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A STATEMENT FROM THE ACPA BOARD OF DIRECTORS

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

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

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

For 35 years, the American Chronic Pain Association (ACPA), a non-profit, tax exempt organization, has offered a support system for people with chronic pain through education in pain management skills and self-help group activities. To learn more about the ACPA and how to become a member, please visit our web site at [http://www.theacpa.org](http://www.theacpa.org), or call the National Office at 800-533-3231.

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

**This Guide is not meant to serve as medical advice for medical conditions or regarding treatment needs.** Remember that the best source of information about an individual’s health and treatment needs is from an open dialogue with his or her health care professional (in this document the word “health care professional” includes physicians, prescribing advanced practice nurses, nurse practitioners, physician assistants and others who do not prescribe medications but provide other health care services including psychologists, physical and occupational therapists and others).

This ACPA Resource Guide to Chronic Pain Medication & Treatment covers medications and treatments. The topics covered are not exhaustive and because something is not mentioned does not imply that it is not useful. Please contact the ACPA for any comments or recommendations of topics to be covered in future editions of this ACPA Resource Guide to Chronic Pain Medication & Treatment.

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

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

There are many treatment approaches to chronic pain. These approaches include passive and active therapies, medications, behavioral-psychological treatments, and a host of other modalities, devices, and interventional techniques including surgery and other procedures. Medications, passive treatments, and invasive interventions alone are not always satisfactory absent the additional use of other active rehabilitation and educational approaches that treat the whole person with chronic pain.
In fact, rehabilitation through cognitive, behavioral, and physical reactivation treatments (also called functional restoration) often lessens the need for medications and other more invasive procedures.

The ACPA believes that people with chronic pain benefit from being well informed about their treatments and especially about their prescribed medications. This knowledge may relieve the fears that can interfere with receiving maximum benefits from such treatment and medications. Information can also prevent unrealistic expectations that can lead to disappointment or even worse, a bad outcome.

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

The “successful” treatment of a person with chronic pain results in that person learning 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.

It's hard to know how to move forward once chronic pain has entered your life. It helps to think of a person with chronic pain as like a car with four flat tires. Our expectation is that all we need is that one medication or treatment that will take away the pain. But it only puts air in one of our tires; we still have three flat tires and can't move forward. Perhaps the medication or treatment has provided 25 or 30 percent relief. Let's leave that there and ask what else we need to fill our other three tires so that we can resume our life’s journey.

For each person the necessary combination of therapies and interventions will be different, based on individual need. Unlike traditional medicine where the “patient” is a passive participant, living a full life with pain requires that we take an active role in the recovery process. We need to work with our health care providers to find what we need to fill up our other three tires. Biofeedback, physical therapy, counseling, pacing, nutritional counseling, a support group, and a host of medical modalities are a few of the ways we can fill our tires.

Once we have all four tires filled, it is our responsibility to maintain our car. We would not take our car back to the dealer and ask them to fill it up or wash our windshield. That is our responsibility---to take good care of our car. We take it in for inspections and if something goes wrong, we go to a professional. It's the same with our wellness. You see, pain management is much more than one simple modality. It takes a team effort, with the person with pain taking an active role, to live a full life in spite of chronic pain. [http://www.theacpa.org/a-car-with-four-flat-tires](http://www.theacpa.org/a-car-with-four-flat-tires)

**The best advice the ACPA can offer is to discuss all treatment and medication questions with a health care professional!** A primary physician is usually a good resource. There may be a referral to a physician who specializes in Pain Medicine who may have more information or experience about the use of different medications for various chronic pain problems. Also, be open to referral
to a psychiatrist, psychologist, or other mental health professional who can help the person with pain reach their goals.
PAIN TREATMENT OVERVIEW

PAIN TYPES & CHRONIC PAIN CLASSIFICATION

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

Acute pain is characterized 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 healing, more than 3 to 6 months, and which adversely affects the individual’s well-being. A simpler definition for chronic or persistent pain is pain that continues when it should not.

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

Central pain syndrome is a neurological condition caused by a process that specifically affects the central nervous system (CNS), which includes the brain, brainstem, and spinal cord. The disorder occurs in people who have or who have experienced strokes, multiple sclerosis, Parkinson's disease, brain tumors, limb amputations, brain injuries, or spinal cord injuries. It may develop months or years after injury or damage to the CNS. This also includes conditions such as chronic headaches, fibromyalgia, and Complex Regional Pain Syndrome (CRPS).

Tailoring selection of analgesics that target underlying pathophysiology is one of the challenges of medication management. For example, opioid analgesics are generally effective for nociceptive pain but may be less likely to be effective for neuropathic and central pain.

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

Flare-up pain (the term break-through pain was coined to refer to cancer-related flare-ups) can be described as a transitory increase in pain in someone who has relatively stable and an adequately controlled level of baseline pain. It may be caused by changes in an underlying disease, including treatment, or involuntary or voluntary physical actions such as coughing or getting up from a
chair. It can also be caused by stress and emotions such as anxiety, anger, fear or worry. Activity imbalance—doing too much or too little—can also flare pain. Flare-up pain may occur at the end of the scheduled pain medicine dose as well and may be related to withdrawal.

Treatment for moderate-to-severe flare-up pain can consist of medication and/or the use of non-pharmacological tools. Non-pharmacological tools are recommended and include relaxation techniques, mindfulness practices, light stretching or activity, and positive self-talk.

Opioid therapy is the mainstay for the long-term management of moderate to severe pain in individuals with active cancer or other types of advanced medical illness and it is common to use a short-acting opioid in the treatment of flare-up pain for these individuals. However, there is no agreement among healthcare professionals about how best to treat this type of pain in people with non-cancer pain. We have come to realize that the regular use of short-acting additional opioids throughout the day for increased pain may only lead to more pain flare-ups and escalating drug usage rather than true pain relief and increased function.

The best strategy to deal with flare-up pain is to speak with a health care professional.
**PAIN IN PREGNANCY**

In January 2015, the U.S. Food and Drug Administration provided a FDA Drug Safety Communication: FDA has reviewed possible risks of pain medicine use during pregnancy – see http://www.fda.gov/Drugs/DrugSafety/ucm429117.htm

The following is an abstracted summary:

The U.S. Food and Drug Administration (FDA) is aware of and understands the concerns arising from recent reports questioning the safety of prescription and over-the-counter (OTC) pain medicines when used during pregnancy. As a result, we evaluated research studies published in the medical literature and determined they are too limited to make any recommendations based on these studies at this time. Because of this uncertainty, the use of pain medicines during pregnancy should be carefully considered. We urge pregnant women to always discuss all medicines with their health care professionals before using them.

Severe and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure in the mother. Medicines including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen can help treat severe and persistent pain. However, it is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines during pregnancy.

Pregnant women should always consult with their health care professional before taking any prescription or OTC medicine. Women taking pain medicines who are considering becoming pregnant should also consult with their health care professionals to discuss the risks and benefits of pain medicine use.

**PAIN IN CHILDREN**

Chronic pain is a significant problem in the pediatric population, conservatively estimated to affect 20% to 40% of children and adolescents around the world. The most common chronic pain conditions in children and adolescence are musculoskeletal pain, headaches, and abdominal pain. They may experience physical and psychological pain and their families may experience significant emotional distress and social consequences as a result of pain and associated disability. Research suggests that the family dynamic and how parents respond to their child’s pain can have a significant impact on the course of the child’s pain and on their function. One of many resources is the book, Conquering Your Child's Chronic Pain: A Pediatrician's Guide for Reclaiming a Normal Childhood by Lonnie K. Zeltzer, M.D., and Christina Blackett Schlank.

Childhood pain brings significant direct and indirect costs from health care utilization and lost wages due to parents taking time off work to care for the child. In addition, longitudinal studies provide convincing evidence to suggest that childhood chronic pain predisposes the continuation of pain later in life and the development of new forms of chronic pain in adulthood (from Assessment and Management of Children with Chronic Pain, A Position Statement from the American Chronic Pain Association

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Growing Pains was created to help adolescents living with pain. See www.growingpains.org.

**PAIN IN OLDER PERSONS**

Persistent or chronic pain is common in older adults. While medications are certainly an important part of treating chronic pain, their use in older persons is fraught with potential problems. Physical rehabilitation and other interventional therapies, including targeted injections and acupuncture, can be helpful to reduce pain, maximize physical function, and reduce the need for medications. In fact the medical literature is full of studies showing the advantage of regular physical exercise in older adults. Additionally, psychological supports including relaxation techniques, mindfulness practices, and positive self-talk, and should always be considered in managing pain in elderly people.

In addition to chronic pain, older adults are more likely to have multiple medical conditions, and to be taking multiple medications. Medication risks are greater for an individual when multiple medications are taken. Certain medications carry greater risks than others.

In general, 30 percent of hospital admissions among the elderly may be linked to an adverse drug-related event or toxic effect from opioids and sedatives (i.e., a tranquilizer). Nearly one-third of all prescribed medications are for persons 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 person 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 should be started low and adjusted slowly to optimize pain relief while monitoring and managing side effects. Multi-modal analgesia, which is the careful use of multiple pain-relieving drugs together, can be seen as potentially advantageous. Combining smaller doses of more than one medication may minimize the dose-limiting adverse effects of using a particular single drug. This statement is not meant to endorse certain drug combinations such as opioids with benzodiazepines which we know are hazardous.

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 or other health care professional, family members, or friends about deciding to join a trial. The results of the clinical trial can lead to new treatments or therapies becoming available for many people coping with chronic pain.

Information about Learn About Clinical Studies can be found at: http://clinicaltrials.gov/ct2/about-studies/learn
MEDICATIONS IN GENERAL

MEDICATIONS AND CHRONIC PAIN

Prescription medications are lawfully available only from a health care professional licensed to prescribe them. Prescription medications should only be taken by the individual prescribed them by a licensed professional. Do not use, buy or sell prescription drugs from family members, friends, or others.

The use of analgesics (pain relievers) and other medications is the most common method of chronic pain treatment. Pain medications can be helpful for some patients in chronic pain, but they are not universally effective. It is important to remember, each person may respond in a different manner to any medication. In fact, in some individuals, pain medications may actually worsen their symptoms over time or cause unwanted or dangerous side effects.

Medication-related problems would rank fifth among the leading causes of death in the United States if they were considered a disease. In particular, the overuse, misuse and abuse of opioid (narcotic) pain medications has now become a national issue. Deaths due to overdoses of opioid prescription drugs have risen sharply, and now outnumber all other causes of accidental death including motor vehicle accidents. The abuse of prescription opioid pain medications now ranks second - only behind marijuana - as the nation’s most prevalent drug problem.

Short-term use of opioid medications for pain is rarely worrisome, although side effects are most problematic while initiating treatment and tend to diminish with prolonged use. On the other hand, in some cases, prolonged use of opioids increases the possibility of adverse reactions such as gastrointestinal distress including constipation, internal organ problems, balance troubles, hormone problems, sexual dysfunction, and memory and concentration problems. After prolonged use, an increase in pain sometimes occurs due to an interaction between the brain and the opioids called opioid-induced hyperalgesia. (See more in the section on Opioid Medications).

A realistic goal when using medications is usually partial rather than full relief of symptoms.

Therefore, each person with chronic pain should be medically managed individually, and the decision to use and continue pain medication should be determined by weighing benefit vs. harm and should be compared with alternative medications and nonpharmacologic techniques, factoring in the cost, potential side effects, and the person’s other medical problems. Reliance on medication alone is rarely satisfactory. Implementing a balanced approach incorporating physical rehabilitation and self-management strategies is generally more effective in restoring one’s ability to function most fully.

In general, people who begin using other methods to relieve pain (such as those taught by ACPA) may be able to reduce or discontinue medication use.
**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.

However, even the most potent medications used for pain rarely completely eliminate pain but rather may reduce the severity of pain. As such, medications are rarely adequate alone and should be considered as part of a comprehensive approach to pain management and functional improvements.

While medications can help relieve 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 a health care professional.

It is important that the health care professional be aware of all prescription medications, over-the-counter (OTC) medications and nutritional and herbal supplements that are being taken for pain or other medical conditions to ensure these are used appropriately and safely. Some substances and drugs may cause serious side effects if they are combined with other medications. Even over-the-counter pills and herbal medications have possible side effects and the potential to cause serious interactions with prescription medications and with each other. These include various OTC supplements and vitamins, items grown in a home garden or bought in a store, and other “substances” such as caffeine, alcohol, tobacco, and even marijuana and illicit drugs.

It is strongly advised that the person with pain bring all current medications in the original pill bottles or boxes and other items that are taken (including OTC pills, vitamins and supplements) to any appointments with the health care professional. It is essential that the person with pain tell the health care professional about all substances that are taken (even if they are not legal).

People with pain should keep a list of all of their medications in their wallet or purse. This list will be useful in an emergency.

The following Internet links may be helpful:

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

- FDA Educational Resources: The Center for Drug Evaluation and Research (CDER) maintains a collection of educational materials on topics related to buying and using medicine safely.
  
  [http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm296593.htm](http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm296593.htm)
Individuals who take medications should know what medications they are taking, why they are taking them, which should be taken every day, and which should be taken just when needed. Optimal pain relief depends on knowing how much and how often each medication should be taken and whether to take the medication before, with, or after meals or at bedtime. Medications can be confusing, especially if taken for more than one condition. The type of medication and dose depends on the medical condition, body size, age, and any other medications that are taken. It is important to understand the potential side effects of the medications and how these can be prevented or managed effectively. 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. This information can be obtained by reading the labels on the medication containers and asking the health care professional or pharmacist.

The ACPA has a MedCard for keeping track of medications which can be found at http://theacpa.org/uploads/documents/acpa_wallet_card2906.pdf.


The label on the medication bottle may show a brand name (for example, Tylenol) or the generic name (for example, acetaminophen) or both. It is often less expensive to buy medications by their generic name rather than by the brand name. The health care professional can be asked to prescribe generic rather than brand-name drugs to hold down the cost of prescription medications. The color and shape of the pill may be different, but FDA-approved generic drugs are considered to be interchangeable with brand name drugs. Any noticeable differences in drug benefit should be discussed with the health care professional.

It is essential that the dose and directions written on the medication label be followed. The dose should not be changed without consulting the health care professional, and medications that have been prescribed for someone else should never be taken.
IF MEDICATIONS ARE NOT RELIEVING PAIN

Successful treatment relieves a person’s distress and restores health, function, and well-being, so they can resume full participation in everyday life (although adjustments may need to be made).

If an individual has been taking pain medicine every day for a long time and it doesn't seem to reduce pain and allow the person to be more functional, the treatment plan should be re-evaluated. Often a treatment is unsuccessful because it needs to be changed.

It is important to periodically evaluate the big picture and ask how life is going overall. Even if months or years have passed, people with pain should tell their health professionals whether they have regained the ability to engage in and enjoy everyday life activities. If not, it is time to discuss how to change the whole treatment plan. A minor tweak may be all that is needed but bigger changes may often be required, such as a more comprehensive approach.

There are many other ways of relieving pain besides pain medications. Suffering can usually be greatly relieved by learning and strengthening self-care skills. Although some self-care methods can be self-taught, they often require instruction and supervision by an experienced peer or professional at the beginning.

Multidisciplinary pain programs and organizations like the ACPA teach many specific self-care techniques that can help to reduce pain. Mastering them may allow the person with pain to find relief and minimize the things that often make pain worse, such as stress, inactivity, uncertainty, feeling powerless, being out of shape, lack of sleep, boredom, fear, and anger, which are all normal human reactions to pain and life disruption.

There are several non-invasive medical treatments that often work as well or better than pills, patches, injections, and surgery, according to scientific studies. These treatments usually have fewer side effects, are less hazardous, and more likely to restore a satisfying everyday life. A health care professional may be able to prescribe these treatments to help relieve the pain while the person with pain learns the self-care approaches that can help get life back on track.

Changing a medication plan should always be done under the direction of a health care provider because it can be dangerous as well as uncomfortable to stop some medications too rapidly and without medical supervision. This is particularly true in those taking high doses or more than one medication. See next section on “Weaning Off of Pain Medications.”
**W**eaning **O**ff of **P**ain **M**edications

In today’s health care system, it is sometimes easier to start taking medications than to stop taking them. The questions to discuss with a health care professional are: Are the medications actually making a difference? Are they making the person’s life better? Are the benefits worth any side effects and negative effects? In other words, taking pain medications is a choice that each person must make weighing the benefits versus the risks.

When the risks appear to outweigh the benefits of taking a pain medication, reducing the dose should be considered. This is called dose weaning or tapering (sometimes referred to as “detoxification” in the case of opioid medications). The goal of weaning down the dose is to safely discontinue medications that do not seem helpful in reducing pain and see what happens. Oftentimes, people discover they feel better taking lower doses, fewer medications, or not taking medications at all.

If a medication has been taken on a daily basis, it is best to check with the health care professional before altering the medication regimen. It is dangerous to abruptly stop taking some medications (sometimes referred to as “cold turkey”). Because the body develops “physical dependence” to some medications when they are taken regularly, abrupt withdrawal or too rapid reduction in the dose of these medications can be very uncomfortable or even hazardous. It depends on what medication, how much, and for how long the medication has been taken.

Some medications may be safe to stop abruptly:

- A medication that is taken for just a few days or only taken once in a while (e.g. once a week).
- Some medications that do not produce physical dependence (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs – like aspirin, ibuprofen and others], omeprazole).

Some medications always require medical supervision when stopped:

- Opioids that have been taken in regular daily doses for several days.
- Benzodiazepines, muscle relaxants, antidepressants, and anticonvulsant medications that have been taken in regular daily doses for several days.

**The safest approach is always to talk to a health care professional before making any medications changes. Following are suggestions that will guide the discussion:**

- Provide the health care professional with a list that includes the following information about all over the counter (OTC) and prescribed medications that are being taken:
  - Name of the medication
  - Dose (e.g., “325 mg”)
Directions on the bottle (e.g., “take 2 tablets by mouth every 6-8 hours as needed for pain”)

- Understanding of why the health care professional prescribed this medication – what it is supposed to do.
- Actual usage: How often and how much of the medication has the person with pain actually been taking.
- What has the individual noticed about its effects – the good AND bad effects.

