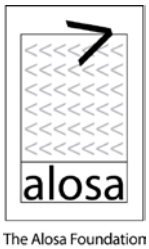
Helping the hurt, without hurting the patient: A guide to outpatient management of chronic pain



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These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

Contents

Introduction

Pain researchers divide this symptom into nocioceptive and neuropathic pain. Nocioceptive pain arises when afferent neurons respond to noxious stimuli from a somatic (e.g., bone, joint, muscle, skin) or visceral source (e.g., gut, gall bladder, or pancreas). By contrast, neuropathic pain is thought to result from abnormal processing of input from the central or peripheral nervous system, and can be resistant to traditional pain medications such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opiates.[1]

This evidence document focuses on the management of chronic non-cancer pain, both nocioceptive and neuropathic. While this encompasses a wide variety of conditions, symptomatic relief and resumption of normal physical and psychological functioning are common goals in management. An Institute of Medicine report in June 2011 estimates that over 116 million Americans suffer from chronic pain, with associated costs of $560-$635 billion. The report advocates viewing chronic pain as a debilitating illness that "requires direct treatment rather than being sidelined while clinicians attempt to identify some underlying condition that may have caused it". [2]

Pain: the 5th vital sign

Chronic pain is often undertreated. One study found that a quarter of nursing home patients with persistent pain report receiving no treatment at all [3] and other studies have found that up to 80% of patients with chronic pain are undertreated. [4] Chronic undertreated pain leads to lost work days and substantial cost, as well as reduced life enjoyment and depression. [4] Patients are also often reluctant to report pain, to take pain medication, and also worry about addiction, dependence, and tolerance. [5] **This has led to a movement to include documentation of pain as "the fifth vital sign."**

The Institute of Medicine report found 3 key barriers to adequate pain prevention, assessment, and treatment, including

- financial incentives working against high-quality individualized care
- unrealistic patient expectations
- lack of an objective pain assessment measurement.

Other barriers are listed in Table1.

Table 1: Most common barriers for opioid prescribing reported by PCPs [5]

Barrier	% PCPs report the barrier
Potential for patients to become addicted	89%
Potential for patients to sell or divert	75%
Opioid side effects	53%
Regulatory / law enforcement monitoring	40%
Hassle and time required to track/refill	28%

The Institute of Medicine suggests that these barriers may be overcome by:

- ✓ tailoring the management of each patient's pain experience, including help with self-management skills)
- ✓ improving clinician education (by both public and private ventures)
- ✓ improving collaborations between primary care physicians and pain specialists
- ✓ revising reimbursement policies to enhance multi-disciplinary pain management
- ✓ increasing funding for pain research and pain specialists. [2]

Overview of treatments

Management of chronic nocioceptive pain usually involves some combination of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), or opiates; treating chronic neuropathic pain usually requires a combination of anticonvulsant and/or anti-depressant drugs. For pain syndromes that have components of both nocioceptive and neuropathic pain, combination therapy can be helpful. For both types of pain, other pharmacologic and non-pharmacologic options exist, which will also be discussed below.

Treating Chronic Nocioceptive Pain

Acetaminophen

Acetaminophen, first introduced in the US market in 1953, has been one of the most widely used over the counter (OTC) medication worldwide. Over 24 billion doses of acetaminophen were sold in the US in 2008 alone, with a 28% increase from 2004 to 2008. Most acetaminophen is sold OTC (80%), while the remaining 20% is sold in prescription combination products, with total sales of $2.6 billion annually.

Efficacy

While often derided by patients as "just Tylenol," acetaminophen provides predictable if modest pain relief, and is often recommended as a first-step treatment. A Cochrane review found acetaminophen superior to placebo in pain reduction in patients with hip/knee OA, with a small effect size (-0.13, 95% CI -.22 to -.04; see Table 2).[6] Although "extra strength" doses (500 mg x 2) are widely promoted, the bulk of the evidence indicates that doses of 1000mg are no better than 650mg in relieving mild to moderate pain, although the higher dose does increase the potential for excessive exposure, especially in combination with other acetaminophen-containing products (see next page).

Table 2: Definition of "effect size"

The **effect size**: [mean of intervention – mean of control] ÷ standard deviation. This is a measure of how far apart two treatment groups are. The larger the number, the greater the difference between the 2 groups. Effect sizes are considered small if <0.5.

Safety

An exhaustive review of the literature found that the overall risk of adverse events was the same for acetaminophen and placebo when given in clinical trials. [6] Despite this overall safety, the primary risk of acetaminophen is hepatotoxicity; acetaminophen liver damage is the leading cause of drug-induced acute liver failure in the U.S.[7] More than 35,000 acetaminophen-related overdose hospitalizations occur in the US every year, and acetaminophen accounts for 5% of all calls to US poison control centers. About half of all acetaminophen-related overdoses and a third of deaths are unintentional, which almost all occur when a patient exceeds the maximum recommended dose of 4 grams per day. The most commonly implicated products in overdoses are acetaminophen/opiate combinations; 25% of patients with acetaminophen-associated hepatotoxicity report using more than one acetaminophen product, usually unknowingly.

Attenuating the risk of adverse events

The risk of hepatotoxicity is highest when acetaminophen is used above recommended doses, or in patients with chronic liver disease. The total daily dose should not exceed 4g/day, or 3g/day in patients > age 65. The drug should be completely avoided in alcoholics, patients who are fasting, or those with chronic liver disease.[8,9] **In 2009, a FDA advisory panel recommended that the maximum single dose of acetaminophen should not exceed 650mg, reserving the 1000mg dose for prescription use only.** The FDA has also requested all manufacturers to limit the amount of acetaminophen in all combination products to 325mg per tablet.

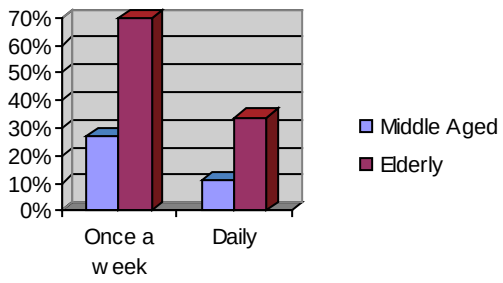
BOTTOM LINE: Acetaminophen is modestly more effective than placebo in pain relief, and very safe at recommended doses. There is no evidence that a dose of 1000mg is significantly more effective than 650mg, and the total daily dose should not exceed 4g/day in younger adults and 3g/day in the elderly (>age 65). Acetaminophen should be avoided in patients with chronic liver disease or alcoholism, and when fasting.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-pyretic, and anti-inflammatory properties. They are some of the most commonly prescribed medications in the U.S., with over 111 million prescriptions written

annually, in addition to widespread use of the over the counter (OTC) NSAIDs [10,11] (see Figure 1).[12,13]

Figure 1: NSAID use rates among middle aged and elderly



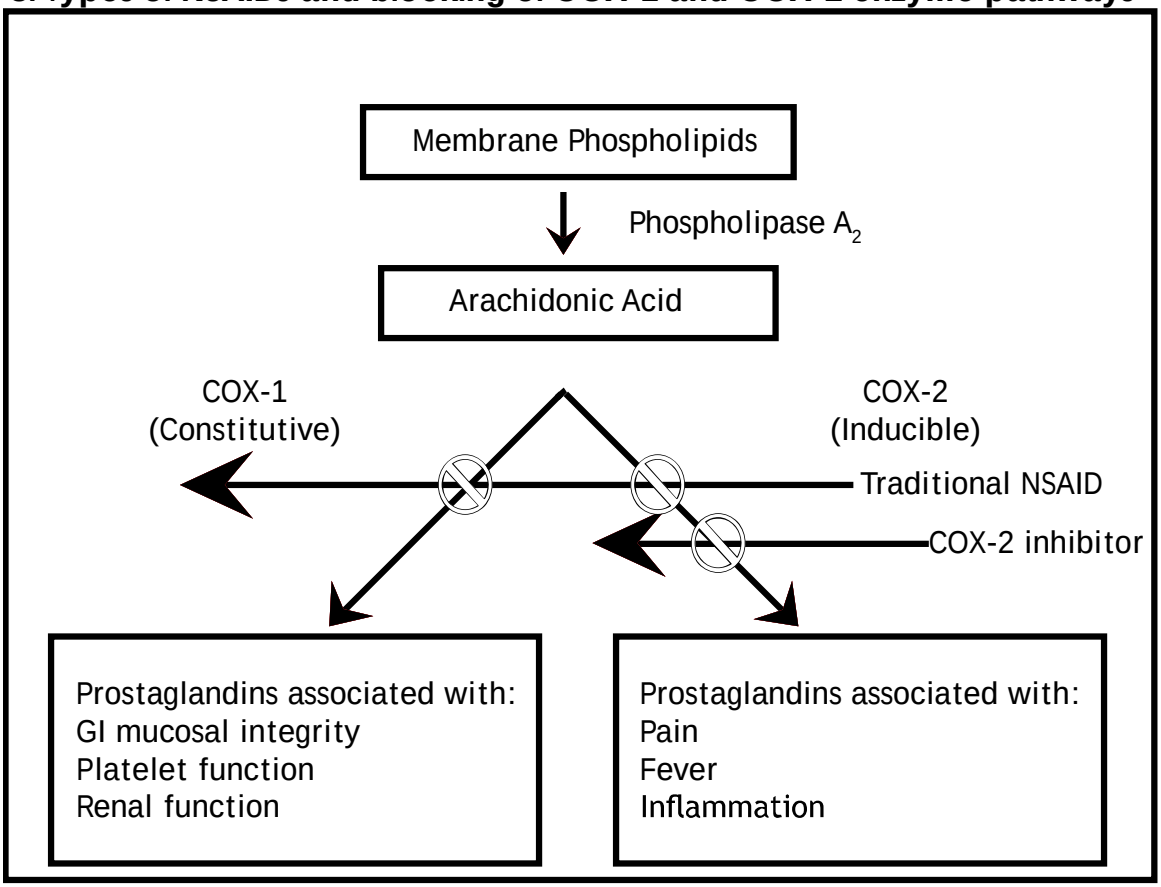
All NSAIDs are cyclooxygenase (COX) inhibitors, blocking one or both COX- enzymes (COX-1 and COX-2). The non-selective NSAIDs inhibit both the COX-1 and COX-2 enzymes and the COX-2 inhibitors ("coxibs") selectively inhibit the COX-2 enzyme (Figure 3). The degree of GI versus CV toxicity of the NSAIDs depend on their spectrum of COX-1 and COX-2 inhibition; there is higher CV toxicity on the COX-2 end of the spectrum, and higher GI toxicity on the COX-1 end of the spectrum (Figure 2). Table 3 lists the most commonly used NSAIDs in the US.

Figure 2: Degree of COX selectivity of various NSAIDs*

*no longer available because of cardiac risk

Adapted from Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation.* Mar 27 2007;115(12):1634-1642.

Figure 3: Types of NSAIDs and blocking of COX-1 and COX-2 enzyme pathways



Adapted with permission from Intellisphere, LLC. Accessed at http://www.pharmacytimes.com/files/ArticleFiles/July06PT_88_f1.gif.

Table 3: Commonly used NSAIDs

Type of COX-enzyme inhibition	Generic name	Trade name	Typical starting dose
Selective COX-2*	celecoxib	Celebrex	200mg qday
Non-selective (COX-1 and COX-2)	ibuprofen	Motrin, Advil, Excedrin, Genpril, Nuprin	400mg bid
	naproxen	Naprosyn, Aleve, Anaprox	250mg bid
	piroxacam	Feldene	20mg qday
	nambumetone	Relafen	1000mg qday
	fenoprofen	Ketoprofen, Nalfon	300mg tid
	ketoprofen	Orudis	75mg tid
	flurbiprofen	Ansaid	50mg bid
	oxaprozin	Daypro	1200mg qday
	indomethacin	Indocin	25mg bid
	sulindac	Clinoril	150mg bid
	etodolac	Lodine	300mg bid
	diclofenac	Voltaren, Cataflam	50mg bid
	meloxicam	Mobic	7.5mg qday

* Rofecoxib (Vioxx) and valdecoxib (Bextra) were withdrawn from the US market in 2004 and 2005, respectively. Celecoxib is the only currently approved coxib on the US market.

