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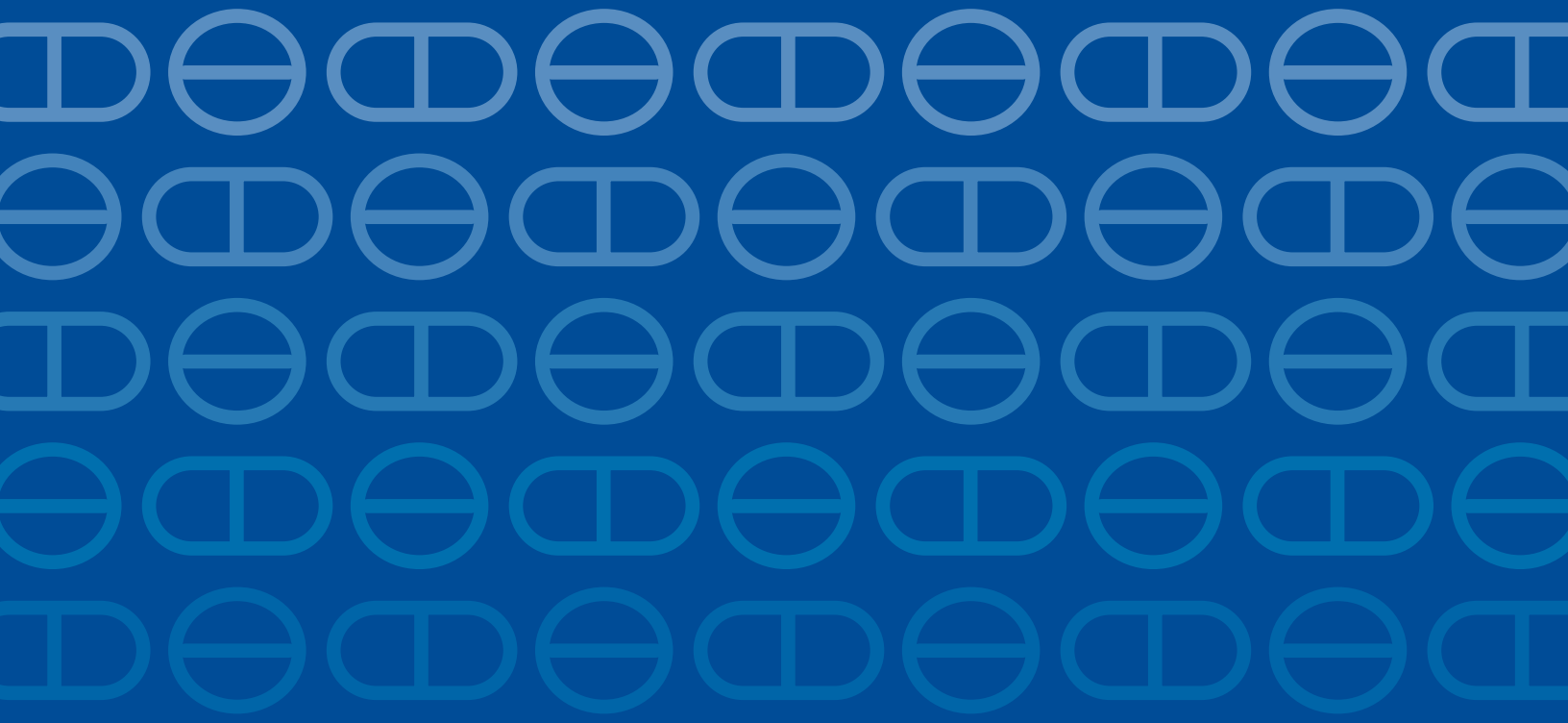
Managing pain without overusing opioids

Implementing safe, effective, and less risky analgesic strategies



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Principal Consultant: Brian Bateman M.D., M.Sc.