- Bring the bottles of all of the OTC or prescribed medications to the appointment so the health care professional can see the labels and examine the pills.
- The health care professional should answer the following questions about each medication, and the person with pain should write down the answers beside the name of each medication during the visit:
  - Is the medication essential?
  - If it is essential, how often should it be taken?
  - If the decision is made to stop taking the medication for a while, can it be abruptly stopped or should the dose be gradually weaned down?
  - If the dose should be weaned down:
    - How can this be done safely?
    - How uncomfortable will this process be?
    - What symptoms are danger signs and which are simply a bother?
    - How long will it take?
  - Are there specific instructions on how to reduce the dose?
  - Will the health care professional help with the weaning process?
  - How often does the person with pain need to see the health care professional during the weaning process?

Weaning off of medications may be complicated by the potential for increased levels of pain that often accompany dose reduction but can be done safely under medical supervision. The health care professional determines the rate at which the dose is reduced, and adjustments can be made as necessary. For example, reasonable opioid weaning protocols suggest decreasing pill intake by 10-20 percent per week, as tolerated. Hydration (drinking water), relaxation, and emotional support are all important to enhance the likelihood of success.

Sometimes weaning or discontinuing opioid medication is most safely accomplished under the close supervision of a specialist (such as an addiction medicine specialist) in a medically-supervised detoxification program to prevent complications and severe withdrawal symptoms.

Symptoms of withdrawal from opioids can include:

- sleeplessness
- anxiety
- sweating
agitation
stomach cramps
nausea, vomiting, diarrhea
body aches (flu-like symptoms)
feeling as though the skin is “crawling”
muscle cramps

Prescription medications that can help diminish symptoms of withdrawal include:

- alpha-2 agonists (clonidine) – blood pressure needs to be monitored while taking this medication
- muscle relaxants (methocarbamol, lioresal, others)
- stomach relaxants (dicyclomine)
- anti-inflammatory pain relievers (ibuprofen, naproxen, others)
- sleep aids (trazodone, amitriptyline, hydroxyzine, others)
- anti-anxiety agents (phenobarbital*, diazepam*, hydroxyzine, others)

On occasion, alternative opioids may be substituted on a temporary basis during detoxification. These include:

- methadone*
- buprenorphine*
- tramadol (not chemically an opioid, but works similarly to opioids)*

*may be habit-forming, so use is limited to short term.

Once the person with pain has discontinued a medication, it is important to dispose of the remaining supply appropriately. For more information, review the FDA website: Medication Disposal: Questions and Answers at http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalof Medicines/ucm186188.htm.
**WARNING ABOUT INTERNET MEDICATION PURCHASES**

Buying medication over the Internet may seem a good way to save money, but up to 96% of online drugstores don’t meet U.S. pharmacy laws or practice standards. The National Association of Boards of Pharmacy (NABP - [http://www.nabp.net/](http://www.nabp.net/))

Internet sites may purport to be legitimate or in a country with drug laws comparable to the United States (e.g., Canada) but may (a) not be located in that country; (b) be located in that country, but dispense prescriptions from another country that has no comparable law; (c) not handle and store medicines in a manner that maintains potency and shelf life; or (d) purchase medicines from dubious sources, including knowingly or unknowingly selling counterfeit medicines that may contain amounts of the expected pharmaceutical ingredients that vary from those stated, may contain other unnamed pharmaceutical ingredients, may contain no active pharmaceutical ingredients, or may contain toxic chemicals or microbial contaminants.

<table>
<thead>
<tr>
<th>Patient Tips for Safe Medication Purchasing*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purchase all medications from state-licensed pharmacies located in the United States.</td>
</tr>
<tr>
<td>2. When purchasing medications from online pharmacies, perform the following checks:</td>
</tr>
<tr>
<td>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 <a href="http://www.nabp.net">http://www.nabp.net</a> or 1-847-391-4406.</td>
</tr>
<tr>
<td>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 <a href="http://www.vipps.info">http://www.vipps.info</a>.</td>
</tr>
<tr>
<td>c. All legitimate online pharmacies will</td>
</tr>
<tr>
<td>i. Make available a licensed pharmacist to answer any medication related questions you may have.</td>
</tr>
<tr>
<td>ii. Require a prescription from a physician or other licensed health care professional who can prescribe medications.</td>
</tr>
<tr>
<td>iii. Provide accurate contact information for customer inquiries.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>5. Carry a list of all medications you currently take (prescription, over-the-counter, herbal, dietary, and vitamin) with you when you visit your doctor or pharmacist so that they can screen for appropriate use and drug-drug interactions. Keep this list on your person at all times.</td>
</tr>
<tr>
<td>6. Be proactive. If you have questions about your medications, ask your pharmacist or physician.</td>
</tr>
</tbody>
</table>

**MEDICATION IDENTIFICATION**

It is always very important to be able to visually identify medications.

Pill identification resources can be used to confirm that the medication is correct. The most definitive tool for identifying a pill is the imprint code that can be on one or both sides of the pill.

Drugs.com has a Drug Pictures Database at: http://www.drugs.com/pill_identification_drug_picture.html

Drugs.com also has a Pill Identifier at: http://www.drugs.com/pill_identification.html where there is a Pill Identification Wizard. After clicking on “I Agree,” the drug name, imprint(s), shape, or color can be typed in.

If a pill cannot be identified, it is best to contact or visit a pharmacist for assistance.
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 titled Postmarket Drug Safety Information for Patients and Providers at:


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 health or even life-threatening. It is important to notify a health care professional of any medication side effects.

When taking any medicine, it is important to be aware of any change in the body and to tell a health care professional if something unusual happens.

It may be hard to know if an adverse reaction is caused by a medical problem or by a medicine. The health care professional will want to know all medications that are being taken, when the symptoms started and whether they are different from other symptoms that have occurred from an illness.

The following are some adverse drug reactions that might be noticed:

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

DRUG ALLERGIES

Drug allergies should be documented appropriately in the medical record and should include a description of the reaction. Some medications can trigger an immune response in individuals with a drug allergy. In other cases, as in a type of reaction to drugs such as aspirin or niacin, allergy-like symptoms may occur but do not involve the immune system. Like many other allergies, a drug allergy can cause a range of responses from a mild rash to life-threatening effects on many body systems.
When reviewing drug allergy information with the health care professional, it is important to differentiate drug intolerance or side effects (e.g., stomach upset) from true allergic reactions.

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

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

It is important to notify the health care professional immediately or possibly seek emergency medical help depending on the symptoms.

More information about drug allergies can be found at the Mayo Clinic web site at:

http://www.mayoclinic.org/diseases-conditions/drug-allergy/basics/definition/CON-20033346

Other sources of information include emedicinehealth or on the American Academy of Allergy, Asthma & Immunology (ACAAI) website at:

http://acaai.org/allergies/types/drug-allergies

**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. It is wise for individuals to try to use the same pharmacy for all their prescriptions so that the pharmacist can screen 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 health care professionals to use a medication “off-label,” but the insurer, health plan, or pharmacist may question its use as recommended by the health care professional. Ask the health care professional to explain to the authorizing party that the medication is being prescribed off-label and for what reason.

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

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 to treat chronic pain were originally designed and marketed for unrelated conditions, such as seizures, cardiac arrhythmias, and depression. The fact that a health care professional recommends such a drug for pain treatment does not mean that the person with pain has epilepsy or some other condition. The same is true with antidepressants; the fact that they are prescribed for chronic pain does not mean that the health care professional has made a diagnosis of depression.

The FDA ([http://www.fda.gov](http://www.fda.gov)) allows drugs to be sold and advertised for specific conditions in which data prove the drug is safe and effective for its intended use. Once on the market, drugs can be prescribed for off-label usage for any condition, particularly those with some clinical data of effectiveness. The process of obtaining approval for another use of the medication can be costly, so a company cannot fund research studies to prove all the uses for a drug. This approval issue is especially true if the medication is no longer protected by a patent, and other companies can sell it.

Further discussion about off-label medication use can be found at:


http://www.webmd.com/a-to-z-guides/features/off-label-drug-use-what-you-need-to-know
Classes of Medications for the Treatment of Pain

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

1. **Non-opioids**: Aspirin, NSAIDs, and acetaminophen.

2. **Opioids (also called narcotics)**: Examples of opioids include but are not limited to morphine, codeine, hydrocodone, oxycodone, and methadone. Tramadol and tapentadol are not opioids but work primarily on the same receptors as opioids.

3. **Adjuvant analgesics**: Medications originally used to treat conditions other than pain but now also used to help relieve specific pain problems; examples include some antidepressants and anticonvulsants.

4. **Other**: Medications with no direct pain-relieving properties may also be prescribed as part of a pain management plan. These include medications to treat insomnia, anxiety, depression, and muscle spasms.

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

**Prescription medications are lawfully available only from a licensed professional. Only use medication that was prescribed for the individual by such a professional.**
NON-PRESCRIPTION PAIN RELIEVERS

OVER-THE-COUNTER (OTC) PAIN RELIEVERS

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

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


The two most common types of OTC pain relievers are acetaminophen and NSAIDs.

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

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

The traditional OTC pain group currently includes aspirin (Bayer®), acetaminophen (Tylenol®), naproxen sodium (Aleve®), ibuprofen (Advil®, Motrin®IB), and various combinations. Most analgesic OTC drugs are based on one of these FDA-approved ingredients. Many manufacturers add other ingredients in an effort to tailor the medication to particular symptoms. For example, a pain reliever, such as acetaminophen, and an antihistamine, such as diphenhydramine hydrochloride (Benadryl®) 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 provide information that Tylenol® PM not only contains acetaminophen but also contains diphenhydramine hydrochloride.

Some OTC medications are labeled “extra strength”. This usually indicates that it contains more amounts (e.g., milligrams) of drug per dosage unit (e.g., tablet) than the standard product by the same manufacturer.
The key to the effective use of OTC medications is to understand the drug(s) that is taken and the maximum safe dosage of all ingredients. This requires reading the medication label, discussing OTC medications with the health care professional or a pharmacist before taking them, especially if prescription medications are also taken. The selected OTC medication should contain an appropriate amount of the drug needed to treat the symptom(s) and should not include medications or ingredients that are not needed.


**THE SAFETY OF OTC MEDICATIONS**

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

As mentioned, the most common OTC medications used for pain are NSAIDs and acetaminophen.

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

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

OTC pain medications can be useful and effective. Even though they are considered safe enough to be dispensed without a prescription, remember they are real medicines. There is often a mistaken belief that because the medication can be obtained without a prescription, they are safe and without potential for harm. Nothing could be further from the truth.

For instance, acetaminophen is the medication most involved in fatal overdoses, but it is important to recognize the relative risk when compared to taking NSAIDs for chronic pain. For example, OTC acetaminophen has been proven to be safe and effective when used as directed. However, when the labeled dosing of acetaminophen is exceeded (overdose), serious liver damage may occur. In contrast, gastrointestinal bleeds, injury, and death from NSAIDs have been known to occur at labeled doses, especially in cases where they are used chronically.
“The Food and Drug Administration (FDA) advises consumers to follow directions when using common pain and fever reducers. **Using more than recommended can cause serious injury.**” The active ingredients, acetaminophen and NSAIDs, are safe and effective when the labeling directions or the advice from a health care professional or pharmacist is followed. This is especially important when taking both OTC medications and prescription medications. “Using Acetaminophen and Nonsteroidal Anti-inflammatory Drugs Safely” can be found at: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/SafeUseofOver-the-CounterPainRelieversandFeverReducers/ucm164977.htm
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 in those with liver problems, even at fairly low doses. Since acetaminophen is contained in many prescriptions, individuals need to pay close attention to their total daily dose of acetaminophen.

The current recommendations are that self-treating users take only the recommended maximum daily dosage of 3,000 mg. Patients may take a higher daily dosage—up to 4,000 mg—if their health care professional instructs them to do so. The maximum daily dosage may be decreased for patients who consume alcohol or for those with elevations in liver enzymes.

**Acetaminophen Overdose and Liver Injury - Background and Options for Reducing Injury**


The abbreviation “APAP” on the label of a drug means the medicine contains acetaminophen. However, not all OTC and prescription drugs with acetaminophen will say APAP, so it is important to ask the health care professional or pharmacist what ingredients are in prescribed medicines before taking them. Some prescription medications have acetaminophen in them, see list below. For example, the label on the bottle may read, Hydrocodone/APAP 5/325. The amount of acetaminophen in each tablet is the number after the “/”. In this case, each tablet has 325 milligrams of acetaminophen in it. The amount of acetaminophen from all sources, both from prescription and OTC medications, must be added together when calculating how much acetaminophen is taken daily.

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

In January 2011, the U.S. Food and Drug Administration (FDA) asked drug manufacturers to limit the strength of acetaminophen in prescription drug products, including combination acetaminophen and opioid products, to no more than 325 mg per tablet, capsule, or other dosage unit. Then in January 2014, the FDA recommended that health care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 mg of acetaminophen per tablet, capsule, or other dosage unit. The FDA has stated that limiting the amount of acetaminophen per dosage unit in prescription products may reduce the risk of severe liver injury from acetaminophen overdosing.

Please visit the FDA website for more information on acetaminophen dosing: [http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm](http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm)  

Acetaminophen is an ingredient in many OTC and prescription medicines. Here are some - but not all - of the most common OTC and prescription drugs that contain acetaminophen. The amount
of acetaminophen varies in combination products, and it is important to note the amount of acetaminophen in each tablet so that accurate accounting of daily dosage can be made.

**Prescription Drugs with Acetaminophen**

- Acetaminophen and Butalbital (Axocet®)
- Acetaminophen and Codeine Phosphate Oral Solution and Tablets (Tylenol® with Codeine)
- Acetaminophen, Isomehtepetne, and Dichloralphenazone Capsules (Midrin®)
- Butalbital, Acetaminophen and Caffeine Tablets (Esgic®, Fioricet®, Zebutal®)
- Oxycodone and Acetaminophen Tablets, Capsules, Elixir (Percocet®, Endocet®, Roxicet®, Tylox®)
- Pentazocine HCl and Acetaminophen Tablets (Talacen®)
- Tramadol and Acetaminophen Tablets (Ultracet™)

**OTC Drugs with Acetaminophen**

- **Backaid®** Maximum Strength Backache 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 Geltcaps or Caplets/Sinus Headache Decongestant Caplets
- **Duane Reade®** Acetaminophen Tablets, Caplets, or Geltabs/Children’s Acetaminophen Elixir/Extra Strength Acetaminophen Geltcaps, 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
- **Premsyn®** PMS 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, Geltabs or Geltabs/Extra Strength PM Gelcaps or Caplets/Regular Strength Acetaminophen Tablets
**HERBAL MEDICINES, SUPPLEMENTS, & VITAMINS**

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

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

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

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

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

**POSSIBLE BENEFIT OF HERBAL MEDICATIONS FOR PAIN**

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

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

There is evidence that the antioxidant alpha lipoic acid (ALA) significantly and rapidly reduces the frequency and severity of symptoms of the most common kind of diabetic neuropathy. Symptoms decreased include burning and sharply cutting pain, prickling sensations, and numbness.
There is also evidence that acetyl-L-carnitine (ALC) not only improves the symptoms of diabetic neuropathy, but also helps regenerate nerve fibers and vibration perception. Unfortunately, studies in people with neuropathy due to cancer chemotherapy revealed no benefit.

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

Coenzyme Q10, or CoQ10 as it is often called, is commonly taken in supplement form to counteract the muscle pain and weakness associated with cholesterol-lowering statin drugs. Whether it is truly beneficial for this purpose is the subject of current studies.

Statins do appear to lower levels of CoQ10, a substance that has several important roles in the body. But those who take it should do so carefully, because in some cases it can blunt or amplify the effects of other drugs, particularly those that are used to control blood sugar and blood pressure.

Curcumin, a compound found in turmeric and ginger roots and spices, is a potent antioxidant. Multiple studies have provided good evidence that it also a potent anti-inflammatory agent. A randomized, placebo controlled study found that curcumin was more effective than placebo and diclofenac sodium (one brand name Voltaren®) for reducing joint pain in patients with active rheumatoid arthritis. Another study found that a curcumin blend was superior to celecoxib for pain relief and increasing walking distance in people with knee osteoarthritis. Taken on its own, curcumin only has about 5% bioavailability. Evidence suggests that piperine (derived from black pepper) and fat (e.g., vegetable oil or butter) increase the bioavailability of curcumin because curcumin is fat soluble, and because the black pepper slows liver metabolism of curcumin. Piperine inhibits CYP 450 enzymes important for drug metabolism. For this reason, check with a healthcare professional before taking piperine to ensure it will not interact with any medications currently being taken. There are several commercially available curcumin products that combine piperine and a lipid agent in the capsule.

Low levels of Vitamin D are associated with chronic pain in general and with reduced immunity. Low levels of Vitamin B are thought to affect neuropathic pain. Pain can be reduced by optimizing vitamin levels. Vitamin B and D levels can be checked to decide if supplementation is indicated.

Consumer Lab is an independent laboratory that tests the quality of nutritional supplements and posts its results at www.consumerlab.com. It is a third party verification group that provides certification for nutritional products and supplements that meet its quality standards.

CAUTIONS REGARDING THE USE OF HERBAL PREPARATIONS, SUPPLEMENTS, & VITAMINS

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

Many adverse events from herbal medicines have been reported including hypersensitivity reactions, anaphylaxis (shock), hepatitis, nausea, vomiting, diarrhea, platelet inhibition, lower seizure threshold, elevated digoxin levels, central nervous system depression, skin sensitivity to light, chest pain, electrolyte alterations, low blood pressure, irregular heartbeat, kidney failure, carcinogenicity, and autoimmune effects. Herbal medicines can also affect the ability of blood to clot. Therefore, information on current use of herbal medicines should be provided to the healthcare professional prior to undergoing any surgery or interventional pain procedure.