Efficacy

NSAIDs are moderately effective in reducing pain from a variety of conditions. While most studies compare an NSAID with a placebo, there is no consistent evidence that any NSAID confers greater analgesic efficacy than any other, at equipotent doss. A Cochrane review found celecoxib to be significantly better than placebo in reducing pain in rheumatoid arthritis and osteoarthritis, with improvements in the ACR-20 score (a validated measure of pain) of 51% in the treatment group versus 29% in the placebo group.[14] In the treatment of chronic low back pain, NSAIDs are also significantly better than placebo, with a mean difference (between the groups) in change in pain scale of 12 (on a 100 point scale).[15]

Evidence that NSAIDs tend to have equivalent analgesic efficacy comes from one large trial of over 13,000 patients with osteoarthritis (the SUCCESS-I trial) that randomized participants to celecoxib, diclofenac, or naproxen, and found that analgesic efficacy was the same among all the groups (with a non-significant difference in pain of 1 point on a 100 point scale).[16] A recent Cochrane review found celecoxib had equivalent analgesic efficacy to non-selective NSAIDs in RA, all of which were superior to placebo.[14] Other meta-analyses have found no evidence of superiority of one NSAID over another in

the treatment of low back pain, OA or RA.[15,17] Individual patients sometimes report that a particular product works better for them than others in the class; such inter-individual differences may be attributable to placebo effect or pharmacogenetic factors that are presently not understood, but most clinical trials do not favor any single drug over another.

Safety

The most serious NSAID side effects involve the GI tract, heart, and kidneys. The degree to which these systems are affected depends on which prostaglandin enzyme pathways they block. The more COX-2 inhibition, the higher the cardiovascular risk; the more COX-1 inhibition, the higher the gastrointestinal risk (see Figure 3).

GI adverse events

NSAIDs damage the gastric mucosa both by direct topical injury and by systemic depletion of protective prostaglandins (by blocking the COX-1 pathway). NSAID-related upper GI complications can range from mild dyspepsia to ulcers with hemorrhage.

- Two meta-analyses found about a 3-4 times higher risk for upper GI events among NSAID users compared to non-users, with a clear dose-response relationship.[18,19]
- NSAIDs result in a lifetime risk of ulcer formation in 1 out of every 20 users (1 out of every 7 older adults).[20]
- NSAID-associated GI complications account for substantial morbidity and mortality, resulting in over 16,000 deaths and 107,000 hospitalizations in the US annually. [21,22,23]

Combining NSAIDs increases the risk of GI complications. Patients using both NSAIDs and aspirin have a relative risk of upper GI ulcer formation 4-6 times higher than those on aspirin alone (which is not attenuated by the use of coxibs or buffered/enteric-coated aspirin).[24-26]

Coxibs cause fewer GI complications than non-selective NSAIDs.[27] In the SUCCESS-I trial, the risk of GI ulcers was significantly lower with celecoxib than a non-selective NSAID. [16] The CLASS study also found lower incidence of GI complications in patients on celecoxib compared to a non-selective NSAID (ibuprofen or diclofenac) in short term follow up, but it was later found that celecoxib had no advantage in long term follow up.[16,28] A subsequent systematic review found coxibs were associated with significantly fewer GI ulcers than non-selective NSAIDs (relative risk of 0.26, 95% CI 0.23-0.30, p<0.01). [29]

Combining a coxib with an aspirin negates the GI protection of the coxib. The GI risk of an aspirin-coxib combination is equivalent to the GI risk of a non-selective NSAID.

Cardiovascular adverse events

NSAIDs clearly increase the risk of CV events, likely as a result of their effects on thrombosis, vasoconstriction, hypertension, and oxidative stress. The increase in CV morbidity seen with coxibs led to the removal of rofecoxib (Vioxx) and valdecoxib (Bextra) from the U.S. market.[30] There is ongoing controversy about the CV risk of celecoxib (Celebrex), but several large-scale, long-term studies have pointed to a celecoxib-induced increase in CV risk (see below).

The CLASS trial randomized patients to celecoxib, ibuprofen, or diclofenac, and found no difference in CV events between celecoxib and the combined non-selective NSAID group. However, the published data only provided follow-up for 6 months, although the trial continued for at least twice that long.[28]

The Prevention of Spontaneous Adenomatous Polyps (PreSAP) study found a higher rate of death from CV events in the celecoxib group compared to placebo, but did not reach statistical significance (1.9% in placebo and 2.5% in celecoxib) (relative risk 1.30, 95% CI 0.65 to 2.62, p value not reported).[31] In contrast, the Adenoma Prevention with Celecoxib (APC) trial found that patients given high-dose (200–400mg BID) long-term celecoxib had increased rates of thrombotic cardiovascular events in a dose-dependent manner, compared to placebo.[32]

- The risk ratio for the 200mg BID dose (compared to placebo) was 2.6 (95% CI 1.1 – 6.1)
- The risk ratio for the 400mg BID dose (compared to placebo) was 3.4 (95% CI 1.5 – 7.9)

A meta-analysis combining PreSAP and APC found a doubling in the rate of CV events in patients treated with celecoxib as compared to placebo.[33]

However, a subsequent meta-analysis comparing CV events with placebo, celecoxib, and non-selective NSAIDs did not find differences between any of the three groups.[34] However, this meta-analysis included studies published before 2004, and therefore did not include the large and important PreSAP or APC trials. It also included a majority of studies with only low dose celecoxib (200mg/day), and adjudicated events at 1 year. Therefore, the discrepancies in the findings of the trials may be a result of the too-low celecoxib doses and too-short durations studied.

The PRECISION trial is currently randomizing OA and RA patients with a history of or risk factors for CV disease to celecoxib, ibuprofen, or naproxen. The primary endpoint of the trial is a composite of CV death, nonfatal MI, or nonfatal stroke. It is hoped that PRECISION will resolve the controversy about the risk of CV events in patients taking different types of NSAIDs.[35]

In addition to these thrombotic CV risks, NSAIDs also increase the risk of heart failure and hypertension. A randomized trial found rofecoxib significantly increased the risk of incident heart failure or pulmonary edema at 3 years compared to placebo (hazard ratio of 4.6, 95% CI 1.5 to 18.8, p=0.004). [36] Another randomized trial found celecoxib significantly increased blood pressure at 3 years compared to placebo in a dose-dependent fashion (see Table 4). [33] Although both of these trials evaluated the risk of heart failure and hypertension in coxibs, there is evidence that similar risk is presented by the non-selective NSAIDs. [37]

Table 4: Mean increase in systolic and diastolic blood pressure at 1 and 3 years in celebrex compared to placebo [33]

Time	Celecoxib 200mg twice daily	Celecoxib 400mg twice daily
1 year*	2.0 / 1.2 mmHg	2.9 / 1.2 mmHg
3 years**	2.6 / 1.8 mmHg	5.2 / 2.1 mmHg

*Neither celecoxib group was statistically significantly different compared to placebo at 1 year
** p=0.02 for both celecoxib groups compared to placebo at 3 years

For now, the burden of evidence suggests that most NSAIDs carry some CV risk. The FDA has ordered that all NSAIDs be labeled as carrying an increased risk of CV disease,[38] but the literature suggests that the risk is not uniform across all drugs in this class. The highest risk is associated with the coxibs (of which celecoxib is the only one not withdrawn from the market for this reason), along with diclofenac; the lowest CV risk across many studies appears to be with naproxen.

In addition, all NSAIDs (especially ibuprofen) can reduce the CV benefit of aspirin. The American Heart Association recommends that in patients who must take both cardioprotective ASA and a NSAID, the NSAID be taken at least 8 hours before or 30 minutes after the ASA, to avoid interactions.[38]

Renal adverse events

NSAIDs can lead to varying degrees of acute and chronic renal dysfunction. This can manifest as sodium retention, an increase in blood pressure (which is very common), hyporeninemic hypoaldosteronism, pre-renal azotemia (which can progress to acute tubular necrosis if untreated), acute interstitial nephritis, and nephrotic syndrome. The risk of kidney injury is twice as high in NSAID users compared to non-users.[39,40] Pre-renal azotemia is common in patients with diminished renal blood flow (especially the elderly), and likely results from inhibition of prostaglandin-mediated protection of renal circulation. Hyporeninemic hypoaldosteronism is of particular concern in diabetics using NSAIDs, and can lead to hyperkalemia and metabolic acidosis.[41]

Protecting against NSAID-induced adverse events

Attenuating GI risk

Many patients are prescribed NSAIDs despite being at high risk for upper GI ulcers (Table 5). A study from the Veterans Administration found that 43% of patients prescribed NSAIDs were already at high risk for upper GI ulcer formation, including 87% of those >age 65.[10] In addition, despite ample evidence supporting the benefit of gastroprotective agents for the prevention of NSAID-included GI complications, many high-risk patients do not receive such therapy. A large retrospective cohort of a state-wide database found only 16% of all patients and 30% of high-risk patients taking an NSAID received appropriate gastroprotective therapy.[42]

Although NSAID-associated GI complications can affect anyone taking an NSAID, all patients with risk factors (Table 5) should be managed in one of the following ways:

-avoiding NSAIDs altogether (with an alternative pain agent),

-using a coxib, or

-combining the NSAID with a gastroprotective medication such as a PPI, high dose H2-blocker, or misoprostol.[19,18,43,44]

Table 5: Risk factors for UGI complications of NSAIDS

Older age (> age 65)
History of UGI bleeding or peptic ulcer
Concomitant use of steroids, other NSAIDs (including aspirin) or anticoagulants

A review of the evidence for primary prevention of NSAID-associated ulcers found that:

- -PPIs are more effective than placebo and regular dose H2-blockers [20,45]
- -PPIs are equivalent to double-dose H2-blockers and misoprostol. [46]

Further information of the risks and benefits of PPI use can be found in the evidence document "Acid suppressive therapy" from the Independent Drug Information Service (see www.rxfacts.org).

For reducing NSAID-associated GI complications:

- prescribing a non-selective NSAID + PPI works as well as prescribing a coxib.[47,48]
- a coxib + PPI is more effective than coxib use alone.[46,49]

In a randomized study of patients with a history of NSAID-associated GI bleeding, patients on celecoxib + PPI had a significantly lower risk of recurrent ulcer formation compared to those taking celecoxib alone (0% versus 9% at 1

year).[49] **An international consensus statement recommends a coxib + PPI for patients with a history of upper GI bleeding who require ongoing NSAID use.**[50]

BOTTOM LINE: All NSAIDs are moderately more effective than placebo in pain relief. In patients at high risk for GI bleeding, NSAIDs should be avoided. If an NSAID is required, adding a PPI to any NSAID provides as much gastroprotection as celecoxib. For patients at greatest risk of GI bleeding, celecoxib + PPI provides the most gastroprotection, though at the price of greater cardiovascular risk than a non-selective NSAID.

Attenuating CV risk

The available evidence suggests that naproxen appears to confer the least CV risk, and may be the best option in patients with (or at high risk for) CV disease that require NSAIDs. In all cases, use the lowest NSAID dose that will effectively control symptoms.(22)

Attenuating renal risk

In patients with normal renal function, a short course of NSAIDs is usually safe, but long-term use of NSAIDs in patients with significant renal dysfunction should be avoided altogether, or with recognition of the risk with regular monitoring of kidney function (every 1-2 months).

BOTTOM LINE: In patients with or at risk for cardiovascular disease, NSAIDs should be avoided, or naproxen should be used if an NSAID is required. Celecoxib and diclofenac appear to confer the greatest cardiovascular risk, and naproxen the least. NSAIDs may reduce the efficacy of cardioprotective aspirin, and concomitant use should be avoided. In patients with renal insufficiency, long term NSAID use should be avoided or used with careful monitoring of kidney function.