Series Editors: Jerry Avorn, M.D., Niteesh K. Choudhry, M.D., Ph.D., Michael Fischer, M.D., M.S., Eimir Hurley, BSc (Pharm), MBiostat, Ellen Dancel, PharmD, M.P.H.

Medical Writer: Stephen Braun

Reviewers: Jane Ballantyne, M.D., F.R.C.A., Jason Block, M.D., M.P.H.

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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.

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Alosa Foundation

Managing pain without overusing opioids

Activity overview:

The primary goal of this educational program is to address the increase in opioid prescribing by reducing the number of people inappropriately started on opioids, tapering and discontinuing opioids in patients who are not achieving functional goals, have serious side effects, or exhibit problematic behavior as well as appropriately screening and monitoring patients who require chronic opioid therapy.

In addition to providing this evidence report, the education program uses an innovative approach, academic detailing, one-on-one educational sessions with specially trained outreach educators (pharmacists, nurses, physicians) who present the educational material interactively. Reference cards for clinicians and education materials for family members are also provided.

Key messages of the module:

1. Describe acute pain management, focusing on non-steroidal anti-inflammatory drugs, acetaminophen, and non-pharmacologic approaches, using opioids only when acute pain is severe and then only for a short duration.

2. Use pharmacologic and non-pharmacologic alternatives to opioids first, resorting to chronic opioid therapy only for severe pain when other alternatives are inadequate.

3. Integrate patient screenings for risk of abuse or misuse before initiating opioid therapy, and periodically during treatment; counsel patients about opioid side effects, safe storage and disposal.

4. Specify clear functional goals and realistic expectations as part of a comprehensive pain management plan when prescribing opioids.

5. Assess patient progress toward functional goals, tapering and discontinuing opioids whenever possible, and particularly in patients who have severe side effects or exhibit problematic behavior.

Disclosures:

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Faculty and Planners:

Jerry Avorn, M.D., is a Professor of Medicine at Harvard Medical School and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 30 years. Dr. Avorn has no relevant financial relationships to disclose.

Niteesh K. Choudhry, M.D., Ph.D., is an Associate Professor of Medicine at Harvard Medical School and a hospitalist at Brigham and Women's Hospital. His research focuses on the use of medications to treat common chronic conditions. Dr. Choudhry has no relevant financial relationships to disclose.

Michael Fischer, M.D., M.S., is an Associate Professor of Medicine at Harvard Medical School and a primary care internist who studies cost–effective drug use in outpatient practices. Dr. Fischer has no relevant financial relationships to disclose.

Brian Bateman, M.D., M.Sc., is an Assistant Professor of Anesthesia at Harvard Medical School. He is a researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and an anesthesiologist at Massachusetts General Hospital. Dr. Bateman has no relevant financial relationships to disclose.

Eimir Hurley, BSc (Pharm), MBiostat is the Program Director at the Alosa Foundation. Her interest lies in the design, implementation and evaluation of programs to improve prescribing. Ms. Hurley has no relevant financial relationships to disclose.

Ellen Dancel, PharmD, M.P.H., is the Director of Clinical Materials Development at the Alosa Foundation. Ms. Dancel has no relevant financial relationships to disclose.

Stephen R. Braun, B.A., is a medical writer based in Amherst, MA. Mr. Braun has no relevant financial relationships to disclose.

Reviewers:

Jane C. Ballantyne, M.D., F.R.C.A., is a retired Professor of Anesthesiology and Pain Medicine at the University of Washington in Seattle. She is currently the President of Physicians for Responsible Opioid Prescribing (PROP). Dr. Ballantyne has no relevant financial relationships to disclose.

Jason Block, M.D., M.P.H., is an Assistant Professor at Harvard Medical School and the Harvard Pilgrim Health Care Institute. He is a primary care internist at Brigham and Women's Hospital and also works in the Brigham and Women's Program for Weight Management. Dr. Block has no relevant financial relationships to disclose.