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

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

<table>
<thead>
<tr>
<th>Possible Herbal Medication Adverse Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe vera</td>
</tr>
<tr>
<td>Astragalus</td>
</tr>
<tr>
<td>Belladonna</td>
</tr>
<tr>
<td>Chaparral</td>
</tr>
<tr>
<td>Ephedra (also called ma huang)</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
</tr>
<tr>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Kava products</td>
</tr>
<tr>
<td>Garlic</td>
</tr>
</tbody>
</table>

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


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
SELF-MEDICATION: ALCOHOL, TOBACCO, MARIJUANA, AND ILLEGAL SUBSTANCES

ALCOHOL & CHRONIC PAIN

Alcohol is also a drug. 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, or increased sedation and respiratory depression in conjunction with opioids and other sedating medications). The mixture of alcohol and opioids along with sedatives or anti-anxiety drugs can cause death.

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, decreased inhibitions, poor judgment, depression, and outbursts of uncontrolled emotion such as rage or tearfulness. Signs of intoxication with alcohol include unsteady gait, slurred speech, and poor performance of any brain or muscle function. Signs of severe alcohol intoxication include stupor or coma with slow, noisy breathing, cold and clammy skin, and an increased heartbeat.

The long-term effects of alcohol addiction (alcoholism) include craving, the compulsive use and continued use despite harm to family, job, health and safety. When alcohol is unavailable to persons who are severely addicted, withdrawal symptoms will occur and may be life threatening if not treated immediately. Even with successful treatment, individuals addicted to alcohol may have a tendency to relapse suggesting the need for ongoing treatment (such as involvement in 12-step programs, counseling and family support).

Simply put, alcohol and pain medications are dangerous when mixed together.

Additional information is available from the Substance Abuse and Mental Health Services Administration (SAMHSA) at http://www.samhsa.gov/atod
Cigarette smoking, mediated by nicotine, causes blood vessels to become constricted; this restricts the amount of oxygen-rich blood flowing to areas of pain. Smoking not only reduces blood flow to your heart but also to other structure such as the skin, bones, and discs. Due to this, the individual may get accelerated aging leading to degenerative conditions. The lack of blood supply caused by cigarette smoke is also responsible for increased healing time after surgery. After back fusion surgery, smoking cigarettes can increase the risk of the fusion not healing properly. Smoking should be avoided both before and after spine surgery. Cigarette smoke triggers the release of pro-inflammatory cytokines, increasing inflammation and intensifying pain. Smoking makes the bones weak and increases the prevalence of osteoporosis, spinal degenerative disease, and impaired bone and wound healing. Symptoms of depression are more commonly seen among smokers. Below are some tips to help individuals become non-smokers.

Assess readiness to quit smoking and ask a health care professional or pharmacist for help. They will make recommendations, modifications, and develop a treatment plan to optimize success. Even one less cigarette a day is a step in the right direction. Keeping a log may help individuals pinpoint when and why they smoking. Knowing these triggers can help replace smoking a cigarette with more healthy habits.

Smoker’s Log:

<table>
<thead>
<tr>
<th>Cigarettes per day</th>
<th>Time of each cigarette</th>
<th>What triggered the craving?</th>
<th>What were you doing while smoking?</th>
<th>How did you feel while smoking?</th>
</tr>
</thead>
</table>

Nicotine replacement therapy, such as lozenges, gum, or patches, is available.

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

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

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

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

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

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

Some health care professionals will prescribe marijuana, some will not prescribe it but not object to its use with other pain medicines, and some will refuse to prescribe medications (especially opioids) to individuals who are using marijuana. Some health care professionals take a “don’t ask, don’t tell” philosophy and don’t check for marijuana when doing urine drug testing. Nevertheless, the use of any substances should be discussed openly and honestly between the person and his or her health care professional.

The most well-known active ingredient found in marijuana (THC) can decrease pain, but can also lead to dependence and addiction in certain individuals and has significant side effects. Some scientific studies have claimed that other active ingredients in marijuana are more effective at reducing pain without creating a “high.”

Although some states allow the legal use of marijuana for health purposes, including pain, 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 (especially in young people).

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

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

Despite some states allowing medicinal marijuana, it is a federal crime for a health care professional to prescribe a scheduled drug to a person known to be using illegal drugs, including...
marijuana. It is also important to remember that, if possessing marijuana when traveling through a state where medicinal marijuana is not allowed, could result in being charged with possession of an illegal substance, even if the person has the proper prescription and home state documentation. Additionally, an individual can be denied employment or fired if the employer or prospective employer conducts drug screenings as a part of the hiring process or has a ‘no-drug tolerance’ policy. Also individuals can be charged with driving under the influence (DUI) if their driving is impaired and they test positive for marijuana, even in states where medicinal marijuana is allowed.
**NON-OPIOID PAIN RELIEVERS**

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

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

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

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

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

The effectiveness of a medication varies by the individual. Therefore, the person may need to try several different medications to determine which one works best.

The cyclooxygenase-2 (COX-2) inhibitors are NSAIDs that can be prescribed and have a lower risk of gastrointestinal (GI) side effects with short-term use. Currently available in the United States is celecoxib (Celebrex®), which is more expensive than some other NSAIDs and does not provide any better pain relief. Although celecoxib is associated with a lower risk for developing a stomach ulcer when taken for less than 6 months, serious stomach ulceration can still occur without warning with this drug. As with other NSAIDs, individuals who take celecoxib should be monitored for this serious side effect. NSAIDs additionally are associated with potential kidney effects and heart (cardiovascular) complications, especially when taken for prolonged periods. Remember also that when acetaminophen (Tylenol®) is used in combination with NSAIDs, there is an increased risk of developing kidney problems. This effect is usually only seen with long-term use.

While the increased risk of cardiovascular events, such as stroke and myocardial infarction, associated with COX-2 inhibitors has been well established, data are emerging that demonstrate similar risk increases associated with NSAIDs that are not selective for COX-2. Currently, data show that celecoxib 200 mg or less per day does not seem to increase the risk of cardiovascular events any more than the risk associated with traditional NSAIDs. Discussing the risk-benefit ratio of NSAIDs with a health care professional is advised. 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 these medications be used for the shortest period and at the lowest dose required to achieve therapeutic improvement. Individuals taking aspirin for its ability to protect the heart should consult with their health care professional prior to utilizing NSAIDs on a long-term basis. The regular use of NSAIDs inhibits aspirin’s ability to protect the heart.

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

Diclofenac Products*: Diclofenac Gel (Voltaren® 1% Gel) has been approved for the treatment of chronic pain associated with osteoarthritis in joints close to the skin surface (e.g., hands, knees, and ankles). In 2007, a topical NSAID patch containing diclofenac (Flector®) was approved by the FDA for the treatment of acute pain due to minor strains, sprains, and contusions. In 2009, the FDA issued an advisory that transdermal and topical patches that contain metal, which includes Flector®, need to be removed prior to MRI procedures. In 2009, a topical solution of diclofenac sodium (Pennsaid®) was approved by the FDA for the treatment of signs and symptoms of knee osteoarthritis. Pennsaid® 2% was FDA approved in 2014 and is now available.

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

Intravenous (IV) formulations of the NSAIDs ibuprofen (Caldolor®) and ketorolac (Toradol®) are given most often in the inpatient setting to manage short-term moderate to severe pain in adults; ketorolac may also be given intramuscularly (IM). Caldolor is approved also for reduction of fever in adults. In November 2010, IV acetaminophen (Oفirmev®) was FDA approved for the management of mild to moderate pain, severe pain with adjunctive opioid analgesics, and reduction of fever in adults and children 2 or more years old. Similar to the IV NSAIDs, IV acetaminophen is administered in an inpatient setting for short-term pain management and helps reduce the amount of opioid medication needed to manage pain. The FDA has approved dosages of up to 4000 mgs per day of IV acetaminophen. The side effect profile for IV acetaminophen is the same as other acetaminophen dosage forms: headache, agitation, nausea, vomiting, and constipation. Injection site reactions such as redness and swelling may occur with any of the IV non-opioids.
GASTROINTESTINAL (GI) PROTECTIVE MEDICATIONS

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

There are four commonly used cytoprotective classes of drugs:

1. Misoprostol (Cytotec®) - 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®).

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

PPIs have been shown to reduce the risk of GI ulcers and are recommended by the American College of Gastroenterology in individuals with moderate to high GI risk and are taking an NSAID. PPIs have been associated with an increased risk of vitamin and mineral deficiencies impacting vitamin B12, vitamin C, calcium, iron and magnesium metabolism. A study published in 2006 raised concerns because the chronic use of PPIs might have a significant impact on the rate of hip fractures. Acid-suppressive therapy may increase the risk of hip fractures by decreasing calcium absorption. Thus, as with all medications, PPIs must be used with caution, and the disadvantages must be weighed against the benefits.

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

Sucralfate (Carafate®) works via interactions with hydrochloric acid found in the stomach. The combination forms a paste-like substance, which forms a protective coating that acts locally to protect the stomach lining.
Treatment with antacids, such as TUMS®, and H₂ blockers offers 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.
NON-OPIOID ANALGESIC DRUGS & THEIR USES

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

<table>
<thead>
<tr>
<th>Medications (Generic) and Brand Names</th>
<th>May Be Useful for</th>
<th>Pros</th>
<th>Cons</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td>Headache, muscle ache, fever, menstrual cramps, arthritis pain, and inflammation. May reduce the risk of heart attack and stroke.</td>
<td>Anti-inflammatory; inexpensive.</td>
<td>May irritate stomach. Inhibits platelets and can cause prolonged bleeding. Can precipitate asthma in aspirin-sensitive patients.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Salicylate Salts</strong></td>
<td>Pain, osteoarthritis, and rheumatoid arthritis.</td>
<td>Fewer GI side effects than other NSAIDs.</td>
<td>May irritate stomach.</td>
<td>Do not affect bleeding time or platelet aggregation.</td>
</tr>
<tr>
<td><strong>Acetaminophen</strong></td>
<td>Headache, muscle ache, backache, fever, and arthritis pain (especially osteoarthritis).</td>
<td>More gentle to the stomach than NSAIDs; safer for children. Does not promote bleeding (or protect against heart attack, stroke).</td>
<td>Does not reduce inflammation; may be less effective than aspirin for soft tissue pain.</td>
<td>May be harmful for people with kidney or liver disease or those who drink alcohol heavily. May increase bleeding time in individuals receiving anticoagulation therapy.</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>Headache, muscle ache, fever, sprains, menstrual cramps, backache, and arthritis pain.</td>
<td>Stronger and generally longer lasting than aspirin.</td>
<td>May irritate stomach. Cardiovascular risks.</td>
<td>May be harmful for people with kidney or liver disease, asthma, bleeding disorders, or those who drink alcohol heavily.</td>
</tr>
<tr>
<td><strong>Ketoprofen</strong></td>
<td>Headache, muscle ache, fever, menstrual cramps, cold or flu aches.</td>
<td>Helps reduce inflammation. More gentle to the stomach than naproxen sodium, ibuprofen, acetaminophen. Cardiovascular risks.</td>
<td>Less gentle to the stomach than naproxen sodium, ibuprofen, acetaminophen. Cardiovascular risks.</td>
<td>May be harmful for people with kidney or liver disease or those who drink alcohol heavily. Not recommended for children without a health care professional’s supervision.</td>
</tr>
<tr>
<td>Medications (Generic) and Brand Names*</td>
<td>May Be Useful for</td>
<td>Pros</td>
<td>Cons</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------------------------------</td>
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<tr>
<td><strong>Naproxen Sodium</strong>&lt;br&gt;Aleve® (OTC)&lt;br&gt;Anaprox®&lt;br&gt;Naprelan®&lt;br&gt;Naprosyn®</td>
<td>Headache, muscle ache, fever, menstrual cramps, backache, arthritis pain and inflammation.</td>
<td>Stronger and generally longer lasting than aspirin for menstrual cramps, toothache, and inflammation.</td>
<td>May irritate stomach; tends to be higher in cost. Cardiovascular risks.</td>
<td>Not recommended for children without a health care professional’s supervision.</td>
</tr>
<tr>
<td><strong>Meloxicam</strong>&lt;br&gt;Mobic®</td>
<td>Arthritis pain</td>
<td>Associated with less risk of ulcers than other NSAIDs.</td>
<td>Still a risk for stomach irritation. Tends to cost more than other NSAIDs. Cardiovascular risks.</td>
<td>Generally well-tolerated but still need to be concerned about GI side effects.</td>
</tr>
<tr>
<td><strong>COX-2 Inhibitors</strong>&lt;br&gt;Celebrex®</td>
<td>Muscle aches, joint pain, arthritis, pain and inflammation.</td>
<td>Helps reduce inflammation; less stomach irritation than other NSAIDs.</td>
<td>Still a risk for stomach irritation. Tends to cost more. Cardiovascular risks.</td>
<td>Generally well-tolerated but still need to be concerned about GI side effects. No effect on bleeding time. These agents are available by prescription only. Use caution with sulfa allergies and celecoxib.</td>
</tr>
</tbody>
</table>

Other NSAIDs include the following:

- Diclofenac (Cataflam®, Voltaren®, Zipsor®, others) – see comments below
- Diflunisal (Dolobid®)
- Etodolac (Lodine®, Lodine® XL)
- Fenoprofen (Nalfon®)
- Flurbiprofen (Ansaid®)
- Ibuprofen (Caldolor™) - NSAID available intravenous for acute pain and fever
- Indomethacin (Indocin®, Indocin® SR)
- Ketorolac (Toradol®, others) – NSAID injectable formulation (intramuscular and intravenous)
- Mefenamic acid (Ponstel®)
- Nabumetone (Relafen®)
- Oxaprozin (Daypro®)
- Piroxicam (Feldene®)
- Sulindac (Clinoril®)
- Tolmetin (Tolectin®)

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

Opioid Agonists

Opioids are morphine-like substances. Some forms have been available for centuries to relieve pain. The term opioid is derived from opium, which is an extract from the poppy plant.

Opioids come in naturally occurring (opiate), synthetic (opioid), and semisynthetic forms. In 1975, it was discovered that the body generates its own (internal or endogenous) opioids (called endorphins, enkephalins, and dynorphins).

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. The body has opioid receptors that, when occupied by an opioid agonist, create the sensation of analgesia (pain relief).

Opioid medications used to be called narcotics. There are numerous opioids available by prescription (see lists below). Examples include morphine, hydromorphone, fentanyl, methadone, and oxycodone.

All of the opioids have similar clinical effects that vary in degree from one drug to another. The potency, speed of onset, and duration are unique to each drug. Opioids differ in the typical route of administration, whether injection, skin patch, or in pill form. There are both short- and long-acting opioid formulations. Some are used around-the-clock in scheduled doses, while others are used as needed for intermittent or breakthrough pain.

Opioid Mixed Agonists/Antagonists

There are a number of opioid analgesics (pain relievers) that are partial agonists, such as buprenorphine (e.g., Buprenex, Butrans, Subutex, Suboxone), and mixed agonists/antagonists, such as butorphanol (Stadol), nalbuphine (Nubain), and pentazocine (Talwin).

The mixed agonists/antagonists are characterized as having an analgesic “ceiling” effect in which the analgesic benefit plateaus and no further benefit is obtained by increasing the dose. Given their antagonist nature, these medications can reverse the effects (analgesia and side effects) of full agonist opioids, such as morphine, fentanyl, hydromorphone, and oxycodone, and therefore should be used with caution in those taking a full agonist opioid.

A partial agonist/antagonist is occasionally initiated in a person already taking an opioid agonist. The doses should be adjusted gradually to avoid symptoms of opioid withdrawal. In most cases,
these two types of agents should not be used together as the partial agonist/antagonist will work against the pure opioid agonist.

Symptoms of withdrawal include sweating, gooseflesh or goose bumps (a temporary local change in the skin when it becomes rougher due to erection of little muscles, as from cold, fear, or excitement), runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. The health care professional or pharmacist should be informed about these symptoms.

**OPIOID DELIVERY**

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

**SHORT-ACTING AND LONG-ACTING OPIOID AGONISTS**

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

Examples of short-acting opioid combination products include:

- codeine
- oxycodone (combined with acetaminophen - Percocet®; combined with aspirin - Percodan®; combined with ibuprofen - Combunox®)
- hydrocodone (combined with acetaminophen - Lorcet®, Lortab®, Vicodin®, Norco®; combined with ibuprofen - Vicoprofen®)
- tramadol hydrochloride with acetaminophen (Ultracet®)
- morphine (Roxanol®)
- hydromorphone (Dilaudid®)
- fentanyl (Actiq®)
- oxymorphone (Opana®)
- tapentadol (Nucynta®)

Short-acting oral opioids, true to their description, exert a rapid-onset but short-lived therapeutic effect. These agents typically start working 15–30 minutes after administration, with peak analgesic effect within 1–2 hours. Sustained pain relief is maintained for only about 3 to 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 to 4 hours. Therefore, these drugs are not ideal for long-term therapy of chronic pain. Short-acting opioids may be effective, however, as an initial “trial” therapy in patients with moderate or severe chronic pain who have not previously received opioid treatment. In this case, short-acting agents are used to establish an individual patient’s response and tolerance to opioid therapy and lay the groundwork for long-term dosing of long-acting opioid therapy.