Opiates

Opiates bind to μ-opioid receptors to reduce the sensation of pain. This class of drugs is commonly used for chronic non-cancer pain, and its use has increased dramatically in the last 3 decades. In the U.S., the proportion of office visits during which opiates were prescribed for chronic pain doubled from 8% to 16% from 1980 to 2000 and the prescribing of potent opiates increased from 2% to 9% in the same time period. [51] The top prescribed opiates are hydrocodone and oxycodone, with about 120 million and 400 million prescriptions dispensed in 2007, respectively. Over 4 million US patients receive a prescription for long-acting opiates each year. [52]

Opiates are regulated by the US Drug Enforcement Agency (DEA) under 5 schedules (I-V); schedule I includes drugs with the highest abuse potential. Most commonly prescribed opiates fall into either schedule II or III categories. Schedule II agents require written prescriptions and cannot be automatically refilled. Schedule III agents include combination products of an opiate with acetaminophen or NSAIDs, do not require a written prescription (i.e. can be called into a pharmacy), and can be automatically refilled.

These drugs vary considerably in their onset and duration of action. Table 6 lists the most commonly prescribed opiates, by schedule and duration of action.

Table 6: Commonly used oral opiates for chronic non-cancer pain, by DEA Schedule

DEA Schedule	Short-acting equivalent	Long-acting equivalent
Schedule II	codeine (generics)	no long-acting equivalent
	no short-acting equivalent	fentanyl transdermal (generics, Duragesic)
	hydromorphone (generics, Dilaudid)	Exalgo
	meperidine (generics, Demerol)	no long-acting equivalent
	no short acting equivalent	methadone (generics, Dolophine, Methadose)
	morphine (generics, Roxanol)	morphine ER (generics, MS Contin, Oramorph SR, Kadian, Avinza)
	oxycodone (generics, Roxicodone, OxyFast)	Oxycontin
	oxycodone/acetaminophen (generics, Endocet, Magnacet, Percocet, Primalev, Roxicet, Tylox) oxycodone/NSAIDs (generics, Combunox) oxycodone/ASA (generics, Percodan)	no long-acting equivalents
	tapentadol (Nucynta)	not available in US
	Oxymorphone (Opana)	Opana ER
Schedule III (no long-acting equivalents except Butrans)	codeine/acetaminophen (generics, Tylenol #3, Tylenol #4) hydrocodone/acetaminophen (generics, Lorcet, Lortab, Maxidone, Norco, Vicodin, Zamicet, Zydone) hydrocodone/NSAID (generics, Vicoprofen, Reprexain, Ibudone) *Buprenorphine transdermal (Butrans patch)	
Non-scheduled	Tramadol (generics, Ultram, Rybix ODT) tramadol/acetaminophen (generics, Ultracet)	Ultram ER, Ryzolt

Note: All propoxyphene products (e.g., Darvon) were withdrawn from the US market in November 2010, due to the risk of fatal cardiac arrhythmias. The FDA

concluded that the risks of the drug far outweighed the benefits as there was longstanding controversy that the drug did not appear to have substantially more analgesic effect than placebo. More information is available from the FDA (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm233800.htm).

Efficacy

OA meta-analysis of 41 RCTs of opiates in chronic pain found that both "weak" (tramadol, codeine) and "strong" (morphine, oxycodone) opiates were significantly better than placebo in pain relief and functional outcomes, with a moderate effect size for pain relief (-0.60, 95% CI, -0.69 to -0.50).[53] Similar results were found in a systematic review of elderly patients with chronic pain.[54,55] A Cochrane review of opiates versus controls in the treatment of hip or knee OA found smaller effect sizes for pain relief (-0.36, 95% CI -0.47 to -0.26), and functional improvement (-0.33, 95% CI -0.45 to -0.21).[56]

Patients vary in how they respond to different opiates due to individual variations in the μ-pain receptor and other genetic factors, including pharmacogenetic differences in the capacity to convert codeine (which l actually a pro-drug) into its active form. However, for most patients there is no high-quality evidence that *a priori,* any one opiate will be significantly better than another in pain relief.[57,58] Caution should be used in relying on opiate conversion charts to determine dose conversions when switching from one opiate to another. Dosing equivalents are derived from relative potencies using single doses in opiate-naïve patients. This, combined with patient variability in responses to different opiates, makes opiate conversion tools unreliable to convert expected pain relief with one opiate vs. another.

Codeine may be particularly difficult to predict a dose-response, as it must be hepatically converted to morphine to have an analgesic effect, and there are significant differences in the capacity of some patients to perform this important metabolic step. "Fast metabolizers" of codeine will have a faster and higher response to the same dose of drug than "slow metabolizers,"who will report much less pain relief with the same dose of codeine. In addition, for opiates prescribed as transdermal patches (such as fentanyl or buprenorphine patches) absorption rates depend on factors such as skin temperature (high temperatures increase absorption), patch placement (thinner skin increases absorption), and body fat (fentanyl accumulates in fat store; rapid weight loss can lead to accidental overdose due to fat store saturation).

Two recently approved long acting medications include oxymorphone ER (Opana) and buprenorphine transdermal (Butrans). There is no current evidence that either drug is significantly more effective than other currently available long-acting opiates on the market.

Safety

While opiates are very effective pain relievers, it is important to take into account their adverse effects and the longer-term potential of addiction, dependence, tolerance, and accidental overdose. Most side effects are dose dependent.

The most common adverse drug effects are neurologic (somnolence, dizziness), gastrointestinal (nausea, vomiting, and constipation), and pruritis. In randomized trials of opiates, 50%-80% of patients report a side effect, and about 25% withdraw due to an adverse event [55,59,60]. There is also a dose-dependent increase in risk of fractures in opiate users compared to non-users (RR=1.4, 95% CI, 1.2-1.7).[61]

There appear to be important differences in safety between different opiates. A large retrospective cohort study of Medicare beneficiaries found that compared to hydrocodone, 30-day risks of fractures and hospitalizations for adverse events were significantly lower in patients treated with tramadol, and hospital death and all-cause mortality were significantly higher in patients treated with codeine or oxycodone. In addition, patients treated with codeine had a much higher 180-day risk of cardiovascular events than patients treated with hydrocodone. GI safety was not different among the groups (Table 7). [62]

Meperidine is uncommonly used on the US market, as it is metabolized to nor-meperidine which can be neurotoxic and can cause seizures. This occurs more commonly in those with renal insufficiency, but has occurred in those with normal renal function.

Table 7: Comparative 30 day risk of adverse events among different opiates

30 day Outcome and comparison groups	Rate Ratio (lower is better for drug listed first; higher is worse)	95% CI
Fracture (30 days) tramadol vs hydrocodone	0.21	0.16 to 0.28
Hospitalized safety event (30 days) tramadol vs hydrocodone	0.81	0.68 to 0.96
Hospitalized death (30 days) codeine vs hydrocodone oxycodone vs hydrocodone	 4.3 3.8	 1.6 to 11.5 1.4 to 10.4
All-cause mortality (30 days) codeine vs hydrocodone oxycodone vs hydrocodone	 2.1 2.4	 1.2 to 3.5 1.5 to 4.0
Cardiovascular events (180 days) codeine vs hydrocodone	 1.6	 1.3 to 2.1

Longer-term adverse effects include addiction, dependence, tolerance, and overdose.

- Addiction rates in patients on long-term opiates range from 3% to 19%.
- Dependence is a physiological response to the chronic presence of a drug. It will almost always occur with long-term use of opiates (> a few weeks), but is not the same as addiction.
- Tolerance is a pharmacodynamic response to chronic drug administration that results in a reduced response to a given dose after repeated administration. Tolerance is an expected effect of long-term opiate use, and also differs from addiction.

Accidental drug overdose is the second leading cause of accidental deaths in the US (>11,000 in 2007), and its rate has been steadily rising since the 1990's.[52] There is no evidence that any one opiate is any safer than another with respect to addiction, dependence, tolerance, or accidental overdose. [57] Because of these concerns, the FDA is requiring manufacturers of all long-acting opiates to create and dispense provider educational materials that include information on proper pain management, patient selection, patient counseling, and patient medication guides (called a "REMS", or Risk Evaluation and Mitigation Strategy). This will apply (for now) only to companies that make extended-release and long-acting opiate formulations. The drug companies

have 12 months (from April 2011) to have their prescriber educational programs in place. [63]

Sidebar: Methadone is an agent with particular safety issues. It has a long and unpredictable half life and accounts for a higher proportion of accidental overdoses than any other opiate. In addition, it prolongs the QTc interval, and increases the risk of fatal arrhythmias (torsades de pointes), especially in patients taking other QTc prolonging agents. The routine use of methadone for chronic pain in primary care should be avoided.

Protecting against opiate-induced adverse events

The Veterans Administration/Department of Defense (VA/DoD) clinical practice guideline outlines a number of evidence-based strategies to reduce the adverse effects of opiates, summarized in Table 8.[64] Transdermal opioids (e.g. fentanyl patch) have lower incidence of side effects and discontinuation rates compared to long-acting oral opiates, although they can increase the risk of dependence.[59]

Table 8: Grade A and B recommendations for the VA/DOD to prevent opiate-induced side effects, adapted[64]

Constipation	▪ Prophylactic mild peristaltic stimulant (e.g. bisacodyl or senna) ▪ If no bowel movement for 48 hours, increase dose of bowel stimulant ▪ If no bowel movement for 72 hours, perform rectal exam ▪ If not impacted, provide additional therapy (suppository, enema, magnesium citrate, etc.)
Nausea or vomiting	▪ Consider prophylactic antiemetic therapy ▪ Add or increase non-opiate pain control agents (e.g. acetaminophen) ▪ If analgesia is satisfactory, decrease dose by 25% ▪ Treat based on cause
Sedation	▪ Determine whether sedation is due to the opiate ▪ Eliminate nonessential CNS depressants ▪ If analgesia is satisfactory, reduce dose by 10-15% ▪ Add or increase non-opiate or non-sedating adjuvant for additional pain relief so the opiate can be reduced ▪ Add stimulant in the morning (such as caffeine) ▪ Change opiate
Pruritis	▪ Consider treatment with antihistamines ▪ Change opiate
Hallucination or dysphoria	▪ Evaluate underlying cause ▪ Eliminate nonessential CNS acting medications
Sexual dysfunction	▪ Reduce dose ▪ Testosterone injections may be helpful (for men)

Attenuating dependence, tolerance, overdose, addiction and misuse

Although dependence and tolerance are byproducts of long-term opiate use, their risk can be reduced by using the lowest possible dose for the shortest time possible. Accidental overdose is dose-dependent; its risk can be also be reduced by using the lowest dose possible. Compared to patients receiving <20mg/day of morphine, those receiving >100mg/day of morphine have 9 times the risk of overdose, occurring at a rate of about 2% per year.[65,66] Accidental overdose and death have also been reported with fentanyl patches with lining defects (resulting in several batch recalls), causing immediate absorption and overdose (www.fentanylclaimcenter.org)

The risk of addiction and misuse can be predictable in some patients. Guidelines advocate for the following steps to reduce the risk of addiction and misuse:[55,67]

1. Use opiates only for patients whose chronic pain is moderate to severe, in whom it improves function and quality of life, and who have failed other analgesics.
2. Before opiate initiation, assess the patient's potential for of addiction and misuse.[55] A common screening tool is the SOAPP-SF (screener and opioid assessment for patients with pain – short form) (in Appendix 1). This tool can help to identify patients at high risk for addiction and misuse (aberrant behavior). For those at high risk (Table 9), monitor drug use closely (see monitoring below), or refer the patient to a chronic pain specialist (if available).

Table 9: Risk factors for aberrant opiate behavior [55]

Younger age
Personal or family history of substance abuse disorder (including illicit drugs, alcohol, smoking, prescriptions)
Legal history (DUI or incarceration)
Mental health problems (including mood disorders)

3. A "medication agreement" can help the patient adhere to a shared understanding of opiate prescription use. [55] These agreements should be written and signed by the provider and the patient, and should include the elements listed in Table 10:

Table 10: Components of an opiate medication agreement

Rationale (what you are treating and why)
Risks of the drug (side effects as well as risk of dependence, tolerance, addiction, misuse, and overdose; and risk of driving, working, etc under the influence of the drug)
Treatment **goals** (pain level, function level)
Monitoring plan (how often to return for follow up; see #4 below)
Refill policy
Action plan for suspected **aberrant behavior** (may include urine drug screens to ensure the patient is not diverting the medication)
Conditions for **discontinuing** opiates (lack of efficacy, pain resolution, aberrant behavior)

A copy of a sample medication agreement can be found at: www.sdcpms.com/pdf/form_sample_opiate_contract.pdf (see Appendix 3).