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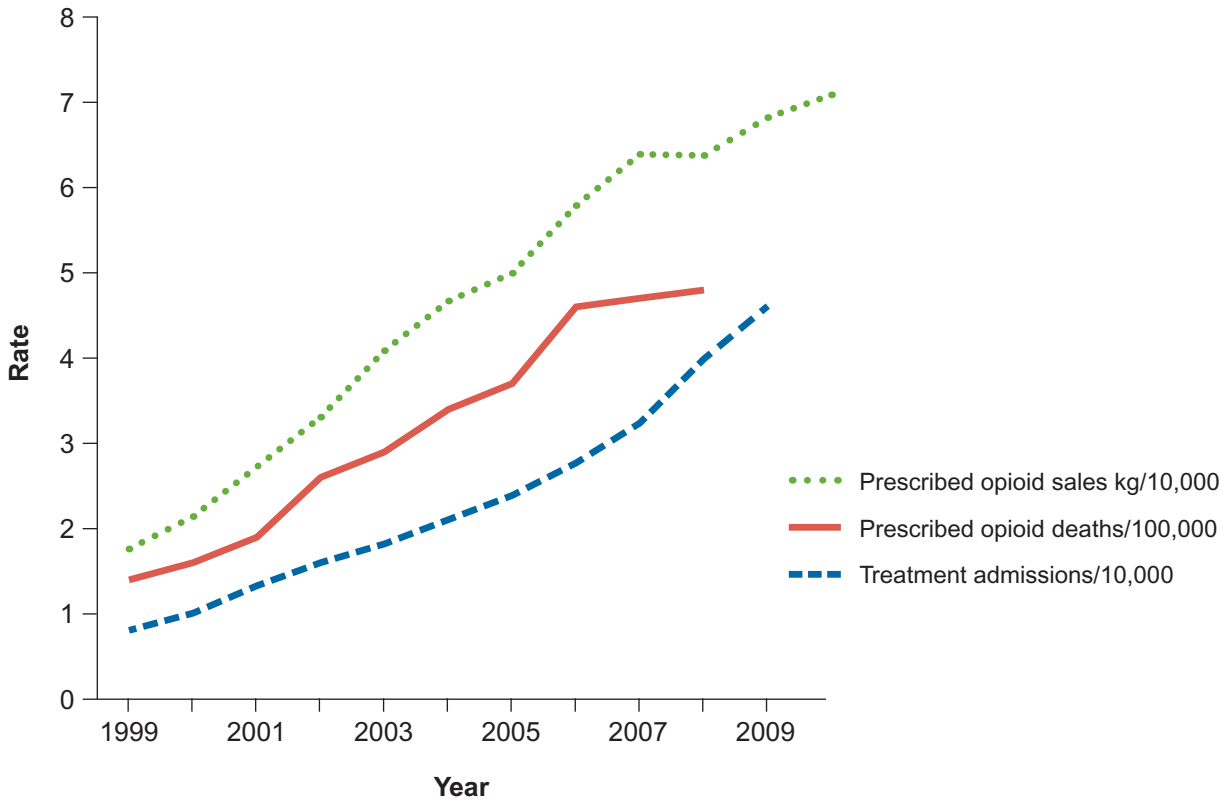
Scope of the opioid epidemic

The use of opioid analgesics quadrupled in the United States between 1999 and 2010.[2] Much of this expanded use has been for the treatment of pain beyond moderate-to-severe acute pain or intractable end-of-life pain, for which opioids have historically been used. In the past two decades, opioids have been widely prescribed for chronic non-cancer conditions, such as back pain, osteoarthritis, fibromyalgia, and headache.[3] The evidence base supporting such a vastly expanded use, however, is weaker than was generally appreciated or acknowledged by many physicians until recently.[4]

As opioid prescriptions have risen, so, too, have rates of opioid abuse, addiction, and diversion for non-medical use. The current level of prescription opioid abuse has been described as an "epidemic" by the Centers for Disease Control and Prevention.[2]

Figure 1. Rates* of opioid pain reliever (OPR) overdose death, treatment admissions, and kilograms sold in the United States, 1999-2010[2]



* Age-adjusted rates per 100,000 population for prescribed opioid deaths, crude rates per 10,000 population for treatment admissions related to prescribed opioid abuse, and crude rates per 10,000 population for kilograms of prescribed opioid sold.

