

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; 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 (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.

Ziconotide (Prialt[®]) 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 (directly to the spinal nerves) by continuous infusion through a pump directly into the fluid surrounding the spinal cord. Common side effects include dizziness, nausea, vomiting, constipation, diarrhea, loss of appetite, and muscle weakness. More serious side effects such as cognitive dysfunction or rhabdomyolysis (a disease characterized by the destruction of skeletal muscle) can also infrequently occur. 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 (1) hip and buttock pain, (2) low back stiffness and (3) pain that is made worse by



prolonged sitting or standing. Patients with cervical (neck) facet joint syndrome often complain of (1) neck pain, (2) headache, and/or (3) 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.

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.



PART VIII – 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.

The American Pain Foundation publishes a Newsletter, The Pain Community News, and the spring 2008 issue (volume 8 – issue 2) has an article titled “The Evolving Role of Complementary and Alternative Medicine for Pain Relief,” which can be found on the Internet at <http://www.painfoundation.org/learn/publications/pcn/PCN08spring.pdf>.



PART IX – PASSIVE NON-INVASIVE INTERVENTIONS

HYPERBARIC OXYGEN

Hyperbaric oxygen (HBO) involves the administration of oxygen in a pressurized chamber to increase the 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 chronic pain. It has gained wide and increasing acceptance and is now covered by many insurance policies.

PASSIVE THERAPIES AND 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. Passive therapies may be useful over the short term but have limited benefit in chronic pain conditions overall.



MANIPULATION & MOBILIZATION

Manipulation and mobilization are two types of manual (hands-on) therapy that include a wide array of different techniques and schools of thought. In general, mobilization involves assisted low force, low velocity movement often directed to one or more restricted vertebral segments. Manipulation involves high force, high velocity, and low amplitude action with a focus on moving a target joint. As commonly used, “adjustment” is generally a synonym for manipulation.

MAGNET THERAPY

Biomagnetic therapy has been proposed for the relief of chronic painful conditions; it is proposed that magnets, worn close to the skin, create an electromagnetic field within the body that suppresses pain. Magnets are not particularly expensive. But despite anecdotal positive comments, there is no scientific evidence to support their effectiveness for a person with chronic 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. Other devices (such as H-wave stimulation (devices), Interferential Current Stimulation, Microcurrent electrical stimulation (MENS devices), RS-4i sequential stimulator, Electroceutical Therapy (bioelectric nerve block), and Neuromuscular electrical stimulation (NMES devices), Sympathetic therapy, Dynatron STS) have been designed and are distinguished from TENS based on their electrical specifications.

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.

PROLOTHERAPY (SCLEROTHERAPY)

Most evidenced treatment guidelines do not recommend prolotherapy. Prolotherapy describes a procedure for strengthening lax ligaments by injecting proliferating agents/sclerosing solutions directly into torn or stretched ligaments or tendons or into a joint or adjacent structures to create



scar tissue in an effort to stabilize a joint. Agents used with prolotherapy have included zinc sulfate, psyllium seed oil, combinations of dextrose, glycerin and phenol, or dextrose alone. Proponents claim that "proliferatives" act to promote tissue repair or growth by prompting release of growth factors, such as cytokines, or increasing the effectiveness of existing circulating growth factors. In all quality scientific studies, the effects of prolotherapy did not significantly exceed placebo effects.

SURGERY

Due to the number of possible surgical procedures and the controversy surrounding this topic, it will not be covered in this document.



PART X – ACTIVE INTERVENTIONS

EXERCISE (ACTIVE THERAPY)

The overwhelming theme in the treatment of most persons with chronic pain is to keep as physically active as possible. There is usually no reason to avoid using the affected body part. 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. There is no sufficient evidence to support the recommendation of any particular exercise regimen over any other exercise regimen. 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.

Persons with chronic pain can become discouraged when their pain increases due to therapeutic exercise and will sometimes terminate treatment too early before achieving maximal benefit. It is important to have a physician and physical therapist 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 one hundred different stances to learn.

PSYCHOLOGICAL AND BEHAVIORAL APPROACHES

Psychological interventions for chronic pain are numerous, and a full discussion is outside the scope of this Guide. Cognitive behavioral therapy and self-regulatory treatments have been found to be particularly effective. There is considerable evidence of efficacy for mind-body therapies such as yoga, mindfulness meditation and other similar approaches in the treatment of chronic pain.

MIND-BODY INTERVENTIONS

There are numerous mind-body interventions including relaxation, meditation, imagery, biofeedback, and hypnosis.

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, 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 chronic pain in which spine pain tends to tense muscles, which often causes increased pain due to muscle fatigue.

EDUCATION

Education of the patient and family should be the 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.

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 and is 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 doctors 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 exercise 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 use a cognitive behavioral therapeutic (CBT) approach consistent with the biopsychosocial view of chronic pain/disability.

Ultimately, the successful individual with chronic pain takes control of and reengages in life activities and minimizes interactions with the medical community. 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.

CONCLUSION

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 physician 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 Consumer Guide to 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 Consumer Guide to 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 healthcare regarding treatment and medication needs is from an open dialogue with your doctor and therapist.

LINKS TO CHRONIC PAIN SITES AND 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 Internet Web Address to find sites that can help you learn more and better manage your chronic pain: <http://www.theacpa.org/people/links.asp>.

REFERENCES ON THE INTERNET

MEDICATION RELATED

1. <http://www.webmd.com/drugs>
2. <http://www.drugfonet.com/drug.htm>
3. <http://www.pdr.net>
4. <http://www.medscape.com/druginfo>



5. <http://www.fda.gov/cder/drug/default.htm>
6. <http://www.nlm.nih.gov/medlineplus/druginformation.html>
7. <http://www.healthsquare.com/drugmain.htm>
8. <http://www.drugs.com/>
9. <http://www.rxlist.com>
10. <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://www.ampainsoc.org/advocacy/promoting.htm>.
12. <http://www.mayoclinic.com/health/drug-information/DrugHerbIndex>
13. Mayo Clinic Pain medications: Read the label before you buy: <http://www.mayoclinic.com/health/pain-medications/PN00066>
14. Nonsteroidal anti-inflammatory drugs (NSAIDs): http://www.stoppain.org/pain_medicine/content/medication/nsaids.asp
15. Adjuvant Medications: http://www.stoppain.org/pain_medicine/content/medication/adjuvants.asp
16. Opioid Analgesics: http://www.stoppain.org/pain_medicine/content/medication/opioids.asp
17. American Society of Health-System Pharmacists: <http://www.safemedication.com/>
18. eMedicineHealth: http://www.emedicinehealth.com/pain_medications/article_em.htm
19. WebMD: <http://www.webmd.com/pain-management/guide/pain-relievers>

OTHER REFERENCES

20. Treatment Options: A Guide for People Living with Pain by the American Pain Foundation can be found at <http://www.painfoundation.org/learn/publications/files/TreatmentOptions2006.pdf>