4. Institute a monitoring plan that includes regular assessments of pain levels, activities of daily living, adverse events, and aberrant behavior. The PADT tool can be used for these ongoing assessments (in Appendix 2) http://www.painknowledge.org/physiciantools/opioid_toolkit/components/PADT.pdf
5. Use long-acting agents instead of short-acting agents. There is some evidence that short acting agents have a higher risk of accidental death and fractures than long acting agents. [68] [69] [55,67]
6. Use the lowest dose possible to achieve adequate pain relief. Higher opioid dose is associated with higher risk of accidental overdose and fractures. [69] [68]
7. For patients who do not improve, or show signs of aberrant behavior, refer to a chronic pain specialist for management advice.

Many primary care physicians do not use such risk reduction strategies when prescribing opiates for chronic non-cancer pain; one retrospective analysis found only 50% of these patients were seen regularly (at least every 6 months), and 25% received opiate refills before they were scheduled to be refilled. [70] For more information on risk reduction strategies, an on-line module is very useful, available free of charge, and provides CME credit for completion (www.opioidprescribing.com).

Novel agents to dissuade misuse

A new agent FDA approved in June 2011 has been formulated to dissuade misuse by injecting or inhaling. It is a formulation of the drug oxycodone, but has added ingredients to make the drug gel if crushed/dissolved (to dissuade injection) and to make the drug irritate nasal passages (to dissuade nasal inhalation). The drug is being marketed as Oxecta,

the dose, efficacy, and safety of which are the same as oxycodone. More information on the drug can be found at www.fda.gov.

Tapering patients off opiates

Some patients on opiates are appropriate candidates for discontinuing the drug. These include patients who cannot achieve adequate analgesia, or who experience more harm than benefit from the drug. In some situations, the need for opiates has resolved (e.g. those with arthritis after a successful joint replacement). Primary care opiate tapering is appropriate for motivated patients that may have dependence, but do not have addiction. Patients with addiction and/or suspected aberrant behavior should be referred to, and managed by, a pain specialist.

For most patients, taper the opiate dose by 20% to 50% per week (of the original dose). The longer the patient has been on the drug, and the higher the initial dose, the slower should be the taper. [64]

Symptoms of withdrawal should prompt a discontinuation of the taper. These include early symptoms (anxiety, muscle aches, insomnia, tearing, runny nose, sweating, and yawning) and later symptoms (diarrhea, nausea, abdominal pain, goose bumps, and dilated pupils).

Opiate-like agents

Tramadol (Ultram) and tapentadol (Nucynta) are opiate-like agents that bind the opiate μ-receptor and inhibit serotonin and norepinephrine uptake. Blocking of serotonin and norepinephrine may provide additional analgesic effect. Tramadol is available in the U.S. in short and long acting formulations with generic preparations, while tapentadol is only available in a short acting formulation without an available generic. Neither of them can be combined with other serotonergic agents, including TCAs, SSRIs, or SNRIs.

Efficacy: Tramadol

A Cochrane review in OA patients found a mean pain reduction of 8.5 points more with tramadol + acetaminophen compared to acetaminophen alone (on a 100 point scale) (95% CI 5-12), with a number needed to treat for moderate pain improvement of 6 (95% CI 4-9), which means that 6 patients must be treated to achieve moderate pain relief in 1 patient.[71] A meta-analysis in patients with neuropathic pain found a number needed to treat to achieve at least 50% pain reduction of 3.4 (95% CI 2.3-6.4) compared to placebo, which means that 3-4 patients have to be treated to achieve this amount of pain relief in 1 patient.[72]

In a direct comparison of tramadol and hydrocodone/acetaminophen in patients with chronic non cancer pain, the groups were found to have equivalent pain relief.[69]

Efficacy: Tapentadol

The efficacy of tapentadol has been shown in two trials of short duration. The first was a 12-week trial in OA patients randomized to extended release tapentadol , controlled release oxycodone, or placebo, the results found at least 50% pain improvement occurred in:

- 32% of patients given tapentadol ER (100-250mg)
- 24% of patients given placebo ($p<0.01$)

A second similar 12-week trial in chronic low back pain patients found tapentadol ER significantly better than placebo, but equivalent to oxycodone ER (20mg-50mg) in pain relief. Both studies found a mean decrease in pain between 0.7 to 0.9 points better than placebo (on an 11-point scale).[73]

Safety: Tramadol

Tramadol carries an FDA warning on the risk of suicide, and is contraindicated in those with suicidal ideation or past suicide attempts. The drug also lowers the seizure threshold, and should not be used in patients with a seizure disorder. Compared to placebo, the relative risk of adverse events is 2.3, with a number needed to harm of 5, which means for every 5 patients treated, 1 will experience an adverse event; the relative risk of drug discontinuation due to an adverse events is 2.6, with a number needed to harm of 8, which means that for every 8 patients treated, 1 will discontinue the drug due to an adverse event.[65]

Minor adverse events are similar to those seen with other low potency opiates, including GI and neurologic effects, although a direct comparison between tramadol and hydrocodone/acetaminophen found side effects were less common in the tramadol group; compared to tramadol, the relative risk of side effects with hydrocodone/acetaminophen were:[74]

- Nausea (RR=1.69, 95% CI 1.03-2.77)
- Vomiting (RR=2.21, 95% CI 1.14-4.32)
- Dizziness (RR=2.12, 95% CI 1.17-3.86)
- Loss of appetite (RR=3.27, 95% CI 1.12-9.55)

A study of older patients found tramadol had a lower risk of serious adverse effects, including fractures and safety events requiring hospitalization, compared to hydrocodone (see Table 7). [62]

Safety: Tapentadol

Rates of adverse effects with tapentadol and placebo:

- 76% tapentadol ER
- 61% placebo(67)

Rates of GI adverse effects with tapentadol and placebo:

- 43% tapentadol ER
- 26% placebo[75]

Discontinuation rates for tapentadol ER and oxycodone CR:

- 44% tapentadol ER
- 62% oxycodone CR[76]

Tapentadol cannot be used in patients with severe liver or renal impairment, and its long term safety has not been established (released in the U.S. in June 2009).

BOTTOM LINE: Opiates are useful tools in pain relief, but have to be used with a recognition of their adverse effects and limitations. The low potency opiates (codeine, hydrocodone, and tramadol) do not differ in their efficacy, but have significant differences in serious adverse effects. These are most frequent with codeine, and least with tramadol. There are no significant differences in efficacy or safety among the high potency opiates, although the transdermal opiates may cause fewer minor side effects. Minor adverse effects can be reduced by proactively addressing the common GI and neurologic adverse effects (Table 8). Methadone is particularly prone to cause side effects, and should be avoided in most primary care settings. For all opiates, the risk of dependence, tolerance, and accidental overdose can be limited by using the lowest effective dose possible.

Tools measuring baseline pain (SOAPP-SF) and ongoing assessments (PADT) can help guide therapy. Patients beginning long-term opiates can be asked to sign a medication agreement. Those with high opiate requirements, lack of improvement on appropriate opiate doses, or signs of aberrant behavior should be referred to a chronic pain specialist (if available).

Comparative efficacy

Acetaminophen vs. NSAIDs

NSAIDs and acetaminophen appear to be equivalent in treating low back pain.[15,77] In a series of N-of-1 trials, patients with OA alternated acetaminophen with NSAIDs in 2-week intervals, and 80% of them could not discern between the drugs in terms of symptom relief.[78] A Cochrane review was inconclusive in determining if acetaminophen was equivalent to NSAIDs for treatment of pain associated with RA.[79] One review found NSAIDs better than

acetaminophen in hip / knee OA for pain reduction, global assessments, and functional status, with effect sizes corresponding to a small treatment effect (ranging from -0.19 to -0.46).[6]

Acetaminophen vs. opiates

There is no available direct evidence comparing acetaminophen to opiates in efficacy of pain relief in chronic non-cancer pain. Indirect evidence from meta-analyses supports the conclusion that opiates are more effective for pain relief than is acetaminophen, as summarized in Table 11.

Table 11: Effect sizes for pain and function for acetaminophen and opiates*

Compared to controls	Effect size for pain	Effect size for function
Acetaminophen[6]	-0.13	No significant difference
Opiates[54,56]	-0.36 to -0.56	-0.31 to -.43

*Generally effect sizes <0.5 are considered small.

NSAIDs vs. opiates

A meta-analysis of 41 RCTs of opiates in the management of chronic pain found: [53]

- "strong" opiates (morphine, oxycodone) were superior to naproxen for pain relief, although the magnitude of the difference was small (effect size 0.34, 95% CI 0.67 to 0.01).
- "weak" opiates (tramadol, codeine) were not more effective than NSAIDs.
- NSAIDs were slightly better than opiates for functional outcomes, with a small effect size (0.16, 95% CI, 0.03-0.30).
-

Two randomized trials of patients with chronic low back pain suggest that tramadol is less effective than celecoxib, with 30% or more improvement in pain occurring in two thirds of celecoxib patients but in only about half of tramadol patients.[80]

BOTTOM LINE: Although comparative differences in efficacy are relatively small, high potency opiates are more effective than both low potency opiates and NSAIDs, which in turn are more effective than acetaminophen.

Comparative Safety

Acetaminophen versus NSAIDs

A Cochrane review found the relative risk of all adverse events and drug withdrawals were not significantly different between acetaminophen and NSAIDs, but traditional NSAIDs have a 50% higher risk of GI events (RR=1.5, 95% CI 1.1 to 2.0; number needed to harm=12). The relative risk of GI events between

acetaminophen and coxibs was not significantly different.[81] The CV risk of NSAIDs is also higher than acetaminophen (which is comparable to placebo).

Acetaminophen versus opiates

There is no available direct evidence comparing the safety of acetaminophen to opiates in long-term use for chronic pain. Based on indirect comparisons, adverse events occur in about 25% of patients taking acetaminophen (equivalent to placebo and none requiring discontinuation)[81], whereas adverse events occur in about 50%-80% of patients taking opiates, requiring discontinuation in about 25%.[59,60]

NSAIDs versus opiates

A meta-analysis of opiates versus other drugs (primarily NSAIDs) found 3 side effects occurred significantly more commonly in the opiate groups: nausea (risk difference 14%), constipation (risk difference 9%), and somnolence or drowsiness (risk difference 6%).[53] Evaluation of a large cohort of Medicare patients found opiates had a higher risk of several safety outcomes compared to non-selective NSAIDs (Table 12).[82]

Table 12: Hazard ratios of adverse events in opiates compared to non-selective NSAIDS

Outcome	Hazard ratio* (95% CI)	Number needed to harm after 1 year of treatment
Cardiovascular events	1.8 (1.4-2.2)	17
Fractures	4.5 (3.1-6.4)	26
Hospitalized safety events	1.7 (1.4-2.1)	19
All cause mortality	1.9 (1.4-2.5)	27

*Hazard ratio is an estimate of relative risk; a hazard ratio of 1.8 means the risk of an event is 80% higher in the identified group.

BOTTOM LINE: There are important differences in comparative safety between acetaminophen, NSAIDs, and opiates. Acetaminophen has the fewest adverse events when used at appropriate doses. Both NSAIDs and opiates have significantly higher rates of adverse events compared to acetaminophen. NSAID adverse effects are primarily GI bleeding and CV events. Opiate adverse events can be serous and include fractures, other events requiring hospitalization, and higher mortality compared to NSAIDs.

Treatments for neuropathic pain

As there is sometimes overlap between neuropathic and non-neuropathic pain, medications to treat the former can be combined with traditional pain

treatment as "adjuvant therapy". The goal is to better control pain and improve function, with as few side effects from either drug class as possible. Neuropathic pain drugs falls into two main treatment categories: anticonvulsants and anti-depressants.