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

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

Examples of long-acting opioids include:

- morphine (oral sustained release, e.g., MS Contin®, Avinza®, Kadian®)
- oxycodone (oral controlled release, e.g., OxyContin®)
- oxymorphone (oral extended release Opana® ER)
- hydrocodone (oral extended release Zohydro® ER, Hysingla®)
- hydromorphone (oral extended release EXALGO®)
- methadone (oral, e.g., Dolaphine®, Methadose®)
- fentanyl transdermal system (Duragesic®)
- tapentadol (Nucynta® ER)
- buprenorphine transdermal system (Butrans®)

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

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

<table>
<thead>
<tr>
<th><strong>Codeine</strong> (with acetaminophen - Tylenol® with codeine No. 2, No. 3, No. 4)</th>
<th>Codeine is metabolized by the liver to morphine. Some individuals do not have the enzyme required to convert codeine to morphine, and therefore the medication is ineffective. Even though they do not receive benefit, they are still at risk for the associated side effects. Codeine often is associated with higher levels of nausea and vomiting and constipation compared to other opioids.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydrocodeine bitartrate, Aspirin, Caffeine</strong> (Synalgos-DC®)</td>
<td>This combination drug of dihydrocodeine, aspirin and caffeine is rarely prescribed in chronic pain states.</td>
</tr>
<tr>
<td><strong>Fentanyl</strong> (Actiq® lozenge, Fentora® buccal tablet and ONSOLIS™ buccal film, Abstral® buccal film, Duragesic® transdermal patch, Lazanda® nasal spray)</td>
<td>There have been reports of death and other serious side effects from overdoses while on fentanyl transdermal patches. Furthermore, patients that have not been on opioids (opioid naïve) should not be initially started on the fentanyl transdermal patch because of the inherent inaccuracies in dosing which can lead to an overdose. Exposure to heat (hot bath, heating pad, hot sun, etc.) can increase the speed of fentanyl release. The directions for using the fentanyl skin patch must be followed exactly to prevent death or other serious side effects from overdose. Do not cut fentanyl patches. Oral transmucosal fentanyl is available in multiple formulations for the treatment of breakthrough pain in cancer patients receiving opioid treatment and who have become tolerant to it. The FDA warns that serious adverse events, including deaths, can occur in patients treated with oral fentanyl. The deaths that have occurred were due to respiratory depression as a result of improper patient selection, improper dosing, and/or improper product substitution. Actiq® (oral transmucosal fentanyl lozenge on a plastic stick) is absorbed by swabbing the drug-containing lozenge over and under the tongue and between the cheeks and gums. It is contraindicated for acute postoperative pain and migraine headache.</td>
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<td>Examples of Medical Opioid Agonists*</td>
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<tr>
<td><strong>Hydrocodone</strong></td>
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<td>• Hydrocodone alone – Zohydro® ER, Hysingla® ER</td>
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<tr>
<td>• With acetaminophen – Anexsia®, Lorcet®, Lortab®, Norco®, Vicodin®, Hycet®, Xodol®, Co-Gesic®, Zydone®</td>
<td></td>
</tr>
<tr>
<td>• With ibuprofen – Reprexain™, Vicoprofen®</td>
<td></td>
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<tr>
<td>• With aspirin – Azdone, Lortab ASA, Panasal</td>
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<tr>
<td>Hydrocodone is a short-acting opioid available alone or in combination with other ingredients, and different combination products are prescribed for different uses. Zohydro is the only extended-release hydrocodone available for pain, in an acetaminophen-free formulation with twice-daily dosing. Some hydrocodone products are used to relieve moderate to severe pain. Other hydrocodone products are used to relieve cough.</td>
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<tr>
<td><strong>Hydromorphone</strong> (Dilaudid®, Dilaudid-5®, EXALGO®)*</td>
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<tr>
<td>EXALGO® tablets are an extended-release oral formulation.</td>
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<tr>
<td><strong>Levorphanol</strong> (Levo-Dromoran®)</td>
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<tr>
<td>Levorphanol has the same properties as morphine with respect to the potential for habituation, tolerance, physical dependence and withdrawal syndrome. It is 4 to 8 times as potent as morphine and has a longer half-life.</td>
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<tr>
<td><strong>Meperidine</strong> (Demerol®)</td>
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<tr>
<td>Due to its low potency, short duration of action, and unique toxicity (i.e., seizures, delirium, and other neuropsychological effects) relative to other available opioid analgesics, meperidine has fallen out of favor and is not recommended or typically used in chronic pain states.</td>
<td></td>
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</tbody>
</table>
### Examples of Medical Opioid Agonists*

| **Methadone** (Dolophine®, Methadose®) | Although methadone possesses analgesic properties, it must be used carefully and with a great deal of caution. It has a long half-life and can accumulate in the body, which can lead to an overdose. It interacts with a large number of other medications, including OTC drugs. It is strongly recommended that the individual on methadone not use any OTC or herbal medications without the approval of the prescribing health care professional. The addition of other commonly used pain medications (e.g., antidepressants, anticonvulsants, and NSAIDS) can increase the likelihood of methadone negatively influencing the heart’s ability to conduct electrical signals properly. Prior to starting methadone, patients should undergo an electrocardiogram to check for any pre-existing heart abnormalities that may contraindicate its use. Methadone can also be associated with the development of central sleep apnea. Benzodiazepines should be utilized with extreme caution by individuals who take methadone, secondary to the synergistic negative respiratory and cardiac effects. |
| **Morphine** (Avinza™, Duramorph®, Kadian®, MS Contin®, Oramorph SR®) | Morphine is considered to be the prototypical opioid and is available in many formulations. |
### Examples of Medical Opioid Agonists*

<table>
<thead>
<tr>
<th><strong>Oxycodone</strong> (OxyContin®, Roxicodone™, Oxecta®)</th>
<th>The manufacturer of OxyContin® reformulated its product and began shipping in August 2010. The current reformulated OxyContin® is 100% extended-release. Reformulated OxyContin has physicochemical barriers to crushing, dissolving and breaking; manipulations often required for abuse through intravenous and intranasal routes. Reformulated OxyContin requires more time and effort to defeat the tablet’s time-release properties compared to original OxyContin; however, the physicochemical properties of reformulated OxyContin do not in any way influence the ability to abuse by swallowing intact tablets without legitimate purpose, and as with other opioid analgesics, intact tablets can lead to overdose and death when abused. There is currently no generic for the reformulated OxyContin®, which is the only form available in the United States.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Combunox® (containing ibuprofen, oxycodone)</td>
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<tr>
<td>• Endocet® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Endodan® (containing aspirin, oxycodone)</td>
<td></td>
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<tr>
<td>• Lynox® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Magnacet® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Narvox® (containing acetaminophen, oxycodone)</td>
<td></td>
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<tr>
<td>• Percocet® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Percodan® (containing aspirin, oxycodone)</td>
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<tr>
<td>• Perloxx® (containing acetaminophen, oxycodone)</td>
<td></td>
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<tr>
<td>• Primlev® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Roxicet® (containing acetaminophen, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Roxiprin® (containing aspirin, oxycodone)</td>
<td></td>
</tr>
<tr>
<td>• Taxadone® (containing acetaminophen, oxycodone)</td>
<td></td>
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<tr>
<td>• Tylox® (containing acetaminophen, oxycodone)</td>
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<tr>
<td>• Xolox® (containing acetaminophen, oxycodone)</td>
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<tr>
<td>Examples of Medical Opioid Agonists*</td>
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</table>

**Oxymorphone** (Numorphan®, Opana® and Opana® ER)*

Opana® ER is an extended-release crush resistant oral formulation of oxymorphone.

**Tapentadol** (Nucynta®, Nucynta® ER)*

Tapentadol is a dual mechanism drug with both opioid and anti-depressant-like activity. The drug binds to opioid receptors and also inhibits the reuptake of the neurotransmitter norepinephrine. The short-acting formulation is approved for acute pain treatment, and the extended-release formulation is approved for continuous moderate to severe chronic pain. Tapentadol may have an improved GI side effect profile in comparison with other opioids.

**Tramadol** (Ultram®, Ultram® ER)* and Tramadol combined with acetaminophen (Ultracet™) is considered a “weak” opioid-like analgesic

*In July 2014, the DEA, citing evidence of possible abuse, dependence and diversion, reclassified all meds containing Tramadol as Schedule IV controlled substances (those with a recognized medical use and relatively low potential for abuse & dependence).

Tramadol is a weak analgesic that acts on the central nervous system in two ways. It binds modestly to opioid receptors and thus produces some analgesia by the same mechanism as opioids. It also affects certain neurotransmitters in the brain to decrease the perception of pain. While a weak opioid-like drug, tramadol is not completely free of this risk and may trigger addiction even in those without a history of drug abuse or previous addiction. Tramadol reduces the respiratory rate to a lesser extent than opioids in overdoses and does not cause the sort of GI irritation produced by NSAIDs. Tramadol reduces the threshold for seizures, which may occur in overdose. Seizures may also be provoked in those with a history of seizure disorders, head trauma, etc., or in those taking other drugs that reduce the seizure threshold such as certain antidepressants. Since tramadol is a centrally acting synthetic analgesic, not an NSAID, it has no anti-inflammatory activity. Also unlike NSAIDs, tramadol does not have the potential to compromise the efficacy of certain antihypertensive agents (diuretics and ACE-inhibitors). Tramadol should be used cautiously, if at all, in patients with underlying liver and kidney disease.
### Examples of Medical Opioid Partial Agonists & Mixed Agonists/Antagonists

<table>
<thead>
<tr>
<th><strong>Buprenorphine</strong></th>
<th>In addition to its use for the treatment of chronic pain, buprenorphine is used to help alleviate unpleasant withdrawal symptoms associated with opioid detoxification and to treat addiction. Buprenorphine has been thought to exhibit a ceiling effect, which means increasing the dose of buprenorphine beyond a certain point results in no additional pain control. Doses greater than 32 mg / day are thought to be ineffective for pain control but are not used due to cardiac concerns regarding prolongation of the QT interval. Some clinicians believe that the “ceiling effect” with buprenorphine offers advantages when compared to other medications used to manage addiction because there is a lower abuse potential, lower level of both physical dependence and withdrawal, and there is possibly decreased incidence of dose related side effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>- (Buprenex® injectable (indicated for pain relief/analgesia))</td>
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</tr>
<tr>
<td>- Butrans® Transdermal (indicated for pain relief/analgesia)</td>
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<tr>
<td>- Subutex® (indicated for the treatment of opioid dependence/addiction)</td>
<td></td>
</tr>
<tr>
<td><strong>Buprenorphine/naloxone</strong></td>
<td>Buprenorphine/naloxone (Suboxone®) is a combination drug. Naloxone is a pure opioid antagonist, meaning it blocks the effects that opioid drugs have on the receptors. Naloxone inhibits respiratory depression, hypotension, sedation, and analgesia. When given sublingually (under tongue), naloxone has no significant effects on buprenorphine. However if Suboxone® is crushed or injected, naloxone will block the effects of buprenorphine. This characteristic discourages misuse of the formulation. If Suboxone® is swallowed instead of dissolved under the tongue, the patient may experiences no effect due to the poor bioavailability and first pass metabolism of buprenorphine.</td>
</tr>
<tr>
<td>- Suboxone® (indicated for the treatment of opioid dependence/addiction)</td>
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</tr>
<tr>
<td><strong>Dihydrocodeine bitartrate, Aspirin, Caffeine (Synalgos-DC®)</strong></td>
<td>This combination drug of dihydrocodeine, aspirin and caffeine is rarely prescribed in chronic pain states.</td>
</tr>
<tr>
<td><strong>Butorphanol (Stadol®)</strong></td>
<td>Available in injection or nasal spray formulations but not typically used for chronic pain treatment.</td>
</tr>
<tr>
<td><strong>Nalbuphine (Nubain®)</strong></td>
<td>Administered subcutaneously, intramuscularly or intravenously but not used for chronic pain treatment.</td>
</tr>
<tr>
<td><strong>Examples of Medical Opioid Partial Agonists &amp; Mixed Agonists/Antagonists</strong></td>
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<tr>
<td><strong>Pentazocine</strong> (Talwin®; with acetaminophen-Talacen®; with aspirin-Talwin® Compound)</td>
<td>Side effects are similar to those of morphine, but pentazocine may be more likely to cause hallucinations and other psychosis-like effects. It is not used for chronic pain treatment.</td>
</tr>
<tr>
<td><strong>Pentazocine/naloxone</strong> (Talwin® NX)</td>
<td>Talwin® NX is a combination of pentazocine and naloxone, an opioid antagonist. This oral formulation was developed to prevent tampering and reduce abuse. The goal of this drug design is to reduce the possible misuse of this medication when it is tampered with by crushing, chewing, or injecting. If the drug is taken as directed, the naloxone will not release and will pass through the body with no effect.</td>
</tr>
</tbody>
</table>
**GENERAL OPIOID ADVERSE SIDE EFFECTS**

Common opioid side effects, particularly with higher doses, include:

- Nausea
- Vomiting
- Constipation
- Thought and memory impairment
- Drowsiness

The majority of these side effects can usually be treated with dose adjustments, wane over time (with the exception of constipation), or can be offset by other alternate medications.

Lower opioid dosages carry the lowest risks.

Remember also that taking opioids does not result in being pain-free but rather the goal should be less pain, more function and either no or little side effects that are manageable.

Approximately 40% of individuals taking opioid therapy for non-cancer pain experience **constipation** (less than three bowel movements per week) secondary to opioid treatment. Most individuals taking opioid medications will not develop tolerance to opioid-induced constipation. Therefore, an effective preventive bowel regimen including diet changes and a stimulant laxative plus a stool softener will have to be maintained throughout the course of opioid treatment. Even individuals that utilize appropriate laxative therapy often still experience constipation that may impede the appropriate use of opioid pain medication and thus result in higher levels of pain, so attention to and prevention of this side effect is essential. Medications used for constipation include OTC stool softeners (pills, suppositories, enemas, etc.) and prescriptions drugs such as lubiprostone (Amitiza®), naloxegol (Movantik™, and methylnaltrexone (Relistor®). [http://www.theacpa.org/opioid-induced-constipation](http://www.theacpa.org/opioid-induced-constipation)

Non-pharmacological interventions that can be taken to assist with constipation include: 1) increasing dietary fiber intake, 2) increasing fluid intake, 3) increasing physical activity, and 4) encouraging daily bowel movements at the same time, often after a meal.

In cases that do not respond, other forms of laxative treatment can be considered. Bulk forming laxatives, such as psyllium, are often not useful and can actually worsen opioid-induced constipation by producing colon obstruction. New approaches to treating opioid-induced constipation are being developed. Currently, these new medications have only been FDA approved for the postoperative period and the treatment of opioid-induced constipation in patients with advanced illness.

**Mild nausea** is also common with opioid therapy. It can be treated with medications, but if it does not resolve within a few days, a trial of an alternate opioid may be appropriate.
Mild sedation and impaired judgment or coordination also should be anticipated, especially at the beginning of opioid therapy and with significant dose increases. If safe to consume, caffeinated beverages may help to reduce mild sedation until tolerance to this side effect develops. Until tolerance or a baseline is reached, the patient and family need to be warned against driving and the potential for falls. Psychostimulants can be useful in selected patients to treat sedation but can be habit-forming and have serious side effects.

Hormonal Changes: A side effect of long-term opioid use is a decrease in certain hormones, particularly sex hormones. This reduction may cause a loss in ‘sex drive’, sometimes called libido. This tends to be associated with using these medications regularly for many years. Because of hormonal abnormalities (decreased estrogen levels), bone density may be diminished which may result in the risk of fractures.

Respiratory Depression: A serious side effect, particularly in opioid-naïve individuals (those who have not been taking opioids regularly), is respiratory depression (slowed rate of breathing or loss of urge to breathe). Tolerance to respiratory depression can occur with regular opioid use but this has been called into question now and it is even thought that respiratory depression may increase with prolonged use contributing to some postoperative respiratory morbidity in people receiving long-term opioid therapy.

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 (Demerol) belong to a different class.

Summary of Possible Opioid Side Effects

- Central nervous system (CNS)
  - A sense of emotional well-being and euphoria
  - Drowsiness, sedation, and sleep disturbance
  - Hallucinations
  - Potential for diminished psychomotor performance
  - Dysphoria and agitation
  - Dizziness and seizures
  - Aberrant behavior (see addiction definition below)
  - Hyperalgesia (see definition below)

- Respiratory system
  - Respiratory depression is the most serious adverse effect and may result from toxicity
  - Risk for slowed breathing and death is greatly increased when opioids are taken with benzodiazepines or other CNS depressant drugs or with alcohol. To minimize risks, do not take opioids with benzodiazepines and never consume alcohol with opioids

- Ocular system
- Constriction of the pupil of the eye

- Gastrointestinal system
  - Constipation, nausea and vomiting
  - Delayed gastric emptying

- Genitourinary
  - Urinary retention

- Endocrine
  - Low Testosterone in men and low estrogen in women
  - Reduced fertility in reproductive age women
  - Sexual dysfunction resulting from low hormone levels

- Cardiovascular
  - Decreased blood pressure
  - Slowed heart rate
  - Peripheral edema (swelling)

- Musculoskeletal system
  - Muscle rigidity and contractions
  - Osteoporosis

- Skin system
  - Itching is common and not an allergic reaction

- Immune system
  - There are data suggesting that long-term administration of opioids suppresses the immune system. Research is being conducted to determine its clinical significance.

- Pregnancy* & Breast Feeding: When at all possible avoid opioid use during pregnancy to minimize fetal risks
  - All opioids cross the placenta
  - Neonatal central nervous system depression can occur if opioids are used during labor
  - Neonatal abstinence syndrome can occur in infants born to mothers who are taking regular daily doses of opioids
  - Avoid breastfeeding when taking opioids for chronic pain
  - If an opioid is used in breast feeding, use caution and only under a health care professional’s supervision
  - Timing of opioid dose administration is important for safe opioid use during breast feeding
  - Use of opioids during pregnancy and breastfeeding may result in fetal or newborn toxicity including central nervous system and respiratory depression along with opioid dependency

- Analgesic Tolerance
  - Decreased duration of analgesia and then decreased effectiveness

- Withdrawal Syndrome
  - Withdrawal symptoms may occur with abrupt opioid cessation and can include runny nose, shivering, “gooseflesh,” diarrhea, and dilation of the pupil of the eye
**DEFINITION OF TERMS REGARDING OPIOIDS**

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

**Opioid-induced Hyperalgesia** occurs when continued opioid use causes 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, under the supervision of a health care professional. Naloxone (Narcan) should not be administered in an attempt to reverse opioid-induced hyperalgesia.

Addiction is one of the primary concerns that limits opioid prescribing. This is a term that requires clarification. Addiction is not the same thing as physical dependence (see below). **Addiction** is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual **pathologically pursuing reward and/or relief** by substance use and other behaviors.

Addiction is characterized by the inability to consistently abstain, by impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death. (From American Society of Addiction Medicine, www.ASAM.org)

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. In the case of pain, the “need” and craving present as the intense desire to relieve the pain. 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, biological, 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. Physical dependence is common among people who take opioids, but it is not a sign that anything is wrong. A person taking opioids can become physically dependent without being addicted. However, there is a risk that addiction will develop in anyone who takes opioids, and some people have more risk of addiction than others.

When addiction develops, the pain medication has become a liability rather than an asset to the person. An older description of addiction includes four core elements (the four C’s):
Compulsive use and preoccupation with the drug and its supply,
Inability to consistently control the quantity used,
Craving the psychological effects of the drug, and
Continued use despite adverse effects from the drug.

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

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

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

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

Craving, in this sense, does not mean taking a medicine as directed to relieve pain, but rather, an intense desire for a mental effect (“buzz”, “high”, or “trip”) caused by a medicine. It may also include an intense desire to relieve pain “at any expense”, even though, in the long run, the medicine is not truly helping much at all.

People sometimes worry that they may become addicted to their opioid pain medications. Risk is increased in those who have a personal or family history of problems with drugs or alcohol and those who have a history of anxiety, depression, or other emotional conditions. People with a history of adverse experiences (including sexual abuse) during childhood or adolescence are also at risk. The risk of addiction should be discussed with a health care professional prior to taking an opioid for pain treatment.

Similarly, individuals should let their health care professional know if they are concerned about becoming addicted to opioid pain medications. There are many misconceptions that surround the use of opioids for pain relief, and a knowledgeable health care professional can provide accurate information. Signs to be aware of during opioid treatment include taking more medication than prescribed without checking with a health care professional first, loss of control over the medication, feelings of craving the medication or taking the medication for the euphoric (mental) effects rather than for pain relief.

**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, fear, anxiety, sleeplessness, etc. Some use pain medications to fall asleep, others to relax, still others to get along better with a spouse. A major hallmark of chemical coping is the overly important 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 or unwilling to treat pain non-pharmacologically; that is, they do not take advantage of other treatment options provided (i.e., functional restoration), such as exploring recommendations to exercise, to see psychologists or physical therapists. Further, they remain on the fringe of appropriate use of their medication but are able to comply with their health care professional’s opioid agreement enough to avoid being removed from treatment. Chemical copers often self-escalate their medication dosage when they are faced with stress and need to have their prescriptions refilled early.

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

**Withdrawal** involves developing signs of illness/discomfort when intake of the substance is abruptly stopped. Withdrawal is not addiction but can occur in people who are addicted. Many people who have taken opioids or sedatives for more than a few doses will show some tolerance with use and withdrawal on abrupt drug cessation. In addition, numerous drugs can produce tolerance and withdrawal, yet do not produce addiction (e.g., epilepsy medications, some blood pressure drugs). Symptoms of withdrawal to monitor for include sweating, goose flesh, runny nose, abdominal cramping, diarrhea, nervousness, agitation, hallucinations, and a fast heartbeat. Tell a health care professional or pharmacist these or other side effects occur. Obtaining refills on time will prevent withdrawal.

**Opioid Tolerance** is a phenomenon or adaptation of the body over a period of time in which one or more effects of a drug diminish 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 including pain relief. 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 but does occur in people who are addicted.

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. However, if not prevented, they do continue to experience constipation, as individuals do 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 to be 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 require increased doses and still have unsatisfactory relief. Older patients may not become tolerant as quickly to the analgesic effects of opioids as younger patients. In some patients a progression of their disease may lead to increase pain signals or to pathology that leads to pain that is not sensitive to opioids. This disease progression can be misinterpreted as opioid tolerance.

**Pseudo-tolerance** is the need to increase medications such as opioids for pain when other factors are present that may be the underlying cause, such as disease progression, new disease, increased physical activity, prescription of inadequate doses, lack of compliance, change in medication, and drug interactions.

**Functional Impairment** and physical inactivity are additional concerns that make health care professionals reluctant to provide long-term opioid therapy. 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.

**Diversion** is allowing others to have access to another person’s 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 diversion has been a major contributor to the steep rise in opioid-related deaths in the U.S.
THE OPIOID DILEMMA

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

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

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

A person who is deciding whether or not to use opioids for pain relief should not just consider the risks vs. benefits of these medications. They should ask themselves whether they are at higher risk for misuse, abuse or addiction than others (See Addiction below). They should look at the bigger picture, and compare the risks and benefits of opioids to those of other treatments, many of which are safer and as or more effective for chronic pain.

In the opioid naïve person (someone new to opioid use), the use of opioids may heighten the risk of accidental death from respiratory depression. These risks greatly increase with higher doses, and when opioids are taken in combination with other drugs that also slow breathing, such as benzodiazepines. In fact, current medical evidence suggests that with rare exception, opioids and benzodiazepines should not be prescribed at the same time.

According to the US Centers for Disease Control, opioid poisoning was the second leading cause of injury death overall and the leading cause of injury death for people ages 35–54 years, surpassing both firearm-related and motor vehicle-related deaths in this age group between 1999 and 2006. The number of poisoning deaths and the percentage of these deaths involving opioid analgesics increased each year during that period. In 2008 there were 14,800 deaths from overdose of prescription pain medications, which exceeded deaths from heroin and cocaine deaths combined.

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

**OTHER RISKS ARE MUCH MORE COMMON**

One out of every two patients taking oral opioids experience at least one adverse event/effect. Approximately one out of five patients taking oral opioids discontinue their use because of an adverse event or an associated side effect.

Prolonged use of opioids may result in problems including hyperalgesia (increased pain sensitivity), hormonal effects (decreased testosterone levels, decreased libido and sex drive, irregular menses, etc.), depression, impaired sleep patterns, and suppression of the immune system. The long-term use of opioids may also impair functional improvement in an individual’s recovery from surgery or long-standing musculoskeletal disorders. The prolonged use of opioids usually causes tolerance and physical dependence. As a separate issue, the use of opioids may trigger or worsen substance abuse and addiction. (See Dependence and Addiction below)

Opioids can actually prolong or even increase pain. Research shows that long-term use of large quantities of opioids may interfere with the body’s natural pain relievers, the endorphins. Since physical activity is thought to promote release of endorphins, it is also possible that opioids could inhibit the body’s own mechanism of reducing pain by causing a person to be less active. Additionally, long-term opioid use may cause depression in some patients, which may impede their ability to recover. And, in some people, a mechanism called hyperalgesia actually increases the brain’s sensitivity to pain. For an article on this topic, A Comprehensive Review of Opioid-Induced Hyperalgesia go to [http://www.integration.samhsa.gov/pbhci-learning-community/Opioid-Induced_Hyperalgesia_Article.pdf](http://www.integration.samhsa.gov/pbhci-learning-community/Opioid-Induced_Hyperalgesia_Article.pdf). Stopping the opioid reduces this type of pain.

For all of the reasons listed above, reducing opioid dosage or eliminating it entirely may create short-term increases in pain, but long-term reduction in symptoms and improved well-being. However, it is important to remember that opioids should be stopped under the direction of a health care professional.

**THE EVIDENCE FOR OPIOID EFFECTIVENESS**


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

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

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

The fact that opioids reduce the natural drive to breathe is a serious concern. In addition, opioids become particularly dangerous when used in conjunction with other medications that can also depress respiration—sedative-hypnotics, benzodiazepines, antidepressants, and muscle relaxants—or with alcohol. Those taking opioids should speak with a health care professional about other medications being taken to make sure there are not medication interaction risks. Opioids and benzodiazepines may be prescribed together in very select cases, but in general, this combination of medications should be avoided. Never drink alcohol while taking opioids or benzodiazepines.

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


or http://www.er-la-opioidrems.com/IwgUI/remshome.action
The Substance Abuse and Mental Health Services Administration (SAMHSA) provides additional information about Prescription Drug Misuse and Abuse at http://www.samhsa.gov/prescription-drug-misuse-abuse

**KEY STEPS TO USE OPIOIDS SAFELY**

1. **Keep the health care professional informed.** Inform the 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 taking what the health care professional prescribed, side effects should be reported. Do not crush, break, or dissolve pills. This can alter the rate at which the medication is absorbed and lead to overdose and death.

3. **Reduce the risk of drug interactions.** Do not mix opioids with alcohol, antihistamines, barbiturates, or benzodiazepines. All of these substances slow breathing, and their combined effects could lead to life-threatening respiratory depression.

4. **Prevent theft and diversion.** Do not store opioids in the medicine cabinet or where others have access to the medications. The best strategy is to store medications in a locked box. Do not share medications with anyone else.

5. **Keep track of when refills are needed** to prevent going without medications, leading to withdrawal. Discuss refill strategies with the prescriber ahead of time. Some pain clinics will not fill prescriptions without a visit to the clinic. Other clinics will not fill prescriptions on Friday afternoons or weekends/evenings.
OPIOIDS & THE GOALS OF PAIN MANAGEMENT

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

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 at the expense of function, 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.

If you use opioids to help manage your pain, it's important to take them, store them, and dispose of them properly. Watch this video to learn more. http://www.theacpa.org/opioids/default.aspx
MONITORING MEDICATION USE

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

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

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

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

- **Is the person’s day centered around taking medication?** If so, consultation with the health care professional may clarify long-term risks and benefits of the medication and identify other treatment options.

- **Does the person take pain medication only on occasion, perhaps three or four times per week?** If this is the case, then the likelihood of addiction is low.

- **Have there been any other chemical (alcohol or drug) abuse problems in the person’s life?** If so, then it is important to inform the health care professional, who will need to take that into consideration when prescribing. Often, patients with a previous history of substance use disorders are not ideal candidates for consideration for opioid treatment for pain management because the opioids may trigger craving for alcohol or the prior drug that was the problem, or they may develop addiction to the opioids themselves.

- **Does the person in pain spend most of the day resting, avoiding activity, or feeling depressed?** If so, that suggests the pain medication is failing to promote rehabilitation. Daily activity is necessary for the body to produce its own pain relievers, to maintain strength and flexibility, and to keep life full and meaningful. Encourage the person with pain to request recommendations from a health care professional for a graduated exercise program.

- **Is the person in pain able to function (work, household chores, and play) with pain medication in a way that is clearly better than without?** Chances are that the pain medication is contributing to wellness. Most people who are addicted to pain medications or other substances do not function well.

- Is the person a smoker? Smoking increases pain and reduces the effectiveness of opioids. Smokers tend to take higher doses of opioids and have greater risks for problems and addiction. Smoking itself is an addictive behavior and therefore a clear risk for opioid addiction. Opioids should be avoided in smokers.

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
• Escalation of pain
• Continual dose escalation
• Increasing number of medications prescribed to treat the side effects of opioids

A useful tool for tracking many of the symptoms and impact that pain has on a person can be tracked with the ACPA Pain Log. [http://www.theacpa.org/painLog/default.aspx](http://www.theacpa.org/painLog/default.aspx)

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 their loved one’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.

ACPA offers a three-part video series focused on the many challenges that family members experiences when living with a person with pain. [http://www.theacpa.org/family-matters](http://www.theacpa.org/family-matters)

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 for chronic non-cancer pain. 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. Those who take opioids should not have the expectation of prolonged opioid use without concomitant benefits.
**Opioid Treatment Agreement**

Individuals with pain have an important responsibility with respect to opioids to ensure that both they, as well as others, will be able to have access to opioids in the future. When opioids are prescribed, people with pain are usually requested to formally communicate their agreement with the written therapeutic plan (Opioid Treatment Agreement——sometimes termed an Opioid Contract or Opioid Therapy Plan), and, in particular, their understanding that the goal of opioid therapy is not the elimination of pain but, rather, its reduction to the point where measurable and meaningful increases in function are apparent. This would also include agreeing that they will obtain opioids only from one pharmacy and one medical provider, abstain from using other sedatives without express permission from the health care professional prescribing the opioids, and not engage in activities that would be interpreted as representing misuse or diversion of their medication. The health care professional should clarify what activities would be interpreted as such to ensure a common understanding.

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

The discussion of safe storage and disposal not only helps to prevent theft and subsequent abuse but also prevents accidental overdose by children, cognitively impaired family members, and pets. Patients should always be aware of how many refills and how many pills remain in their prescription. The goal of the agreement is to ensure that patients and caregivers have clear communication and safe, effective procedures when opioids are used.


An opioid treatment agreement also includes random urine drug testing.

**Urine Drug Testing (UDT) / Urine Drug Screening (UDS)**

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

ANTIDEPRESSANTS

One of the most important classes of drugs used to treat chronic pain is the antidepressant group. Prescription of an antidepressant for pain treatment does not mean that the pain is psychiatric in origin. Antidepressant drugs have been used for many years to relieve pain.

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

- They do not work for pain only by relieving depression. In fact, they work as well for non-depressed people with pain as for those with depression.

- They do not work equally well for all types of pain. For example, they tend to be helpful for fibromyalgia, headache, and pain due to nerve (“neuritic”) damage (e.g., diabetic neuropathy), but generally are less helpful for most acute musculoskeletal sports-type injuries.

- How well they work has little to do with how effective they are as antidepressants. Some very effective antidepressants have virtually no ability to reduce pain.

HOW ANTIDEPRESSANTS MAY HELP

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

The antidepressants that increase norepinephrine seem to have better pain relieving capabilities than those that increase serotonin. This helps to explain why the selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac®) and paroxetine (Paxil®), 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 while some cause 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 (TCAs) can have significant anticholinergic effects, which can include confusion, blurred vision, constipation, dry mouth, light-headedness, and difficulty with urination or loss of bladder control. In older patients with decreased cognitive abilities, the use of a tricyclic antidepressant can lead to significant confusion. Patients with Alzheimer’s disease should not be started on TCAs.

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

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

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

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

**Pain States That May Respond To Antidepressants**

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<thead>
<tr>
<th>Postherpetic neuralgia</th>
<th>Migraine &amp; Tension Headache</th>
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<tr>
<td>Diabetic neuropathy</td>
<td>Chemotherapy induced peripheral neuropathy</td>
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<tr>
<td>Phantom limb pain</td>
<td>Fibromyalgia</td>
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<tr>
<td>Stump / neuroma pain</td>
<td>Irritable Bowel Syndrome</td>
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<tr>
<td>Central pain (following stroke)</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Sympathetic dystrophy (CRPS / RSD)</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Chronic musculoskeletal pain</td>
<td>Low back pain with radiculopathy</td>
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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 trazadone (Desyrel®), maprotiline (Ludiomil®) and mirtazapine (Remeron®), which are tetracyclic antidepressants.

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

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

Common side effects caused by TCAs include dry mouth, blurred vision, constipation, difficulty urinating, worsening of glaucoma, impaired thinking, and tiredness. These antidepressants can also lower blood pressure and may cause palpitations (pounding heart). They may increase appetite and be associated with weight gain. Go to the following web site for further information about TCA toxicity:

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

Mirtazapine (Remeron®) 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™), escitalopram (Lexapro®), and vilazodone (Viibryd®).

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

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

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

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

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

SELECTIVE SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

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

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

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

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

These medications have no cholinergic inhibition and, thus, they are associated with fewer side effects.
Venlafaxine has been shown to have therapeutic benefit in the treatment of neuropathic pain. Venlafaxine is available in an extended-release formulation which has a better tolerability profile than the immediate-release formulation. Blood pressure should be monitored in these patients because venlafaxine can increase systolic blood pressure.

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.

**NOREPINEPHRINE-DOPAMINE REUPTAKE INHIBITORS (NDRIs)**

The fourth class includes a number of drugs that are norepinephrine-dopamine reuptake inhibitors or NDRIs. They are primarily used in the treatment of depression, but are also prescribed for smoking cessation and for the treatment of attention deficit disorder.

The only NDRI that is approved by The Food and Drug Administration for the treatment of depression is bupropion (Wellbutrin®).

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

**OTHER ANTIDEPRESSANTS**

Trazodone is a tetracyclic 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 (Nardi®), 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. For example, tramadol and the antidepressants have shared mechanisms on serotonin reuptake and may need to be used together with caution.

**STOPPING ANTIDEPRESSANTS**

As stated earlier, antidepressants should not be stopped abruptly. Even with a relatively slow taper, withdrawal symptoms may occur as the body becomes dependent on these drugs. An extended, slow taper may help ease symptoms. Omega-3 Fatty Acids may help the body and brain adjust as the medications are weaned.
**Alert: Mixing Anti-migraine Agents & Certain Antidepressants**

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

The Food and Drug Administration warned people taking certain anti-migraine medications and certain drugs to treat depression that they may be at risk for a dangerous chemical imbalance. Antidepressant medications included in this warning are fluoxetine, sertraline, paroxetine, escitalopram, duloxetine, milnacipran, and venlafaxine. Migraine drugs include naratriptan (Amerge®), almotriptan (Axert™), sumatriptan (Imitrex®), and zolmitriptan (Zomig®).

Serotonin is a brain hormone that keeps mood stable and appetite in check, as well as serving other functions. More than 50 commonly prescribed medicines boost the amount or effect of serotonin in the body. When two or more drugs that affect serotonin levels are taken, 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 brain serotonin level. Mild serotonin symptoms from even one medicine can occur (common serotonin-related side effects from antidepressant medicines include headache, pain in the stomach, diarrhea, nausea, flushing or trembling).

A much more severe form of serotonin syndrome can occur if several medicines with a serotonin effect are combined. 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, restless 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.

Those who take an antidepressant or anti-anxiety medicine (or a close friend or family member who does) should review the following list of drugs that can add to one’s serotonin load. This is a reasonably comprehensive list. Be very careful about overlapping medicines and watch for serotonin symptoms when doses of any of these medicines are increased is also recommended.