Anticonvulsants

Table 13: Overview of anticonvulsants for neuropathic pain

Agent (brand name)	FDA approval	Trials supporting efficacy in non-FDA approved conditions	Drug interactions	Reduce dose in renal insufficiency
pregabalin (Lyrica)	DM neuropathy PH neuralgia FMG	Central neuropathic pain	Few	Yes
gabapentin (generics, Neurontin)	PH neuralgia	DM neuropathy FMG	Few	Yes
carbamazepine (generics, Tegretol, Equetro, Carbatrol)	Trigeminal neuralgia	Peripheral neuropathy	Many	Yes

PH=post-herpetic; DM=diabetic; FMG=fibromyalgia

Pregabalin

Efficacy

Pregabalin produces a dose-dependent reduction in pain compared to placebo in a variety of pain syndromes. A Cochrane review found a dose of 150 mg to be no more effective than placebo, but doses of 300-600 mg were significantly better than placebo:[76]

Table 14: Number needed to treat with pregabalin to achieve 50% pain relief over baseline in various painful conditions, compared to placebo [76]

Condition	Number needed to treat
Postherpetic neuralgia	4
Diabetic neuropathy	5
Central neuropathic pain	6
Fibromyalgia	11

Safety

The most common side effects include peripheral edema, weight gain, and CNS side effects (including dizziness, somnolence, ataxia, and headache). At 600mg doses:

- somnolence occurs in 15-25% of patients
- dizziness occurs in 27%-46%
- treatment discontinuation occurred in18%-28%. [83]

Gabapentin

Efficacy

Gabapentin is effective in reducing neuropathic pain in diabetics; in a trial comparing gabapentin to placebo, pain on 10-point scale decreased from 6.4 to 3.9 in the treatment group as compared to 6.5 to 5.1 in the placebo group after 8 weeks of treatment.[84] An uncontrolled trial of patients with diabetic neuropathy found at least moderate pain relief was achieved in 52% of treated patients (at a mean effective dose of 1600mg/day).[85] Gabapentin is also effective in treating both fibromyalgia and post-herpetic neuropathy. A large placebo controlled trial of patients with fibromyalgia found a difference in pain reduction between the groups of -0.92 (95% CI -1.75 to -0.71) on a 10-point scale. A 30% or more reduction in pain was achieved by 51% of the intervention group (vs. 31% of the placebo group).[86] In post-herpetic neuralgia, pain was reduced from 6.3 to 4.2 (on a 10-point scale) in the intervention group (vs. 6.5 to 6.0 in the control group).[87]

Safety

In randomized trials, the frequency of withdrawals due to adverse effects was not significantly different from that seen in control groups.[87] Side effects are primarily neurological. In a randomized trial:

- dizziness occurred in 24% (vs 5% of placebo)
- somnolence occurred in 23% (vs 6% of placebo)
- confusion occurred in 8% (vs1% of placebo).[84]

Carbamazepine

Efficacy

A Cochrane review found 14 studies evaluating the efficacy of carbamazepine in the treatment of neuropathic pain, all of which had small sample sizes (mean 34 participants) and were of short duration (mean 3 weeks). Using any definition of improvement, 70% of carbamazepine patients had some improvement in pain (versus 12% of placebo) with a number needed to treat of about 2.[88]

Safety

In the Cochrane review, 66% of participants had at least 1 adverse event (versus 27% of placebo), leading to withdrawal in 4%, and a number needed to harm of 2.6. The most common adverse effects are nausea, dizziness, and rash.

Others

Lamotrigine, topiramate, valproate, phenytoin, and oxcarbazepine are not FDA approved for use in any chronic pain syndromes, and are lacking adequately sized randomized controlled trial data to support their use.[89,90,91]

BOTTOM LINE: Pregabalin and gabapentin are both effective in the treatment of diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia. There is less efficacy data to support the use of carbamazepine in these pain syndromes. All are limited by CNS side effects, with discontinuation rates highest in pregabalin, and lowest in carbamazepine.

Antidepressants

Table 15: Overview of anti-depressants for neuropathic pain

Agent	Blocks reuptake	FDA approval	Trials supporting efficacy in non-FDA approved conditions
TCAs	serotonin noradrenaline	Not approved for chronic pain	DM neuropathy Neuropathic pain
SSRIs	serotonin	Not approved for chronic pain	Neuropathic pain
SNRIs	serotonin noradrenaline	duloxetine: DM neuropathy, OA, FMG,CLBP	
		venlafaxine: not approved for chronic pain	DM neuropathy polyneuropathy
		milnacipran: FMG	

FMG=fibromyalgia; OA=osteoarthritis; CLBP=chronic low back pain; DM=diabetic
TCA=Tricyclic anti-depressants; SSRI=selective serotonin reuptake inhibitors; SNRI=serotonin norepinephrine reuptake inhibitor

Tricyclic antidepressants (TCAs)

Efficacy

In a randomized trial of patients with diabetic neuropathy, at least moderate pain relief was achieved by:

- 74% of amitriptyline group (mean dose 105mg)
- 61% of desipramine group (mean dose 111mg)
- 41% of placebo group. [92]

A systematic review found about 1/3 of all patients treated with a TCA achieved at least a 50% improvement in neuropathic pain.[93] There are no significant differences in efficacy between the different TCAs.[92,94]

Safety

All TCAs are limited by anti-cholinergic side effects (dry mouth, urinary retention) and somnolence, which are dose dependent. These side effects are less common with nortriptyline and desipramine than with amitriptyline. ***Side effects occur more commonly in elderly, so dose titration should be increased cautiously***. TCAs can also cause cardiac conduction abnormalities and should be avoided in patients with existing cardiac disease. TCAs should not be combined with the SSRIs or SNRIs (discussed in the next section).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Efficacy

Paroxetine and citalopram are both superior to placebo in relieving neuropathic pain, based on 2 small randomized trials (<50 patients each), but fluoxetine is not better than placebo in diabetic neuropathy.[92,93]

Safety

The SSRIs are associated with weight gain, sexual dysfunction, and minor increase in the risk of bleeding due to platelet dysfunction.

Serotonin / noradrenaline reuptake inhibitors (SNRIs)

Duloxetine

Efficacy

Duloxetine is significantly more effective than placebo in the relief of pain from a number of conditions. A Cochrane review found 6 trials comparing duloxetine to placebo, 3 in the treatment of diabetic neuropathy, and 3 in the treatment of fibromyalgia. At a dose of 60mg, the number needed to treat to achieve a 50% improvement in pain was:

- 6 for diabetic neuropathy
- 8 for fibromyalgia.

Increasing the dose to 120mg did not improve the effect (and a dose of 20mg was ineffective).[95]

Safety

The most common side effects include nausea, somnolence, dizziness, constipation, and decreased appetite (it is recommended that the drug should not be taken on an empty stomach). These side effects are dose dependent, and led to discontinuation of the drug in 16% of patients.[95]

Venlafaxine

Efficacy

A trial of patients with diabetic neuropathy found 6 weeks of therapy reduced mean pain scores by 50% in the venlafaxine group versus 27% in the placebo group (at a dose 150mg-225mg; no difference was seen between placebo and a 75mg dose of venlafaxine). The NNT to achieve 50% reduction in pain was 4.5.[96] Another trial of patients with polyneuropathy found a reduction in mean pain scores (on a 10-point scale) from 7.2 to 3.1 in the intervention group and from 7.2 to 5.5 in the placebo group.[97]

Safety

In this trial, somnolence and nausea were the most common adverse effects, which occurred at rates similar to duloxetine.

Milnacipran

Efficacy

In two large randomized trials of patients with fibromyalgia, milnacipran significantly reduced pain scores compared to placebo (as well as global status, physical function, and fatigue).[98,99]

Safety

Most common side effects are similar to those seen with other SNRIs, which include nausea, headache, and constipation, leading to discontinuation in 19-24% of patients (at 100mg and 200mg doses, respectively, compared to 10% of placebo).

BOTTOM LINE: The TCAs and SNRIs are effective for a variety of neuropathic pain syndromes, but there is less efficacy data to support the use of SSRIs for this use. The TCAs are limited by anti-cholinergic side effects, which are dose dependent; the lowest dose possible should be used, particularly in the elderly. Within the SNRIs, duloxetine has the most efficacy data for a variety of pain syndromes. The data for venlafaxine are primarily for use in diabetic neuropathy, and for milnacipran primarily for fibromyalgia. All SNRIs are limited by GI and CNS side effects, and should be taken on a full stomach.

Comparative efficacy

A systematic review evaluated the comparative efficacy and adverse event rates of numerous pain medications in diabetic neuropathy. It calculated the odds of achieving 50% (or moderate) reduction of pain, as compared to placebo, as well as the odds of an adverse event:[100]

Table 16: Comparative efficacy of diabetic neuropathic pain medications

Medication Category	Medication type and dose ranges used	Odds ratio of achieving a 50% reduction in pain (higher is better) (95%CI)	Odds ratio of withdrawal due to an adverse event (lower is better) (95% CI)
TCA	amitriptyline (25-100mg) desipramine (200mg) imipramine (100mg)	22.2 (5.8 to 84.8)	2.3 (0.6 to 9.7)
Traditional anticonvulsants*	carbamazepine (200-600mg) lamotrigine (25-400mg) valproate (1000-1200mg)	5.3 (1.8 to 10)	1.5 (0.3 to 6.9)
Newer anticonvulsants	pregabalin (75mg-600mg) oxcarbazepime (600-1800mg) gabapentin (3600mg)	3.3 (2.3 to 4.7)	3.0 (1.8 to 5.1)
SNRI	duloxetine 60mg**	2.6 (1.7 to 3.8)	2.4 (1.1 to 5.4)
Opiates	tramadol (200-400mg) oxycodone CR (10-120mg)	4.3 (2.3 to 7.8)	4.1 (1.2 to 14.2)

*Total number of participants was 181, with only 1 trial for each drug
**Duloxetine 120mg was not significantly more efficacious, and had a significantly higher incidence of withdrawals, compared to 60mg

Based on this comparative analysis, the benefits of TCAs exceed their risks, but the risk-benefit ratio is less clear for the other drug categories (the traditional anticonvulsants only had 1 trial for each drug).

A subsequent systematic review found the following pain reductions in patients with diabetic neuropathy, based only on high quality studies

Table 17: Systematic review in diabetic neuropathy[103]

Agent (# high quality trials)	% pain reduction, compared to placebo
Amitriptyline (3)	58%-63%
Pregabalin (4)	11%-13%
Gabapentin (2)	11%
Venlafaxine (2)	23%
Duloxetine (3)	8%-13%

Due to these studies and a few subsequent randomized trials, recent consensus guidelines for diabetic neuropathy recommend using TCAs, pregabalin (or gabapentin a reasonable cost-effective alternative), and duloxetine (or venlafaxine as a reasonable alternative) as first line agents because their efficacy is supported by at least 2 high quality randomized controlled trials (RCTs).[101 102] Second tier agents, whose efficacy is supported by 1 or fewer RCTs, include carbamazepine, lamotrigine, and tramadol.

For fibromyalgia, a meta-analysis found the following effect sizes for reducing pain compared to placebo (generally effect sizes <0.5 are considered small):

- TCAs (-1.64, 95% CI -2.57 to -0.71)
- SSRIs (-0.39, 95% CI -0.77 to -0.01)
- SNRIs (-0.36, 95% CI -0.46 to -0.25).[103]

BOTTOM LINE: Of the neuropathic agents, TCAs are the most effective for both diabetic neuropathy and fibromyalgia, but must be used cautiously in the elderly. Pregabalin and gabapentin are also effective for neuropathy and fibromyalgia, as are the SNRIs (duloxetine for all indications, venlafaxine for diabetic neuropathy, and milnacipran for fibromyalgia). Other anticonvulsants (valproate, lamotrigine) and anti-depressants (SSRIs) have limited RCT data to support their use in neuropathic pain.

Comparative safety

As noted in Table 16, neuropathic pain medications differ in the number of adverse effects requiring drug discontinuation (ranging from an odds ratio of 1.5 to 3) but there is substantial overlap in the confidence intervals. Of note, the TCA doses used in many of these studies may be higher than can be tolerated by elderly patients.

BOTTOM LINE: There is no definitive evidence that any neuropathic drug is significantly safer than another.