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, (Eskalith®), 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 (Axert™), 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, Actiq®), pentazocine (Talwin®), duloxetine (Cymbalta®), tapentadol (Nucynta®) 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 (Zyvox™).
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, painful diabetic neuropathic pain, and fibromyalgia. Nevertheless, most use of anticonvulsants for pain is “off label.”

Although these medications are not habit forming, abrupt discontinuation can be hazardous. They should be stopped only after discussing how to do so with a health care professional. Common side effects are drowsiness, peripheral edema (lower extremity swelling), and unsteady gait or poor balance. These symptoms tend to diminish over time.

Gabapentin (Neurontin®) is widely utilized and has proven to be effective in many people for nerve injury or neuropathic pain. Decreased mental alertness or awareness is possible at higher doses (e.g., 3600 mg/day) but this is variable and is person specific. Generic gabapentin is now available. In January 2011, Gralise®, a once-a-day gabapentin, was approved by the FDA. Gralise is indicated for the management of Postherpetic Neuralgia (PHN). Gralise is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration. Dosage and administration: Gralise should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal. Gralise should be swallowed whole. Do not crush, split, or chew the tablet. Dosage forms and strengths: 300 and 600 mg tablets. There is a difference in individual tolerability and experience of adverse effects with each medication.

A similar drug to gabapentin, 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 to 600 mg/day). Its side effect profile is similar to gabapentin, and it is generally well tolerated. Side effects are mostly mild to moderate and transient, with dizziness and somnolence being the most common. Other adverse effects include dry mouth, peripheral edema, blurred vision, weight gain, and concentration or attention difficulties. Often, gabapentin and pregabalin require a period of time before their effectiveness in treating a patient’s pain is seen because the medications need to be titrated to the appropriate dose. The FDA issued a warning on the use of anticonvulsants and the risks of suicidal thoughts and suicide. Patients utilizing anticonvulsants for pain control should be monitored for any signs and symptoms of suicidal thoughts.
**ANTICONVULSANTS POSSIBLY USEFUL IN CHRONIC PAIN**

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

<table>
<thead>
<tr>
<th>Anticonvulsant</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin* (Neurontin®)</td>
<td>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.</td>
</tr>
<tr>
<td>Pregabalin* (Lyrica®)</td>
<td>Found effective in postherpetic neuralgia, diabetic neuropathy, and fibromyalgia. Some advantage over gabapentin. It is generally well tolerated.</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol®)</td>
<td>Interacts with some other drugs, can affect the liver and white blood cells. Used for trigeminal neuralgia.</td>
</tr>
<tr>
<td>Valproic acid (Depakote®)</td>
<td>Used in headache or nerve pain. May affect platelets as an adverse effect.</td>
</tr>
<tr>
<td>Phenytoin (Dilantin®)</td>
<td>Stronger evidence supports the use of the above agents over phenytoin. The risk of adverse effects and drug interactions also precludes its regular use.</td>
</tr>
<tr>
<td>Clonazepam (Klonopin®)</td>
<td>A benzodiazepine (Valium®, Xanax® family).</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal®)</td>
<td>May be useful for pain refractory to carbamazepine. Used in trigeminal neuralgia, central pain. Not FDA approved and clinically not recommended for neuropathic pain. May cause dizziness, constipation, nausea, decreased mental awareness, etc.</td>
</tr>
<tr>
<td>Tiagabine (Gabitril®)</td>
<td>Used in combination with other anticonvulsant agents in the management of partial seizures. Possibly useful in treating neuropathic pain. Most common side effects include nonspecific dizziness, drowsiness, and difficulty with concentration. Has been associated with new onset seizures and status epilepticus in patients without epilepsy.</td>
</tr>
<tr>
<td>Lacosamide (Vimpat®)</td>
<td>Lacosamide is being studied as an anticonvulsant with potential for reducing diabetic neuropathic pain.</td>
</tr>
<tr>
<td>Topiramate (Topamax®, Topiragen®)</td>
<td>Generally well tolerated but sometimes causes confusion, dizziness, fatigue, and problems with coordination and concentration. Minimally useful in treating neuropathic and sympathetically maintained pain. It is also being used as a preventive migraine treatment. Side effects include strange sensations and loss of appetite. May cause secondary angle closure glaucoma and, if left untreated, may lead to permanent vision loss. It may also cause dose-related weight loss, and cause or predispose to kidney stones.</td>
</tr>
<tr>
<td>Levetiracetam (Keppra®)</td>
<td>Indicated for use as adjunctive therapy in the treatment of partial seizures in adults. It is possibly effective in neuropathic pain.</td>
</tr>
<tr>
<td>Zonisamide (Zonegran®)</td>
<td>Indicated for use as adjunctive therapy for treatment of partial seizures (or focal seizures) in adults with epilepsy. Possibly useful in treating neuropathic pain.</td>
</tr>
</tbody>
</table>
SODIUM CHANNEL BLOCKING & ORAL ANTI-ARRHYTHMIC AGENTS

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

Those anti-arrhythmics with local anesthetic properties are occasionally used in refractory or difficult to treat pain. They are approved for the prevention of disturbances in heart rhythm but, just as they interrupt premature firing of heart fibers, they also diminish premature firing of damaged nerves. This leads to less firing of the nerve, and hence less capability of the nerve to trigger pain.

Due to safety concerns, the only anti-arrhythmics that are used for chronic pain are mexiletine (Mexitil®) and flecainide (Tambocor™). They reduce pain in diabetic neuropathy, post stroke pain, complex regional pain syndrome (CRPS) formerly called reflex sympathetic dystrophy (RSD), and traumatic nerve injury.

Mexiletine is chemically similar to lidocaine, an anesthetic frequently used by dentists. Common side effects of mexiletine include dizziness, anxiety, unsteadiness when walking, heartburn, nausea, and vomiting. Consult a health care professional if pregnant or planning to get pregnant, have a history of heart attack, are a smoker, or take any of the following medications: amiodarone, fluvoxamine, dofetilide (Tikosyn®), bupropion, or sodium bicarbonate. It should be taken three times daily with food to lessen stomach irritation. Infrequent adverse reactions include sore throat, fever, mouth sores, blurred vision, confusion, constipation, diarrhea, headache, and numbness or tingling in the hands and feet. Serious symptoms occur with overdose including seizures, convulsions, chest pain, shortness of breath, irregular or fast heartbeat, and cardiac arrest.

Flecainide (Tambocor™) was approved to treat arrhythmias and can slow a fast heart rate. It has also been effective for treating certain painful conditions related to neuropathic pain. Although cardiac side effects with flecainide may be infrequent, they can be catastrophic. An EKG is recommended before treatment is started. This drug should probably not be used for pain management in patients with a history of cardiovascular or heart disease. The health care professional should be of any kidney or liver problems because this may require monitoring of drug levels or a dosage reduction. Flecainide interacts with amiodarone, several antipsychotic and anti-arrhythmic medications, and ranolazine (Ranexa®). 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*. Topical agents have also gained popularity for use in certain neuropathic pain conditions such as diabetic neuropathy, postherpetic neuralgia (PHN), or neuroma pain. They are also prescribed in CRPS states. Many are available without a prescription.

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

Some of the OTC topical agents contain salicylates, a family of drugs that reduce inflammation and pain. They come from the bark of the willow tree and are the pain relieving substances found in aspirin. Small amounts relieve mild pain. Larger amounts may reduce both pain and inflammation. Salicylates decrease the ability of the nerve endings in the skin to sense pain. Large amounts can be absorbed and lead to similar adverse effects as when given orally.

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

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

Even though many of these products are sold without a prescription, they still carry some risk of adverse effects (mostly skin irritation). Topical products containing NSAIDs (diclofenac or Voltaren) carry less risk of side effects versus the oral NSAIDs (e.g., ibuprofen), but they still apply. Also, these products should not be applied on wounds, damaged skin, or the face. Lastly, after application, hands should be washed thoroughly to avoid getting these products in sensitive
areas such as the eyes. When removing and discarding used patches, fold the used patches so that the adhesive side sticks to itself. Safely discard used patches where children and pets cannot get to them.

Aspirin in chloroform or diethyl ether, capsaicin (Zostrix®, Zostrix®-HP, Qutenza™), EMLA® (eutectic mixture of local anesthetics; contains lidocaine and prilocaine) cream, and local anesthetics such as the lidocaine patch 5% (Lidoderm®) are topical treatments for neuropathic pain. Of these, the topical lidocaine patch 5% and capsaicin patch are the only FDA-approved treatments for neuropathic pain, and they require a prescription. There are additional topical agent combinations, which can be compounded at a 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. Most insurance companies will not pay for these medications.

Capsaicin (cap-SAY-sin) is the active ingredient in hot peppers, which produces a characteristic heat sensation when applied to the skin (dermal drug delivery). Several studies have suggested that capsaicin can be an effective analgesic in at least some types of neuropathic pain and arthritic conditions (osteoarthritis and rheumatoid arthritis). An adequate trial of capsaicin usually requires four applications daily, around the clock, for at least three to four weeks. Some individuals may experience a burning sensation, which usually lessens within 72 hours with repeated use. Gloves should be worn during application, and hands should be washed with soap and water after application to avoid contact with the eyes or mucous membranes.

In late 2009, the FDA approved Qutenza™ (capsaicin) 8% patch for the management of neuropathic pain attributed to PHN that may occur after an episode of herpes zoster (shingles). The Qutenza™ patch releases a synthetic form of capsaicin through a dermal delivery system at a much stronger dosage than capsaicin creams available over the counter. Only physicians or other 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. A topical anesthetic is applied before Qutenza™ application as it can create significant pain during application. In clinical trials, the most common adverse reactions were application site redness, pain, itching, and bumps. The majority of these reactions were transient and self-limited. Among patients treated with Qutenza™, 1% discontinued treatment prematurely due to an adverse event. Serious adverse reactions included application-site pain and increased blood pressure. Information can be found at http://www.qutenza.com/_docs/qutenza_full_PI_.pdf.

Topical anesthetics, such as EMLA® (Eutectic Mixture of Local Anesthetic; contains lidocaine and prilocaine) cream and L.M.X.4 (contains lidocaine 4%), are used primarily prior to painful procedures such as blood draws, lumbar puncture (spinal tap), and wart removal. EMLA® 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. Pain relief can be expected to increase for up to 3 hours under occlusive dressing and persist for 1 to 2 hours after removal of the cream. Side effects to EMLA® 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). EMLA requires a prescription in the U.S.

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

Lidoderm® 5% (lidocaine) patches can be cut to fit over the area of pain. The 5% lidocaine patch is FDA approved for the treatment of a neuropathic pain condition, specifically PHN, and requires a prescription. It measures 10 cm x 14 cm and has a clear plastic backing that must be removed before application of the patch to the skin. The manufacturer states that up to three patches can be applied simultaneously to intact skin for up to 12 hours in any 24-hour period.

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

Potential hazards still exist, however. In 2007, the FDA issued a public health advisory to notify consumers and health care professionals of potential life-threatening side effects associated with the use of topical anesthetics, particularly before cosmetic procedures. At risk are consumers, especially those without the supervision of a health care professional. They may apply large amounts of anesthetics or cover large areas of the skin, leave these products on for long periods of time, or use materials, wraps, or dressings to cover the skin after anesthetic application. Application to areas of skin irritation, rash, or broken skin may also increase the risk of systemic absorption. The FDA recommends that if topical anesthetics are needed prior to medical or cosmetic procedures, consumers ask their health care professional for instructions on the safe use of these products, use only FDA-approved products, and use products with the lowest amount of anesthetic while applying the least amount possible to relieve pain.
**COMPOUNDED MEDICATIONS**

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

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

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

Other compounded agents include those injected into the epidural and spinal canal. An outbreak of meningitis in 2012, secondary to epidural steroids that were compounded, produced much more scrutiny of compounding pharmacies.

Many intraspinal or intrathecal (injection into the sheath surrounding the spinal cord) analgesics need to be compounded for improved pain relief and delivered via intraspinal drug delivery systems or pumps. The best recommendation is to work with a compounding pharmacy that has a history of quality care and can answer questions about stability and sterility of their compounding techniques.
SEDATIVES AND ANTI-ANXIETY MEDICATIONS

Proper sleep hygiene is critical to the individual with chronic pain and often is hard to obtain. Various medications may provide short-term benefit. While sleeping pills and anti-anxiety agents are commonly prescribed for people with chronic pain, pain specialists rarely, if ever, recommend them for long-term use. They can be habit-forming, and 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. See discussion below regarding proper sleep hygiene. When combined with opioids, the incidence of side-effects and overdose increases.

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 zolpidem, especially those taking serotonin-booster antidepressants, have experienced unusual changes in their thinking and/or behavior. Zolpidem and other sleep medicines can cause a special type of memory loss associated with behaviors such as eating and driving. Older adults, in particular, should be aware that they may be more apt to fall and suffer a head injury or fracture. Zolpidem 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 which can increase the drug's side effects. If the individual has breathing problems, they may become worse if with using zolpidem.

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.
**Sleep Hygiene**

Chronic sleep problems, also known as insomnia, are a significant problem in society and almost a universal issue for persons with persistent or chronic pain. People who have chronic sleep problems may be getting substantially less sleep than is needed for good health.

Sleep problems can be called “chronic” when they last more than three weeks, and can last for months or years. These sleep disturbances are more serious; sorting them out and restoring good sleep may require the help of a health care professional.

Insomnia is not a disease, but a symptom of a problem; one of which includes pain. Insomnia can be a side effect of many medications. Alcohol and drug abuse or addiction can also interfere with sleep. According to national statistics, at least one half of all instances of insomnia are caused by psychological problems. Waking up too early is common for people who are depressed. Difficulty falling asleep is often caused by anxiety.

Our pain is worsened by both the physical and emotional consequences of lack of restful sleep.

When we are deprived of the restful sleep we need:

- We become fatigued and less alert and attentive.
- We are more inclined to irritability and other mood problems that can make relationships with family, friends and co-workers difficult.
- Our cognitive ability, concentration, and judgment suffer.
- Our ability to perform even simple tasks declines, our productivity is sabotaged.
- We make mistakes resulting in reducing productivity at home and on the job and increasing the opportunity for human error and fatigue related accidents.

Scientific studies have confirmed that practicing good sleep hygiene is as effective as or more effective than medication treatment in improving the quality and quantity of sleep. It is common for people with persistent pain to believe that they sleep poorly because of pain, which may be true; however, studies demonstrate that it often happens the other way – poor sleep increases pain.

The costs of poor sleep are significant. In addition to the general lack of feeling refreshed both physically and emotionally, there are other consequences of sleep deprivation. The negative health and economic consequences of poor quality sleep and sleep deprivation are significant.

Some medications prescribed for chronic pain may disrupt the normal sleep cycle and some may be activating and make quality sleep difficult. Substances, including caffeine, theophylline and other stimulants, steroids, and some anti-hypertensive and antidepressant medication can precipitate insomnia.

People who snore or have sleep apnea (a condition in which the flow of air into the lungs is repeatedly blocked during the night resulting in periods when they stop breathing while asleep) are likely to have fitful, low-quality sleep, often leading to daytime drowsiness. They half-waken...
several times a night, and wake up unrefreshed. Increased weight and obesity are often associated with chronic pain, probably because of decreased activity, the use of certain medications and even depression that can lead to poor dietary habits. Obesity can cause or worsen sleep apnea, and people with chronic pain have a tendency to gain weight due to decreased activity.

Here are some sleep hygiene tips:

- Limit consumption of caffeine after early afternoon as well as nicotine and alcohol before sleep.
- Avoid late-afternoon naps.
- Use the bedroom only for sleep-related activities.
- Restrict time in bed to sleep hours.
- Limit strenuous exercise before sleep.
- Turn off electronic devices while preparing for bedtime.
- Avoid watching action or violence on TV before bed.
- Develop a bedtime routine—have a regular bedtime and wake time every day.
- Develop a meditation and relaxation therapy program before bed as this can reduce physiologic arousal and promote sleep onset.
- Warm milk or mild tea (herbal or decaffeinated) can be soothing.
- Light can be blocked with an eye mask.
- Resolve emotional distress issues before going to sleep.
- Decrease bedroom temperature.
- Use a white noise machine.
- Make sure the bed frame and mattress are adequate.
- In general avoid naps during the day if they are interfering with getting to sleep at night.

The NIH has created a web page that brings sleep information from the many institutes that fund sleep-related research into one place. Learn more at:

Information on sleep can be found at:
and
**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 should be limited to only short term as they do not work well when used continuously each night to produce sleep.

Most benzodiazepines are recognized for causing depression and physical dependence when used for long periods.

Most benzodiazepines are not recommended for chronic pain.

Side effects are similar to those of alcohol and include sedation, slurred speech, and gait unsteadiness. Other adverse reactions include chest pain and a pounding heartbeat, psychological changes, headache, nausea, restlessness, vision problems, nightmares, and unexplained fatigue. Alcohol and tobacco should be avoided while taking these drugs. Another major side-effect is respiratory depression, particularly when combined with long-acting opioids. Extreme caution should be used when prescribing both opioids and benzodiazepines concomitantly:. In fact, it should be avoided. The majority of unintentional overdoses occurs when opioids and benzodiazepines are used at the same time.

Because of withdrawal symptoms, these drugs should be discontinued slowly under a health care professional’s supervision. Withdrawal reactions may be mistaken for anxiety since many of the symptoms are similar. Without medical supervision, benzodiazepine withdrawal can be associated with seizures or death.
**MUSCLE RELAXANTS**

Many drugs have been marketed as muscle relaxants, even though most do not seem to have any direct effect on muscle. Perhaps they should be called “brain relaxants,” since they are all sedating, and this may be how they actually work. They should be used with caution with opioids. In the vast majority of cases, these medications should not be taken with opioids. If prescribed both classes of medications, be sure to have a discussion with a health care professional about the risks from taking these medications. Also be sure medications prescribed are from only one health care professional who clearly knows everything being taken.

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 (TCAs) and may have a similar mechanism. Muscle relaxants have limited efficacy in the treatment of 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol (Soma®)</td>
<td>Primarily a depressant marketed as a muscle relaxant. Converted by the body into meprobamate, a barbiturate-like drug. It may cause physical dependence. It should be avoided in kidney or liver disease. With prolonged use, it is associated with dependence. Use in chronic pain should be avoided.</td>
</tr>
<tr>
<td>Cyclobenzaprine (Flexeril®, Amrix®)</td>
<td>Skeletal muscle relaxant that is structurally similar to the TCAs. Side effects include dizziness, drowsiness, dry mouth, constipation, confusion, and loss of balance. Long-term regular use in chronic pain should be avoided.</td>
</tr>
<tr>
<td>Methocarbamol (Robaxin®)</td>
<td>Skeletal muscle relaxant with sedative properties. Side effects include drowsiness and urine discoloration to brown, black, or green.</td>
</tr>
<tr>
<td>Metaxalone (Skelaxin®)</td>
<td>Skeletal muscle relaxant. It should be used with caution in those with liver disease.</td>
</tr>
<tr>
<td>Chlorzoxazone (Parafon Forte® DSC)</td>
<td>Skeletal muscle relaxant with sedative properties. It should be used with caution in those with liver disease.</td>
</tr>
<tr>
<td>Baclofen (Lioresal® - oral and injectable), Gablofen® - injectable</td>
<td>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. It is not typically recommended for muscle spasm.</td>
</tr>
<tr>
<td>Dantrolene (Dantrium®)</td>
<td>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.</td>
</tr>
<tr>
<td>Orphenadrine (Norflex™)</td>
<td>A skeletal muscle relaxant with analgesic properties.</td>
</tr>
<tr>
<td>Drug</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tizanidine (Zanaflex®)</td>
<td>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.</td>
</tr>
<tr>
<td>Diazepam (Valium®)</td>
<td>Diazepam is a primarily a depressant but like other benzodiazepines also has muscle-relaxant properties. Most pain specialists avoid prescribing diazepam for muscle spasm. Toxicity of benzodiazepines is discussed at <a href="http://www.emedicine.com/emerg/topic58.htm">www.emedicine.com/emerg/topic58.htm</a>.</td>
</tr>
</tbody>
</table>

**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.

Commonly used medications in this class include chlorpromazine (Thorazine®), aripiprazole (Abilify™), clozapine (Clozaril®), haloperidol (Haldol®), olanzapine (Zyprexa®, Zydis®), quetiapine (Seroquel®), risperidone (Risperdal®), and ziprasidone (Geodon®).

In general, their use in chronic pain is poorly established, they are often used as anti-anxiety or sleep medications. They are strong drugs and 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 (neuroleptics) is discussed at [http://www.emedicine.com/EMERG/topic338.htm](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). It is available as a tablet for oral administration, as an injectable solution for administration in an epidural or implanted pump, or as a once-weekly patch. As mentioned previously, clonidine may be helpful controlling withdrawal symptoms from opioids.

Side effects can include dry mouth, drowsiness, dizziness, and constipation. Transient localized skin reactions can occur with the patch. Since clonidine lowers blood pressure, it should be used cautiously in patients who have low blood pressure. Safest usage would suggest measuring blood pressure prior to taking a dose of oral clonidine and holding for a blood pressure less than 90/60.

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

**BOTULINUM TOXINS**

Botulinum toxins, Botox® (onabotulinumtoxinA), Dysport® (abobotulinumtoxinA), Xeomin® (incobotulinumtoxinA) and Myobloc® (rimabotulinumtoxinB) have been found to be effective in decreasing tone in overactive (hypertonic) muscles, which may be present in a number of chronic pain conditions. A recent review article regarding the treatment of refractory pain by Dr. Jabbari summarizes that botulinum toxins have “established efficacy” to control pain of cervical dystonia, chronic migraine, and chronic lateral epicondylitis (tennis elbow).

The review also found a lower level of evidence and classified botulinum toxin as “probably effective and recommended” for post-herpetic neuralgia (PHN), post-traumatic neuralgia, pain of plantar fasciitis, piriformis syndrome, and pain in total knee arthroplasty; “possibly effective, may be used at discretion of clinician” for allodynia of diabetic neuropathy, chronic low back pain, painful knee osteoarthritis, anterior knee pain with vastus lateralis imbalance, pelvic pain, post-operative pain in children with cerebral palsy after adductor hip release surgery, post-operative pain after mastectomy, and sphincter spasms and pain after hemorrhoidectomy; “efficacy not proven due to diverse class I and II results” for myofascial pain syndrome and chronic daily headaches; and “negative” for episodic migraine and tension headaches (Pain Med 2011; 12:1594-1606). There appears to be additional pain relieving properties of botulinum toxin irrespective of muscle relaxation.

Botox®, Dysport®, Xeomin® and Myobloc® are FDA-approved for the treatment of the postural abnormalities and pain associated with cervical dystonia, also known as torticollis (head tilting, neck pain, and neck muscle spasms). Only one botulinum toxin (BOTOX, onabotulinumtoxinA) is additionally approved by FDA to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years or older, and to treat increased muscle stiffness in elbow, wrist, and finger muscles in people 18 years and older with upper limb spasticity.

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

The dosage units for botulinum toxins are unique to each product and are not interchangeable. In addition, the FDA has specified nonproprietary names for each drug to help prevent medication errors. Many physicians are using botulinum toxins off-label for other painful conditions including types of headache other than chronic migraine treated with Botox® (onabotulinumtoxinA), osteoarthritis of the knee and shoulder, and various muscle pain syndromes (myofascial pain), although the evidence for such use is not conclusive.
For treatment of chronic pain conditions, when effective, botulinum toxins typically demonstrate efficacy within 3 to 5 days after intramuscular administration and last for an average of 12 weeks.

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

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

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

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

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

Agents that have clinically relevant NMDA blocking properties include ketamine, amantadine (an anti-influenza medication), memantine (an Alzheimer drug; Namenda™), dextromethorphan (an anti-cough medication), and methadone (an opioid).

Ketamine is a strong NMDA antagonist that has been used orally and intravenously for the treatment of CRPS and other neuropathic pain conditions. It is a dissociative anesthetic and has serious adverse effects reported in studies of lower doses given to adults by the oral route including 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.

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

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

Studies have not shown any functional improvements in patients with CRPS treated with ketamine infusions. Because their potential for harm outweighs evidence of limited short-term benefit in patients with CRPS, NMDA receptor antagonists are not recommended.
**LOW-DOSE NALTREXONE**

Naltrexone is an opioid antagonist and has been shown effective for treating Multiple Sclerosis. The best evidence for pain treatment shows that at low doses (4.5mg) naltrexone effectively reduces fibromyalgia pain intensity and improves mood. Low-dose naltrexone has a low side-effect profile. However, it should never be coadministered with opioids because it is an opioid antagonist. Low-dose naltrexone has shown promise in treating migraine and complex regional pain syndrome (CRPS), though larger studies are needed. The primary mechanism of low-dose naltrexone is thought to be immune modulation.

**KETAMINE INFUSIONS**

While there has been increasing interest and use of the use of ketamine in complex regional pain syndrome (CRPS), pain therapy via the continuous IV infusion of ketamine can lead to pain reduction over a number of weeks. However, serious side effects may occur, especially if treatment is repeated. Much of the evidence is anecdotal but increasing research is suggesting some possible benefit from this therapy although many guidelines do not feel that there is enough evidence to support its use clinically.
ADRENERGIC DRUGS, BISPHOSPHONATES, THALIDOMIDE, & CALCITONIN

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

Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk of fractures in patients with osteoporosis. There are seven FDA-approved bisphosphonates: alendronate (Fosamax®, 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). In October 2010, the FDA also issued a special alert on the association between the use of bisphosphonates and the risk of atypical fractures of the thigh. Patients are encouraged to consult their health care professionals for new hip or thigh pain.

There has been interest in the drug thalidomide due to its immunomodulatory and anti-inflammatory effects. Thalidomide was first introduced in 1957 as a sleep aid and treatment for morning sickness. It was subsequently removed from the market due to severe teratogenic side effects and then returned to the market as a treatment for myelodysplastic syndrome and multiple myeloma. Lenalidomide is an analog of thalidomide with similar efficacy but improved side-effect profile. There are reports and studies of both agents for the treatment of chronic pain, especially CRPS. Evidence of efficacy for chronic pain syndromes such as CRPS remains limited. Further studies are needed before these agents can be recommended for use in CRPS or other chronic pain syndromes.

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 daily activities and work. Rather than give up the benefits of the prescribed medication, some healthcare professionals 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®), armodafinil (Nuvigil®), and combination products (Adderall®).

While these activating drugs may be appropriate for some individuals, consideration for weaning of the pain medication that is causing the drowsiness is recommended. It should be a rare patient who takes medication (with potential side effects) to control the side effects of another medication rather than discontinuing the offending medication.

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 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. 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.

The NIH National Institutes of Drug Abuse has published: DrugFacts: Stimulant ADHD Medications - Methylphenidate and Amphetamines which can be found at: http://www.drugabuse.gov/publications/drugfacts/stimulant-adhd-medications-methylphenidate-amphetamines

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.
Armodafinil (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 typically includes one or a combination of abortive (rescue) and/or prophylactic (preventive) agents. Abortive therapy has been revolutionized with the advent of the triptans. These include sumatriptan (Imitrex® – also available by injection or nasal spray, Sumavel® DosePro® – needle-free delivery), 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®).

Preventive agents include beta-blockers, antidepressants, and anti-convulsant medications that are prescribed to take on a scheduled basis, whereas abortive therapies are typically used on an as needed basis and taken at the first onset of a migraine. Because of frequent unpleasant and sometimes debilitating side effects, preventive drugs are only prescribed for those whose quality of life is significantly adversely affected. The drugs are started at a low dose, and gradually increased until therapeutic effects develop, the ceiling dose for the chosen drug is reached, or side effects become intolerable.

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.

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

Patients taking certain migraine and antidepressant medications together may be at risk for a dangerous chemical imbalance. Antidepressant medications included in this warning are duloxetine (Cymbalta®), escitalopram (Lexapro™), fluoxetine (Prozac®), paroxetine (Paxil®), sertraline (Zoloft®), and venlafaxine (Effexor®). Migraine drugs include almotriptan (Axert™), naratriptan (Amerge®), 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. When two or more drugs that affect serotonin levels are taken together, it can increase the amount of serotonin and may lead to bothersome or dangerous symptoms. This is called “serotonin syndrome.” Please see the discussion about antidepressant medications in this ACPA Resource.
Here are a few web sites about migraine headaches:

- [http://my.clevelandclinic.org/disorders/migraine_headache/hic_migraine_headaches.aspx](http://my.clevelandclinic.org/disorders/migraine_headache/hic_migraine_headaches.aspx)

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

Diclofenac potassium powder for solution (Cambia®) is a NSAID drug indicated for the acute treatment of migraine attacks with or without aura in adults 18 years of age or older. Cambia is not indicated for the prophylactic therapy of migraine. Safety and effectiveness of Cambia is not established for cluster headache, which is present in an older, predominantly male population. Dosage and administration: Single 50 mg dose: mix single packet contents with 1 to 2 ounces (30 to 60 ml) of water prior to administration.
INVASIVE INTERVENTIONS

INTRA-ARTICULAR STEROID INJECTIONS

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

VISCOSUPPLEMENTATION

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

There are currently five available products on the market; Orthovisc®, 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. http://www.theacpa.org/video/implantables

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.

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

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

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

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

Together, the health care professional 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.

Occasional re-programming will be needed to optimize coverage of the painful area.

The reader should understand that this discussion of SCS systems is limited. These devices are invasive and costly, 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. There is some literature to suggest that in carefully selected patients, despite the initial cost, there may be long-term cost savings after a few years related to reduced use of medications and other medical care services.
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 health care professional. A significant advantage of a SCS system is that it is a reversible and nondestructive treatment option.

An important consideration is that the ability to obtain subsequent spinal imaging (such as an MRI) may be compromised after implantation of an SCS system. While some SCS systems are safe to use with MRI, not all are. Patients should discuss current and potential needs for MRI with their health care professional to ensure that they are being treated with a system that will meet their needs.

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

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

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

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

Potential complications that may occur include lead migration or fracture and infection. Lead migration after implantation may require revision surgery to regain appropriate coverage. An infection of any kind requires an immediate assessment by the physician. An unrecognized and untreated infection around the hardware can progress to more serious complications such as an epidural abscess or meningitis.
Implanted Targeted Intrathecal Drug Delivery Systems (Pain Pumps)

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

Intrathecal Drug Delivery is an FDA-approved pain therapy shown to be safe and effective for people who have not had success with other, chronic pain treatments. Intrathecal therapy has been used successfully in long-term pain management for patients with failed back surgery syndrome, complex regional pain syndrome, spinal stenosis, osteoporosis with compression fractures, pancreatitis, phantom limb pain syndrome, and peripheral neuropathies. [http://www.theacpa.org/video/implantables](http://www.theacpa.org/video/implantables)

With Programmable Targeted Intrathecal Drug Delivery Therapy:

- Pain medication is delivered via a drug pump directly to the fluid around the spinal cord, in an area called the intrathecal space.
- The drug pump is connected to a thin, flexible tube called a catheter.
- Both the pump and the catheter are surgically implanted under the skin.
- Pain medication is dispensed according to instructions programmed by the physician which allows noninvasive changes in dose and drug infusion patterns.

The reader should understand that this discussion of programmable, targeted implanted drug delivery systems is limited to a general overview. More information can be found in the anesthesia and pain medicine literature.

These systems are invasive and costly, and their use is limited to selected individuals who find oral opioids beneficial but cannot tolerate the side-effects and 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. There is some literature to suggest that in carefully selected patients, despite the initial cost, there may be long-term cost savings after a few years related to reduced use of oral medications and other medical care services.

A psychological evaluation of the person being considered for an intrathecal pump is usually recommended as a part of the overall evaluation process. These are often done by a psychologist or psychiatrist. The purpose of the evaluation is to see if the person with pain has any emotional or other difficulties that may adversely affect the surgery or recovery and to ensure the person has realistic expectations and goals for what can be achieved with the therapy. During the psychological evaluation, the person with pain will be asked questions about how the pain is currently affecting sleep, mood, relationships, work, and household and recreational activities. Some may also be asked to complete some paper-and-pencil tests. The psychologist or psychiatrist should share the results of this evaluation with the person with pain and with the referring physician who will consider all the information to determine if an intrathecal pump is an appropriate option.
A decision to proceed with an implanted drug delivery system should include:

- Failure of a reasonable trial of other conservative treatment modalities (medication, surgical, psychological, or physical);
- Intractable pain secondary to a disease state with objective evidence 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 can be anticipated with implantation despite any psychiatric comorbidity;
- No contraindications to implantation exist such as body size too small to hold the pump; presence of spinal anomalies that may complicate the implantation and fixation of a catheter; the pump cannot be implanted 2.5 cm or less from the surface of the skin; or, presence of known or suspected meningitis, ventriculitis, skin infection, bacteremia, and septicemia;
- A life span of at least 3-6 months; and
- If the above criteria are met, a successful temporary trial of spinal (epidural or intrathecal) medications must be achieved prior to implantation as defined by a significant reduction in pain and improved function and associated reduction in oral pain medication use.

Opioids (e.g., morphine) are the most common medications delivered by intraspinal infusion. Other medications (e.g., bupivacaine, clonidine, and baclofen) may be added to opioids, particularly in patients with nerve injury pain states (neuropathic pain).

Just as when one is taking opioids orally or transdermally, the doses of intraspinal opioids should be limited to the lowest dose possible required to achieve pain relief and increased function, as complications can occur with any dose of opioids regardless of the route of delivery.

As with any opioid, constipation, urinary retention, nausea, vomiting, and pruritus (itchiness) 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.

High doses of intrathecally-administered morphine or opioid mixtures, including compounded drugs, have uncommonly been linked to the development of a chronic inflammatory or granulomatous mass (an abnormal tissue growth) at the tip of the catheter that can compress the spinal cord or associated nerve roots. Thus vigilance is important just as is the case when one is taking opioids orally or transdermally. Patients on intraspinal morphine therapy should be monitored carefully by their health care professional for any new neurological symptoms because inflammatory mass can, in some cases, produce neurological impairment, including paralysis. Even though a direct cause and effect relationship has not been established, the dose of continuously-administered intrathecal morphine should be limited to the lowest dose possible to achieve pain relief and increased function, as complications can occur with any dose of opioids regardless of the route of delivery.

Apart from morphine, chronic intrathecal infusion of preservative-free, sterile ziconotide solution...
is approved for the management of severe, chronic pain. Ziconotide (Prialt®) is a non-opioid analgesic reserved for patients who are refractory to or who cannot tolerate intrathecal morphine. Typical side effects include dizziness, nausea, vomiting, and confusional states. Other potential adverse effects include psychosis, convulsions, rhabdomyolysis (muscle breakdown), and problems with the intrathecal infusion system. These side effects can be prevented entirely or well managed by raising the dose very slowly to achieve the right level of pain relief with the least amount of drug.

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 people suffering solely 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 people who have residual pain after the first injection may receive a second epidural steroid injection. However, individuals 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 the spine, can become arthritic and cause neck or back pain. Facet joints allow bending and twisting movements in the back and neck. For an individual with facet joint disease, these movements can be very painful and may limit daily activities. People with lumbar (low back) facet joint syndrome often complain of hip and buttock pain, low back stiffness, and pain that is made worse by prolonged sitting or standing. People with cervical (neck) facet joint syndrome often complain of neck pain, headache, and/or shoulder pain. In addition, they will often have pain when they rotate or bend their neck.