Table 18: Neuropathic agents and relative dosing

Agent	Starting daily dose	Maximum daily dose	Usual Divided doses
gabapentin (generics, Neurontin)	300mg / day	3600mg/day*	tid
pregabalin (Lyrica)	150mg/day	300mg/day*	bid-tid
carbamazepine (generics, Tegretol, Tegretol XR, Equetro, Carbatrol)	200mg/day	1200 mg/day*	bid
despiramine (generics, Norpramin)	10-25mg/day	300mg/day**	qhs
amitriptyline (generics, Elavil)	10-25mg/day	150mg/day**	qhs
nortriptyline (generics, Pamelor)	10-25mg/day	150mg/day**	qhs
doxepin (generics, Silenor)	10-25mg/day	150mg/day**	qhs
paroxetine (generics, Paxil, Paxil CR, Pexeva)	10-20mg/day CR: 25mg/day	50mg/day (40 in elderly) 62.5mg/day (50 in elderly)	qday
citalopram (generics, Celexa)	20mg/day	60mg/day	qday
duloxetine (Cymbalta)	60mg/day	120mg/day (no more effective than 60mg/day)	qday
venlafaxine (generics, Effexor, Effexor XR)	75mg/day	225mg/day	qday-bid
milnacipran (Savella)	12.5mg/day	100mg/day	bid

*adjust for renal insufficiency

**** In elderly, start at lowest starting dose, and do not exceed half the maximum daily dose**

Combination therapy

The goal of combining analgesic medications is to maximize efficacy while limiting the side effects of each drug category. Certain analgesic combinations appear to be more effective than either drug alone. Serotonergic

agents should not be combined with one another (tramadol, tapentadol, TCAs, SSRI, SNRIs) due to the risk of serotonin syndrome.

Morphine, gabapentin, or both

A randomized trial of patients with diabetic neuropathy or post-herpetic neuralgia found the combination of morphine and gabapentin was more effective than either drug alone, with mean pain scores (on a 10-point scale):

- 5.7 at baseline
- 4.5 with placebo
- 4.2 with gabapentin
- 3.7 with morphine
- 3.1 with combination therapy.[104]

Gabapentin, nortriptyline, or both

A randomized trial of patients with diabetic neuropathy or post-herpetic neuralgia found the combination of gabapentin and nortriptyline was more effective than either drug alone, with mean pain scores (on a 10-point scale):

- 5.4 at baseline
- 3.2 with gabapentin
- 2.9 with nortriptyline
- 2.3 with combination treatment.[105]

BOTTOM LINE: Combining some pain medication categories can relieve pain more than either drug alone. Serotonergic agents (tramadol, tapentadol, TCAs, SSRI, SNRIs) should not be combined.

Other pharmacologic agents

OTC medications

In a large randomized trial, glucosamine/chondroitin (1500mg/1200mg) was more effective than placebo in reducing pain from OA, but only in patients with moderate to severe pain (79% of the intervention group and 54% of the placebo group achieved at least 20% pain relief).[106] A Cochrane review also found glucosamine was superior to placebo in reducing pain and improving function in patients with OA.[107] These preparations are available in a variety of strengths and are relatively inexpensive (about $10 for a month's supply). They are not regulated by the FDA and preparations vary in purity and content.

Injections

Intra-articular steroid injections can provide significant short-term improvements in knee OA pain, but their effect after 4 weeks is not significant.[108] Intra-articular injections of viscosupplements (such as hyaluronan and hylan derivatives) also provide significant improvements in knee pain and function from 5-13 weeks after they are injected, but at a cost of >$100 per injection.[109,110] Epidural steroid injections for lumbosacral radicular pain are effective for short term pain improvements, but injection techniques require specialists who may not be locally available in some areas.[111]

Topical therapies

Capsaicin

Capsaicin cream is a naturally occurring component of hot peppers that locally depletes substance P, and results in modest improvements in painful diabetic neuropathy. A randomized trial found it superior to placebo in improving

- pain (70% vs. 53%)
- walking (26% vs. 15%)
- working (18% vs. 9%)
- sleeping (30% vs. 20%).[112]

However, 2 subsequent randomized placebo controlled trials did not find any pain benefit with capsaicin.[113,114] A subsequent Cochrane review of capsaicin for chronic neuropathic pain found:

- low dose treatment (0.075%) resulted in an NNT of 6.6 to achieve any pain relief
- single application high dose treatment (8%) resulted in an NNT of 12 to achieve a 30% reduction in pain.

Local skin reactions are very common, but tolerable and attenuate over time, and systemic adverse effects are rare.[115] Some have questioned whether the very apparent local reactions make it impossible to have a truly blinded randomized trial of these agents. Capsaicin cream is available over the counter, at a cost of $10-$20 for a 60g tube, and can be applied up to 4 times a day.

Salicylate products

Several topical salicylate-based therapies are commonly used in acute and chronic pain conditions. A systematic review found that short term use of these agents in acute pain was significantly more effective than placebo (number needed to treat of 2 for a 50% reduction in pain); however, long term use in chronic pain conditions was not significantly better than placebo in the

higher quality studies. Side effects were minor and well tolerated and these preparations are available over the counter at low cost. [116]

Topical NSAIDs

Diclofenac is available in gel and patch form for local pain relief. A meta-analysis found these topical NSAIDs were less effective than oral NSAIDs for pain relief; they were more effective than placebo (effect size 0.40, 95% CI 0.15 to 0.65), but the effect only lasted for 2 weeks. In weeks 3 and 4, there was no evidence of efficacy superior to placebo. Topical diclofenac is expensive at a cost of about $150-$300 a month if used as directed (1 patch twice a day, or gel application 4 times a day).[117]

Lidocaine

Lidocaine patches reduce discharges in superficial nerves. These patches are applied locally, and have been reported to improve pain and quality of life in patients with post-herpetic neuralgia and painful diabetic neuropathy.[118] Their cost can be prohibitive, as each patch is approximately $7-$10, and insurance coverage may be limited. Up to 3 patches can be applied up to 12 hours a day. Each patch is 10cm X 14cm, but can be cut into smaller sizes before application. There is no compelling evidence for their efficacy in treating non-dermal pain, such as arthritis, although they are often used for this purpose.

BOTTOM LINE: Glucosamine may be effective for OA patients with moderate to severe symptoms. Both steroid and viscosupplement injections are effective for short to medium term relief of local joint pain, but the latter may be cost prohibitive. Epidural injections can provide short term pain relief of lumbosacral radicular pain, but will usually require a specialist. Topical capsaicin and salicylates are both effective for short term pain relief, but their long term efficacy is less well known; both are available over the counter at low cost. Topical NSAIDs and lidocaine have been reported to be effective for short term relief of superficial pain with minimal side effects, although both are very costly. None of the topical agents are useful for non-superficial pain.

Non-pharmacologic therapies

Several non-pharmacologic treatments have been evaluated for the management of chronic nocioceptive and neuropathic pain. Interventions that have demonstrated some effectiveness are summarized in Table 19.

Table 19: Non-pharmacologic interventions for reducing pain, improving function, or both in osteoarthritis, fibromyalgia, and chronic low back pain

Condition	GOAL		
	Pain	Function	Both
OA	Quadriceps strengthening[119]	Weight loss (combined with exercise)[120]	Tai Chi [121] Therapeutic ultrasound [122] Electromagnetic stimulation [123] Braces and insoles [124] Acupuncture [125] Exercise [126,127]
FMG	Cognitive behavioral therapy [128] Exercise [129] Acupuncture [130]	…	Tai Chi [131]
CLBP	Spinal manipulation [132] Massage [132] Cognitive behavioral therapy [133]	…	Exercise [134]

OA=Osteoarthritis; FMG=Fibromyalgia; CLBP=chronic low back pain

Medical marijuana

Efficacy:

The Cannabis Sativa plant has been used for centuries in a variety of formulations for various ailments ranging from nausea to glaucoma. Its eaves can be smoked, vaporized, or taken by mouth (by blending into food products or put into blank capsules). However, the medicinal value of cannabis has been limited by restrictive laws in many states and by limits on the clinical research that could be performed on these products.[135]A meta-analysis of 18 randomized trials of cannabis use in various chronic pain syndromes (1/3 of which were cancer) found a standardized mean difference in pain improvement of -0.61 (-0.84 to -0.37) indicating a moderate treatment effect. However, the individual studies were small (sample size ranging from 10-177), short term (mean duration 25 days) and of overall poor methodologic quality. Many of the studies had an "open phase" in which patients took the drug before randomization, to screen out those with low tolerance for side effects. The authors of the meta-analysis concluded they "cannot categorize cannabis as a future first, second, or third line treatment against pain."[136] Synthetic cannabinoids are also available by

prescription in some countries, but none are indicated for chronic pain (e.g. Marinol is approved in the U.S. for nausea/vomiting, anorexia, and weight loss).

Safety:

Smoking cannabis has been associated with twice the odds of pulmonary symptoms (cough, sputum, wheezing) but not associated with changes in lung function.[137] Retrospective cohorts have found cannabis use may be associated with an "amotivational syndrome" and reproductive system changes (including reduced testosterone and libido in men, and increased prolactin in women).[138] The meta-analysis cited above found several adverse events associated with short term cannabis use in randomized trials. [136]

Table 20: Odds of adverse effects of cannabis versus placebo in randomized trials [136]

Adverse effect	Odds of effect with cannabis vs placebo	NNH*
Altered perceptions (confusion, psychosis, hallucinations)	4.5 (95% CI 3.1-6.7)	7
Impaired motor function (speech, ataxia, numbness)	3.9 (95% CI 2.8-5.5)	5
Impaired cognitive function (memory, inattention)	4.5 (95% CI 2.4-8.4)	8

*Number needed to harm

Regulatory:

In the U.S., cannabis is classified as a schedule I drug, and use of any part of the Cannabis plant is illegal by federal law. However, 16 states (listed below) have legalized medical marijuana, which is in conflict with federal law. This federal-state discrepancy in medical marijuana use has not been reconciled.

Alaska	Hawaii	Nevada	Rhode Island
Arizona	Maine	New Jersey	Vermont
California	Michigan	New Mexico	Virginia
Colorado	Montana	Oregon	Washington

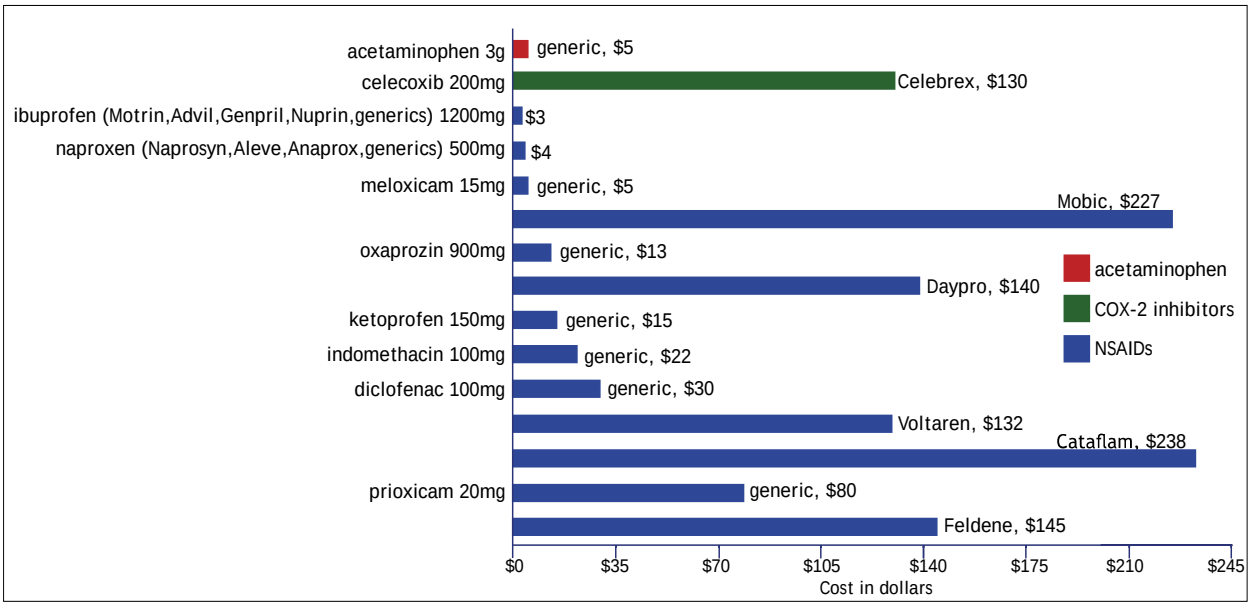
Invasive interventions

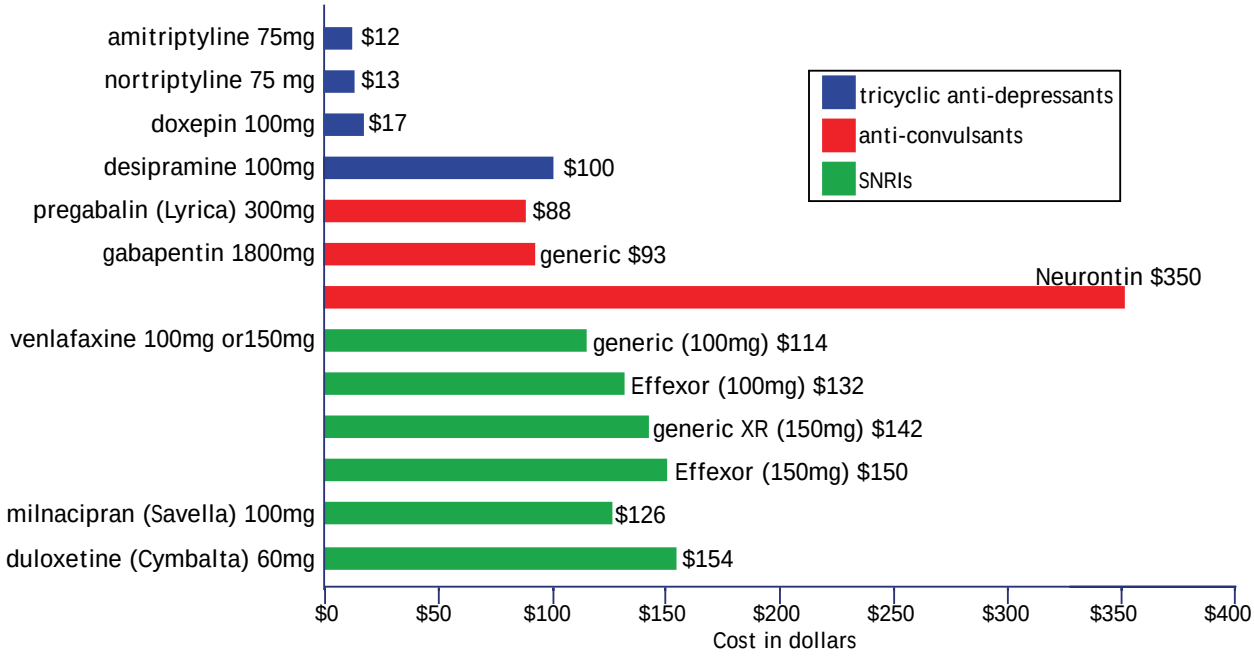
Joint replacement should be considered in patients with severe OA symptoms despite pharmacologic and non-pharmacologic therapies. Often, replacement of a hip or knee will result in very satisfactory pain relief and freedom from dependence of chronic medication use. By contrast,

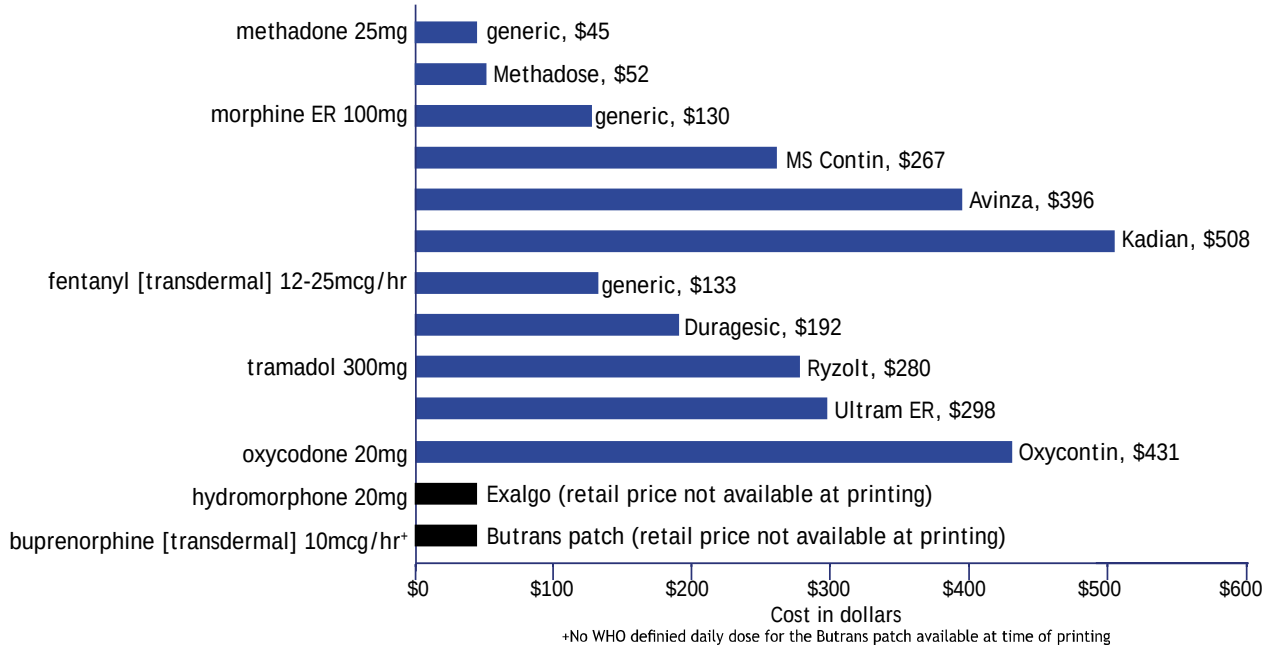
arthroscopic debridement does not improve any outcomes in knee OA,[139,140] and for uncomplicated chronic low back pain, for most patients surgery is no better than exercise therapy in improving long-term disability outcomes .[141]

BOTTOM LINE: Several non-pharmacologic interventions (including exercise) are effective in relieving pain, improving function, or both in OA, fibromyalgia, and chronic low back pain. These options can be pursued based on local availability, cost, and patient preference. For OA, arthroscopy is not effective in reducing pain, but joint replacement can be a powerful means of treating pain in patients who do poorly on medical therapy. Surgery for uncomplicated chronic low back pain should be discouraged.

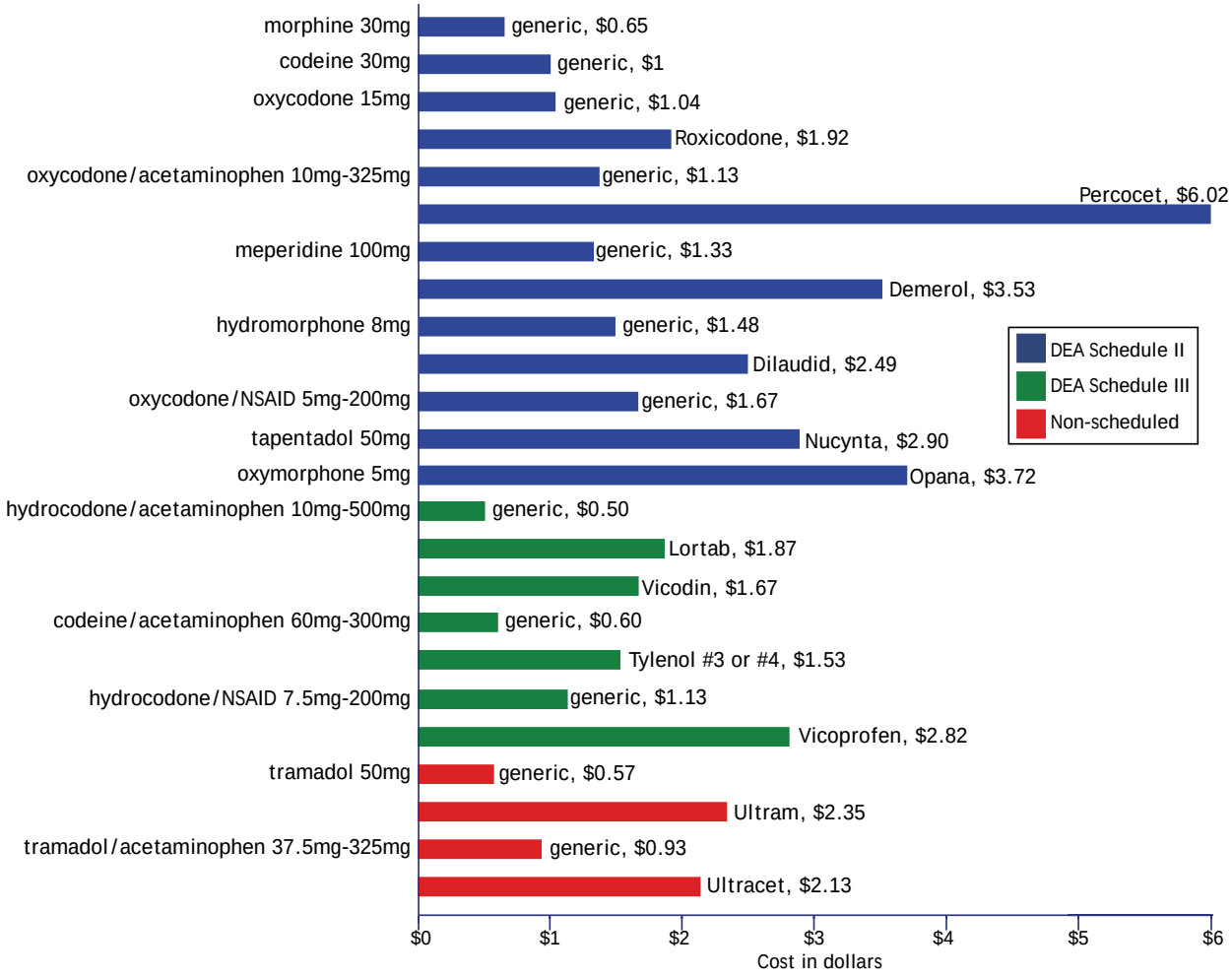
Cost







***The defined daily dose is based on the World Health Organization's average daily maintenance dose of a drug, based on the primary indication of use in adults (available at http://www.whocc.no/atc_ddd_index), June 2011. The lowest available drug cost was obtained from drugstore.com (available at http://www.drugstore.com)**


morphine 30mg
generic, $0.65
codeine 30mg
generic, $1
oxycodone 15mg
generic, $1.04
Roxicodone, $1.92
oxycodone/acetaminophen 10mg-325mg
generic, $1.13
Percocet, $6.02
meperidine 100mg
generic, $1.33
Demerol, $3.53
hydromorphone 8mg
generic, $1.48
Dilaudid, $2.49
oxycodone/NSAID 5mg-200mg
generic, $1.67
tapentadol 50mg
Nucynta, $2.90
oxymorphone 5mg
Opana, $3.72
hydrocodone/acetaminophen 10mg-500mg
generic, $0.50
Lortab, $1.87
Vicodin, $1.67
codeine/acetaminophen 60mg-300mg
generic, $0.60
Tylenol #3 or #4, $1.53
hydrocodone/NSAID 7.5mg-200mg
generic, $1.13
Vicoprofen, $2.82
tramadol 50mg
generic, $0.57
Ultram, $2.35
tramadol/acetaminophen 37.5mg-325mg
generic, $0.93
Ultracet, $2.13
DEA Schedule II
DEA Schedule III
Non-scheduled
$0
$1
$2
$3
$4
$5
$6
Cost in dollars

Value

Key:	Best outcome	Intermediate	Problem

Nocioceptive pain

Drug category	Efficacy	Adverse Effect Profile	Cost	Overall Value
Acetaminophen				
NSAIDs				
Opiates				

Neuropathic pain

Drug Category	Efficacy	Adverse Effect Profile	Cost	Overall Value
Anticonvulsants				
TCAs (low dose)				
SSRIs				
SNRI				

Putting it all together

Basic principles

For all drug treatments, use a low starting dose, and titrate up as needed. Be mindful of expected side effects, and act preventively when appropriate (e.g., laxatives when starting an opiate). In the elderly, increase doses slowly, especially with drugs that have the highest risk of CNS side effects (i.e., opiates and TCAs). The lowest effective dose of any drug should be used, with a shared

understanding between patient and physician of the goals of the pain regimen (adequate pain relief, which may not mean complete resolution of pain). Combinations may be more effective than any single drug alone, and may achieve the goal of adequate pain relief with lower rates of adverse effects. Prescribe generics whenever possible so that patients can afford their medications.