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

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

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

As with any procedure, there are certain risks involved which should be discussed with a treating physician. In order to achieve optimal results, it is important that these interventions be incorporated into a multidisciplinary treatment plan.
**Complementary, Alternative & Integrative Medicine (CAM)**

Complementary and Alternative Medicine (CAM) includes a diverse group of healing systems, practices, and products that are typically considered allopathic 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 Integrative Health (NCCIH) ([http://nccam.nih.gov](http://nccam.nih.gov)) is part of the National Institutes of Health (NIH) and is the lead agency for scientific research on CAM.
PASSIVE THERAPIES & PHYSICAL MODALITIES

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

HYPERBARIC OXYGEN

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

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

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

ACUPUNCTURE

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

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

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

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

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

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

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

ELECTRICAL STIMULATION DEVICES (EXTERNAL)

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

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

**TRIGGER POINT INJECTIONS**

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

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

EDUCATION

Active interventions are some of the best medicine for chronic pain because they engage the individual in learning and making positive changes to increase function and reduce pain.

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

Education regarding chronic pain should start as soon as the pain has been identified as chronic. Early topics should include helping a person understand that they may not be “fixed” but instead their pain must be managed. It can be helpful to think of chronic pain similar to other chronic diseases such as diabetes. A person needs to manage their diabetes and prevent it from getting worse and causing other problems. Diabetes is not quickly cured or fixed. The same is true for chronic pain. Further education on chronic pain should also include understanding that pain is not “all in your head” but that an active approach that focuses on the whole person is the most effective way to treat chronic pain.

What someone can and cannot do should be defined as clearly as possible. Many times, the only guidelines a person may hear are restrictions given right after the injury or surgery. These same restrictions may no longer be needed, but patients are not always told new ones. Unfortunately, it is also common that patients have either been told incorrect information or have misinterpreted education from a past health care provider. Many healthcare providers have only minimal exposure to assessing or treating chronic pain. A lack of consistent information can confuse the patient. Phrases like, “the back of an 80 year old man” or “you will end up in a wheelchair if you sneeze” can keep a person fearful and disabled.
EXERCISE (ACTIVE THERAPY)

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

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

Therapeutic exercise can be classified to include 1) range-of-motion exercises; 2) stretching; 3) strength training; and 4) cardiovascular conditioning.

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

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

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

Chronic pain can limit even the simplest daily activities as well as the ability to perform higher-level work activities. A successful active program focuses on increasing the ability to perform functional tasks. For example, this could mean being able to perform household tasks or return to work again. Being more independent leads to a higher quality of life. Functional activity training is just as important as performing a daily exercise program. Lifting, carrying, pushing, pulling, reaching, bending, digital dexterity, and handling are all examples of functional movements that are used on a daily basis. It is helpful to think of practicing daily activities similar to performing exercises. It is important to first determine the current ability to perform this task. Each task is then practiced with appropriate pacing of activity, flare management and slow progression. Recreational activities are included in this category. The ability to perform a higher level of recreational activities serves many purposes including exercise, socialization, time utilization, and general enjoyment.

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. On-going research suggests that Tai Chi is an effective treatment in improving physical functioning of those with chronic pain including arthritis, low back pain, and fibromyalgia.

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” (opposite and contrary forces) of a person back into natural harmony, exercising emotions just as it does the muscles. Tai Chi revolves around a series of movements called “forms” which can last anywhere from five to 20 minutes. There are over 100 different stances to learn.

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.
Qigong is a Chinese term used to describe human performance and movement that is characterized by focus and concentration, full body presence, breath awareness/coordination, and skill. In theory, Qigong has existed for thousands of years. In practice, contemporary Qigong is the grand category that encompasses many healing Asian practices, including traditional Chinese medicine, breath, and movement practice. “Qi” means vitality or energy, and “gong” means work; and so together in the term “Qigong” the literal translation of the practice is “the work of energy or vitality.” In common everyday terms, such a practice relates to human function, encompassing such things as mental focus, the natural movement of the body’s limbs, blood flow in the body, and a sense of balance and harmony in the body’s systems (nervous system, vestibular system, digestive system, etc).

In the Qigong ‘tradition’, there are forms and practices that are categorized by purpose and appropriateness to the season, the environment, and the practitioner. The form of Qigong that is most appropriate in health settings is the Qigong for improving function and increasing vitality. This type of Qigong has been referred to in some circles as “Bu Zheng Qigong” or “Qigong for Health and Vitality” or “Medical Qigong.” This basic approach is geared toward strengthening the body and mind through various safe and gentle practices. In this type of Qigong, the focus for the practitioner is to perform movement in a slow and restful way while observing the physical phenomena associated with the movement and, in more advanced practice, directing the attention to influence the flow of energy. The practitioner observes such things as range of motion of the limbs, rate of breath and heart, temperature and pressure changes, etc.

In its everyday practical sense, the regular practice of Qigong for health improves concentration, posture, balance, range of motion, and confidence. A Qigong practice session for health can typically involve breath practice, self-massage, and exploratory range of motion exercises that take the joints through their range of motion, and move the spine in six directions: extension, flexion, right side bending, left side bending, and finally twisting left and right. Slow movements keep the muscles mildly engaged to promote circulation, and then the mind/attention is engaged to follow sequences and combinations of movement. Practitioners, however, would agree that Qigong is not only movement of the body, but surprisingly mentally engaging, meditative, and restful.
Yoga helps to manage chronic pain by stretching, strengthening, and relaxing the body. It creates a greater sense of health and well-being by emphasizing mindful practice, breath awareness, and proper body alignment. There are many different styles and schools of yoga. There are multiple poses (asanas), and different props can be used. People with chronic pain should begin with a gentle, slow-paced class. Benefits of yoga include improvements in sleep and the ability to handle stress and feeling more relaxed throughout the day. Studies have shown that yoga is beneficial for fibromyalgia, among other pain conditions.

These three styles of yoga are good for beginning students:

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

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

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

These styles of yoga require strength and endurance:

- **Ashtanga Yoga** is characterized by constant movement, or flow, from one posture to another. It is vigorous and fast-paced, earning it the nickname of Power Yoga. The focus is on deep breathing during each pose.

- **Vinyasa** is similar to Ashtanga Yoga in its emphasis on flowing through postures, particularly Surya Namaskar (Sun Salutation). The goal of Vinyasa is to improve coordination, strength, and balance by following the sequence of active poses.

- **Bikram or "hot" yoga** literally refers to the fact that the practice studio is heated to 104 degrees Fahrenheit. The practice consists of 26 poses that are repeated twice. The intense sweat produced is thought to purify the body.

- **Kundalini yoga** focuses on purifying the emotions, the mind, and the body while placing emphasis on the effects of breathing on each pose. Chanting mantras and meditation are common practices of Kundalini. The word Kundalini refers to an energy, which is said to reside at the base of the spine. The intention of Kundalini practice is to release this energy.
Graded Motor Imagery

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

Graded motor imagery is a set of rehabilitation processes used to treat pain and movement problems related to an altered nervous systems. The three different treatment techniques include limb laterality training, motor imagery exercises, and mirror therapy. These techniques are delivered sequentially or individually.

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

Pain Psychology
The definition of pain is “…a negative sensory and emotional experience.” (International Association for the Study of Pain). This definition recognizes that along with pain comes an emotional response and reaction. People naturally respond to pain by wanting to escape it. After all, pain tends to signal harm or threat, something everyone want to avoid. With chronic pain, one cannot easily escape pain that is coming from inside the body. Sometimes people try to escape pain by retreating to the bed or becoming sedentary. While these strategies (known as fear avoidance) seem like a good idea on the surface, sedentaryism is actually know to worsen pain over time and it leads to deconditioning and contributes to depression. Pain psychology is a specialty discipline that helps people learn about chronic pain and natural emotional responses to pain. A pain psychologist helps people to learn techniques and skills to calm the distress that naturally arises during pain, and this alone can help reduce pain. Research shows that psychological distress about pain actually amplifies one’s experience of pain.

Pain psychology is very much rooted in cognitive behavioral therapy (CBT), a form of treatment that is focused on the here-and-how, and on learning active coping skills to better control one’s experience. These active coping skills involve learning how to identify and change negative thoughts, which in turn decreases negative emotions. Better control over one’s emotions leads to better control over pain and one’s mood. It’s important that people learn ways to control their experience so that they don’t feel at the mercy of their pain. Feelings of helplessness about pain are associated with worse pain and function. Working with a pain psychologist may help to gain better control and therefore lessen suffering.

Pain can be physiological and psychologically stressful. It can cause rapid heart rate, rapid and shallow breathing, tight muscles as one ‘braces’ against pain, constricted blood vessels, and feelings of distress. These negative consequences of pain can be counteracted with relaxation skills, and these skills are a mainstay of psychological treatment for chronic pain. Relaxation skills can help a person cope better with pain, but more importantly they treat the underlying consequences of chronic pain on one’s mind and body.

General Behavioral Medicine and Mental Health Counseling
General psychological therapies are sometimes known as mental health treatment, psychotherapy, talk-therapy or counseling. Pain can be stressful, and strategies to reduce stress and improve coping can be directly beneficial. Chronic pain often co-occurs with anxiety, depression, or sleep problems. The individual can work with a pain psychologist or a mental health professional to treat these problems and therefore reduce pain. Research shows that anxiety, depression, and poor sleep are associated with worse pain. While many people focus on medications to treat these problems, some of the best evidence supports behavioral treatment either as the primary treatment, or in combination with medication.

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

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

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

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

- Psychologists are doctors who have a Doctor of Philosophy (Ph.D.) in Clinical Psychology or Counseling Psychology or Doctor of Psychology (Psy.D.) and specialize in human behavior and emotional health. They have training in working with individuals, couples, and families and do so either in group or individual sessions. They can also administer and interpret psychological tests. They have expertise in dealing with most emotional and behavioral problems. In some states, psychologists can prescribe medications for emotional problems.

- Social Workers have Masters Degrees (MA or MS) and are sometimes called Licensed Clinical Social Workers (LCSW). They receive specialized training in how people function in their environment and solve personal and family problems. Some also have experience in case management and can assist in finding government and local resources in the community that meet the needs of people with pain.

- Masters-Level Counselors have Masters Degrees (MA or MS) in either clinical or counseling psychology. They are sometimes called Licensed Marriage & Family Therapists or Licensed Professional Counselors. They have specialized training in dealing with individuals and families particularly in relationship problems.

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

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

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

Another form of therapy designed to help people with chronic pain is called Acceptance and Commitment Therapy or ACT. It is a psychological intervention that focuses on acceptance and uses mindfulness strategies to increase awareness and psychological flexibility. It differs from CBT by teaching individuals to passively notice, accept, and embrace events rather than teaching individuals to control their worries, thoughts and feelings. There is evidence that ACT can be very helpful for certain people with chronic pain who struggle in trying to change what has happened to them.

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

**Fear Avoidance Training**

It is common for people with chronic pain to associate pain with movement or activity. People often limit activities in an attempt to reduce pain. They may be limiting themselves from a fear of experiencing increased pain or out of a belief that pain is a signal that damage or harm is occurring. A fear of movement is called kinesiophobia and a fear of causing further damage is called a fear of re-injury.

Pain that persists for a long time can cause worry of continued damage or injury that has not been identified. For people that have serious pathology, it can be difficult to figure out if the pain means they are causing further damage or if the pain is only a heightened sensation due to the chronic pain. Negative thoughts and coping styles surrounding fear and pain can also lead to higher levels
of disability.

Treatment for overcoming fear of re-injury includes understanding the diagnosis, the anatomy involved with this diagnosis, the physiology of why movement is not damaging, and the difference between pain and damage. Education on topics such as the role of hypersensitivity and changes in the spinal cord and brain with chronic pain may be helpful. For those who are interested in reading more on the topics of pain versus damage and tissue sensitivity, the book *Explain Pain* by David Butler and Lorimer Moseley, is recommended.

The book *Pain-Related Fear* by Vlaeyen, J et al, offers us an understanding of the fear-avoidance model and how to use graded exposure to overcome this fear. Working with both a psychologist and physical therapist that understand this type of treatment allows the patient to address both the emotional and physical aspects of overcoming fear while increasing activity.

Overall, with any type of fear, treatment includes education, repeated exposure to activities that have been avoided, instruction on active pain management techniques, and taking an active role in recovery.
Mind-Body Interventions

There are numerous mind-body interventions including relaxation, meditation, imagery, biofeedback, and hypnosis. Many psychologists also include mind-body interventions in their treatment.

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

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

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

Relaxation, self-hypnosis, and meditation techniques are a form of physiologic self-management. They assist individuals with muscle relaxation and distraction away from pain perception. As one becomes more familiar with using relaxation skills, these skills should also be used during all physical activity and movement. When one suffers from chronic pain, guarding or bracing of the muscles is common. Integrating relaxation skills into movement can lessen this guarding and decrease stress or tension on the muscles, allowing for smoother, easier, and stronger movement.

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

ACPA offers a five minute relaxation. This five-minute relaxation exercise can help you let go of physical stress and begin to reduce your sense of suffering. The relaxation can be found at: http://www.theacpa.org/Relaxation-Guide
INTERNET PAIN-MANAGEMENT RESOURCES

There are a number of stand-alone and Internet-based programs to help in the management of pain. The American Chronic Pain Association website can be a great source of information (www.theacpa.org). This and other pain management programs include ways to track daily pain and activity and can be a useful vehicle to easily summarize progress over time. They can be especially helpful when starting an exercise routine by tracking progress based on frequency and duration of the exercises. These programs can also suggest warm-up and cool-down stretching routines catered for each individual’s pain problem. They also can be useful for monitoring medication use and giving helpful reminders throughout the day. A daily food diary can help in identifying healthy and unhealthy eating habits. Smart phone applications (apps) are in development just for persons with chronic pain. These programs are useful in identifying important information about the pain, summarizing progress for the health care professional, and offering daily tips and recommendations for improving pain management.

Many things can affect your pain. These can include stress, sleep, money worries, and even the weather. This log can help you track the everyday things that have an impact on your pain.

When you understand what makes your pain worse, you can begin to work on ways to reduce or deal with your pain “triggers.”

The more you know about how your body reacts, the more you can be in control. And being in better control can help you be less afraid and better able to manage your pain. We encourage you to fill a chart out at the end of each day or several times a week. You also can print out a report and take it to your doctor visits. It can help you talk more openly with your healthcare provider so that together you can find ways to improve your quality of life.

http://www.theacpa.org/painlog/default.aspx

Back pain can be complex and difficult to describe in the short time you may have with your health care provider. This tool can help you create a detailed picture of your pain---where it is, how it feels, how much it hurts, and what triggers it. Fill it out before your visit, print it, and share it with your provider.

http://www.theacpa.org/backpainapp/

Begin your journey from patient to person with this workbook designed to help anyone who has a chronic pain problem gain an understanding of how to cope with the problems that their pain creates.

Topics include:
• Understanding Chronic Pain
• Knowing Yourself
• Learning to Live With Others
• Helping Your Body

http://www.theacpa.org/product.aspx?guid=740dd14d-70da-4de5-b2a7-a24002f81f6a
**ACTIVE INTERVENTIONS - INTERDISCIPLINARY**

Although there are many different beneficial active interventions described below, research increasingly supports a “whole person” approach for those dealing with chronic pain. This is often described as a functional restoration approach. Functional restoration encompasses many of the individual interventions in a coordinated, goal-oriented manner.

**FUNCTIONAL RESTORATION PROGRAMS & APPROACHES**

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

Functional restoration involves multiple disciplines that work together in a coordinated fashion with shared treatment goals. Functional restoration approaches are focused on maximizing function, returning to pre-injury productivity (with sufficient functional capacity to avoid recurrent injuries), and preventing needless disability, unnecessary medical and surgical care, and health care 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 professional). All of these factors can strongly influence symptom severity and how quickly the individual can return to function.

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

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

Functional restoration treatment team members act as educators, de-emphasizing passive and/or palliative therapies, while emphasizing independent self-management. There should be a shift of health and well-being responsibility from the health care professionals and therapists to the person.

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

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

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

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

**SELF-MANAGEMENT**

The significant part of being involved in your recovery is being involved with your peers. ACPA groups welcome anyone who is living with an ongoing pain problem. The goal of an ACPA group is to provide support, validation, and education in basic pain management and life skills. Groups are facilitated by group members themselves and the success of the group is a shared responsibility. ACPA groups do not focus on symptoms or provide treatment of any kind. Rather they are a means for people to share what they have learned and to encourage others to create more satisfying lives. Hear members' thoughts about the value of the kind of peer support offered by ACPA groups. [http://www.theacpa.org/What-ACPA-Groups-Offer](http://www.theacpa.org/What-ACPA-Groups-Offer)
**FINAL COMMENTS**

An essential concept in pain management is that each person is different and will respond differently to situations, interventions, surgeries, and medications.

It is important for the person with pain, family members, and others to avoid quick judgments based on what they hear or read about any particular treatment or medication. The best place to get advice about treatments and medications is from the health care professional 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 professional.

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

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

The ACPA once again reminds readers that this ACPA Resource Guide to Chronic Pain Medication & Treatment is not meant to serve as medical advice for pain conditions or treatment or medication needs. The best source of information are health care professionals and therapists who understand the treatment and medication options available to people with chronic pain.
REFERENCES: LINKS TO CHRONIC PAIN SITES & RESOURCES

MEDICATION RELATED


OTHER REFERENCES


Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) maintains a collection of educational materials on topics related to buying and using medicine safely at [http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm296593.htm](http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm296593.htm)


**PAIN RELATED ORGANIZATIONS & WEB SITES**

The American Chronic Pain Association (The ACPA) at [http://theacpa.org/](http://theacpa.org/)

American Society of Pain Management Nurses (ASPMN) at [http://www.aspmn.org/Pages/default.aspx](http://www.aspmn.org/Pages/default.aspx)


Opioid Induced Constipation [http://www.theacpa.org/opioid-induced-constipation](http://www.theacpa.org/opioid-induced-constipation)


Understanding NSAIDS [http://www.theacpa.org/NSAIDs-safety](http://www.theacpa.org/NSAIDs-safety)


Vets In Pain [www.vetsinpain.org](http://www.vetsinpain.org)

Youth Living with Pain [www.growingpains.org](http://www.growingpains.org)