Nocioceptive pain

Based on overall value, acetaminophen should be the first line treatment for most patients with chronic pain. It will adequately relieve pain in many patients and is safe if used at recommended doses (4g/day, or 3g/day in elderly >age 65). A 650mg dose appears to be equivalent to a 1000mg dose. Avoid acetaminophen in patients with chronic liver disease or alcoholism, or those who are fasting. Caution patients about concurrent use of OTC combination products that also contain acetaminophen.

CV RISK	GI RISK	How to manage
+	+	avoid NSAIDs
+	-	naproxen
-	+	Coxib or other NSAID with acid-suppressive med
-	-	any non-selective NSAID

If acetaminophen is inadequate, an NSAID should be initiated if not contraindicated (with continuation of acetaminophen). Avoid NSAIDs in patients with or at risk for cardiovascular disease or GI bleeding; the agent chosen should be based on the patient's risk profile (see box). Many NSAIDs are available as affordable generics.

If an opiate is required, a long-acting drug is preferred over short-acting agents. Before prescribing, assess the risk of addiction; if chronic opiate use is required, execute a medication contract with the patient, reflecting a shared understanding of the goals of therapy and the need for ongoing regular assessments. Transdermal agents and opiate-like agents may have fewer side effects than traditional opiates. There are significant differences the safety profiles of short acting opiates (with tramadol being safer than codeine or hydrocodone in most safety outcomes) but there is less comparative safety data for long-acting opiates. All long-acting opiate choices are expensive (other than methadone which is rarely prescribed by primary care doctors).

Neuropathic pain

Based on overall value, a tricyclic antidepressant is a reasonable first-line treatment for most patients with chronic pain who require a neuropathic agent. Doses should start low and titrate up to desired pain effect, being mindful of adverse effects (primarily anti-cholinergic and sedating); the average effective dose in clinical trials (100mg/day) may be higher than some patients will be able to tolerate. TCAs are contraindicated in patients with cardiovascular disease,

and should not be combined with other serotonergic agents. All are available in affordable generics. Nortriptyline and desipramine have fewer anti-cholinergic side effects, and are preferable in the elderly; amitriptyline is the agent most likely to cause adverse effects in this age group.

If TCAs are inadequate or contraindicated, second line agents include pregabalin, gabapentin, or duloxetine (or milnacipran for fibromyalgia pain). However, all of these agents are expensive, so cost may be limit their affordability for some patients. Despite a favorable safety and cost profile, the SSRIs lack substantial efficacy data and are not routinely recommended for use in chronic pain.

Other agents

Several other pharmacologic and non-pharmacologic agents are available for a variety of chronic pain syndromes, including topical therapies with few adverse effects such as capsaicin and salicylate-based creams (which are affordable), and lidocaine patches and NSAIDs gels and patches (which are more expensive). A number of non-drug approaches (including exercise) can be useful based on availability and patient preferences. Local injections are an alternative for short term relief of localized pain (including OA and chronic low back pain), but the viscosupplements are expensive, and epidural injections require specialty referral. More invasive interventions (such as joint replacement) can be helpful for patients who do poorly on medical therapy. Additional patient pain management resources are available at: www.theacpa.org/9/PainManagementTools.aspx

Glossary of terms

ACR: American College of Rheumatology
AHA: American Heart Association
ASA: Aspirin
COX: Cyclooxygenase
Coxib: Cyclooxygenase-2 Inhibitor
GI: Gastrointestinal
MI: myocardial infarction
NSAID: Non-steroidal anti-inflammatory drug
OA: Osteoarthritis
OTC: Over the counter
RA: Rheumatoid arthritis

Summary of statistical terms

Number needed to treat (NNT): The number of patients needed to treat to benefit 1 patient.

Number needed to harm (NNH): The number of patients needed to treat to harm 1 patient.

Relative risk and hazard ratio (hazard ratio is an estimate of relative risk): The ratio of the probability of an event occurring in one group versus another group.

Odds ratio: The odds of event occurring in one group, compared to the odds of an event occurring in another group.

Effect size: A measure of how far apart two treatment groups are. The smaller the number, the more similar are the 2 groups. Effect sizes are considered small if <0.5

APPENDIX 1, SOAPP-SF (Screener and opioid assessment for patients with pain – short form)

1. How often do you have mood swings?
2. How often do you smoke a cigarette within an hour after you wake up?
3. How often have you taken medication other than the way it was prescribed?
4. How often have you used illegal drugs in the past 5 years (marijuana, cocaine)?
5. How often, in your lifetime, have you had legal problems or been arrested?

0=Never 1=Seldom 2=Sometimes 3=Often 4=Very often

<4 is a Negative screen
4+ is a Positive screen
Sensitivity 86%; Specificity 67% for predicting risk of developing aberrant behavior when prescribed narcotic medication

APPENDIX 2, PADT tool

PROGRESS NOTE
Pain Assessment and Documentation Tool (PADT™)

Patient Stamp Here

Patient Name: _____ Record #: _____

Assessment Date: _____

Current Analgesic Regimen

Drug name	Strength (eg, mg)	Frequency	Maximum Total Daily Dose

The PADT is a clinician-directed interview; that is, the clinician asks the questions, and the clinician records the responses. The Analgesia, Activities of Daily Living, and Adverse Events sections may be completed by the physician, nurse practitioner, physician assistant, or nurse. The Potential Aberrant Drug-Related Behavior and Assessment sections must be completed by the physician. Ask the patient the questions below, except as noted.

Analgesia

If zero indicates "no pain" and ten indicates "pain as bad as it can be," on a scale of 0 to 10, what is your level of pain for the following questions?

1. What was your pain level on average during the past week? (Please circle the appropriate number)

No Pain 0 1 2 3 4 5 6 7 8 9 10 **Pain as bad as it can be**

2. What was your pain level at its worst during the past week?

No Pain 0 1 2 3 4 5 6 7 8 9 10 **Pain as bad as it can be**

3. What percentage of your pain has been relieved during the past week? (Write in a percentage between 0% and 100%.) _____

4. Is the amount of pain relief you are now obtaining from your current pain reliever(s) enough to make a real difference in your life?
❑ Yes ❑ No

5. **Query to clinician:** Is the patient's pain relief clinically significant?
❑ Yes ❑ No ❑ Unsure

Activities of Daily Living

Please indicate whether the patient's functioning with the current pain reliever(s) is Better, the Same, or Worse since the patient's last assessment with the PADT.* (Please check the box for Better, Same, or Worse for each item below.)

	Better	Same	Worse
1. Physical functioning	❑	❑	❑
2. Family relationships	❑	❑	❑
3. Social relationships	❑	❑	❑
4. Mood	❑	❑	❑
5. Sleep patterns	❑	❑	❑
6. Overall functioning	❑	❑	❑

* If the patient is receiving his or her first PADT assessment, the clinician should compare the patient's functional status with other reports from the last office visit.

(Continued on reverse side)

PROGRESS NOTE
Pain Assessment and Documentation Tool (PADT™)

Adverse Events

1. Is patient experiencing any side effects from current pain reliever(s)? ❑ Yes ❑ No

Ask patient about potential side effects:

	None	Mild	Moderate	Severe
a. Nausea	❑	❑	❑	❑
b. Vomiting	❑	❑	❑	❑
c. Constipation	❑	❑	❑	❑
d. Itching	❑	❑	❑	❑
e. Mental cloudiness	❑	❑	❑	❑
f. Sweating	❑	❑	❑	❑
g. Fatigue	❑	❑	❑	❑
h. Drowsiness	❑	❑	❑	❑
i. Other _____	❑	❑	❑	❑
j. Other _____	❑	❑	❑	❑

2. Patient's overall severity of side effects?
❑ None ❑ Mild ❑ Moderate ❑ Severe

Potential Aberrant Drug-Related Behavior

This section must be completed by the physician.

Please **check** *any of the following items that you discovered during your interactions with the patient. Please note that some of these are directly observable (eg, appears intoxicated), while others may require more active listening and/or probing. Use the "Assessment" section below to note additional details.*

- ❑ Purposeful over-sedation
- ❑ Negative mood change
- ❑ Appears intoxicated
- ❑ Increasingly unkempt or impaired
- ❑ Involvement in car or other accident
- ❑ Requests frequent early renewals
- ❑ Increased dose without authorization
- ❑ Reports lost or stolen prescriptions
- ❑ Attempts to obtain prescriptions from other doctors
- ❑ Changes route of administration
- ❑ Uses pain medication in response to situational stressor
- ❑ Insists on certain medications by name
- ❑ Contact with street drug culture
- ❑ Abusing alcohol or illicit drugs
- ❑ Hoarding (ie, stockpiling) of medication
- ❑ Arrested by police
- ❑ Victim of abuse

Other: _____

Assessment: (This section must be completed by the physician.)

Is your overall impression that this patient is benefiting (eg, benefits, such as pain relief, outweigh side effects) from opioid therapy? ❑ Yes ❑ No ❑ Unsure

Comments: _____

Specific Analgesic Plan:

- ❑ Continue present regimen
- ❑ Adjust dose of present analgesic
- ❑ Switch analgesics
- ❑ Add/Adjust concomitant therapy
- ❑ Discontinue/taper off opioid therapy

Comments: _____

Date: _____ Physician's signature: _____

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APPENDIX 3, Sample Pain Management Agreement Form

Opiate Contract Pain Management Agreement

The purpose of this agreement is to prevent misunderstandings about certain medications you will be taking for pain management. This is to help you and your doctor to comply with the law regarding controlled pharmaceuticals.

_____ I understand that this Agreement is essential to the trust and confidence necessary in a doctor/patient relationship and that my doctor undertakes to treat me based on this Agreement.
_____ I understand that if I break this Agreement, my doctor will stop prescribing these pain control medicines.
_____ In this case, my doctor will taper off the medicine over a period of several days, as necessary, to avoid withdrawal symptoms. Also, a drug-dependence treatment program may be recommended.
_____ I would also be amenable to seek psychiatric treatment, psychotherapy, and/or psychological treatment if my doctor deems necessary.
_____ I will communicate fully with my doctor about the character and intensity of my pain, the effect of the pain on my daily life, and how well the medicine is helping to relieve the pain.
_____ I will not use any illegal controlled substances, including marijuana, cocaine, etc., nor will I misuse or self-prescribe/medicate with legal controlled substances. Use of alcohol will be limited to time when I am not driving, operating machinery and will be infrequent.
_____ I will not share my medication with anyone.
_____ I will not attempt to obtain any controlled medications, including opiod pain medications, controlled stimulants, or anti-anxiety medications from any other doctor.
_____ I will safeguard my pain medication from loss or theft. Lost or stolen medications will not be replaced.
_____ I agree that refills of my prescriptions for pain medications will be made only at the time of an office visit or during regular office hours. No refills will be available during evenings or on weekends.

I agree to use: _____(Name of Pharmacy),
Located at: _____,
Telephone number: _____ for filling my prescriptions for all of my pain medicine.

_____ I authorize the doctor and my pharmacy to cooperate fully with any city, state or federal law enforcement agency, including this state's Board of

Pharmacy, in the investigation of any possible misuse, sale, or other diversion of my pain medication. I authorize my doctor to provide a copy of this Agreement to my pharmacy, primary care physician and local emergency room. I agree to waive any applicable privilege or right of privacy or confidentiality with respect to these authorizations.

_____ I agree that I will submit to a blood or urine test if requested by my doctor to determine my compliance with my program of pain control medications.
_____ I agree that I will use my medicine at a rate no greater that the prescribed rate and that use of my medicine at a greater rate will result in my being without medication for a period of time.
_____ I will bring unused pain medicine to every office visit.
_____ I agree to follow these guidelines that have been fully explained to me.

All of my questions and concerns regarding treatment have been adequately answered. A copy of this document has been given to me.

This Agreement is entered into on this _____ day of _____, 2004.

Patient signature:

_____

Physician signature:

_____

Witnessed by:

_____

Reproduced from www.sdcpms.com/pdf/form_sample_opiate_contract.pdf.

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