Between 1998 and 2008, the rate of opioid misuse* increased 400%.[5] In 2009, about 7 million Americans were abusing prescription drugs (5.1 million of whom were abusing pain relievers)—more than the number abusing cocaine, heroin, hallucinogens, and inhalants, combined.[6]

Strikingly, despite a 104% increase in opioid analgesic prescriptions in the U.S. (from 43.8 million in 2000 to 89.2 million in 2010) no improvements in disability rates or health status measures of opioid users has been demonstrated.[7]

The rising tide of abuse and addiction, coupled with growing evidence that opioids are not effective for many patients in chronic pain, has led to a re-evaluation of opioid prescribing practices. In July 2012, the U.S. Food and Drug Administration (FDA) released its Risk Evaluation and Mitigation Strategies (REMS) guidelines for prescriber education related to extended-release (ER) and long-acting (LA) opioid analgesics.[8] In 2013, some Schedule III opioid combination products containing hydrocodone (e.g., Vicodin®, Lortab®) were reclassified to Schedule II in an effort to tighten control. The following day, however, the FDA approved a new extended-release high-dose hydrocodone-only product that has no abuse-deterrent features, a move that has sparked controversy at both state and federal levels.[9,10]

Importance of effectively treating pain

Despite both the rising abuse and greater regulation of opioids, many patients still suffer from pain. Pain remains the most common reason people seek health care.[11] Chronic pain was estimated in a 2011 Institute of Medicine report to affect approximately 100 million Americans and to cost roughly $635 billion annually in treatment and lost productivity.[12] In fact, the incidence of chronic pain in the U.S. is estimated to be greater than that of diabetes, heart disease, and cancer combined.[13,14]

Inadequately treating pain can lead to a wide range of adverse consequences (in addition to causing needless suffering) including diminished quality of life, and a higher risk for anxiety or depression.[15] Pain is also a major cause of work absenteeism, underemployment, and unemployment.[11]

Barriers at many levels continue to thwart the accurate assessment and effective treatment of patients with a wide range of painful conditions. Time pressures often hinder clinicians from performing the in-depth history and careful assessment of comorbid conditions necessary for accurate diagnosis and effective treatment of patients with chronic pain.

Despite these barriers, clinicians must treat their patients in pain, and they must confront the complexities of helping patients in chronic pain find relief in ways that are safe, sustainable, and supportive of the patient's overall quality of life. Opioid analgesics may—or may not—play a role in this effort. Opioids do not address all of the physical and psychosocial dimensions of chronic pain, and they pose a wide range of potential adverse effects, including challenging side effects and the risk of abuse, addiction, and death.

This evidence document outlines core principles of responsible pain management in the primary care setting that can improve the quality of care, while minimizing the risks that opioids pose to patients and society. As such, this document focuses on the pharmacologic and non-pharmacologic treatment options generally available in the primary care setting. Cognitive/behavioral approaches, rehabilitative approaches, and

* Misuse is defined as use of prescription drugs that were not prescribed for the person using them or the use of these drugs recreationally and not for medical necessity.

invasive or surgical treatments for pain conditions are not covered in this monograph, although these options may be both appropriate and very helpful for certain patients.

Key terms

Pain is often classified by how long it lasts. *Acute* pain is caused by obvious tissue injury and typically fades with healing. *Chronic* pain lasts longer than would be expected for the usual course of a condition or lasts longer than arbitrary cut-off times such as 3 months.[3] Another, and perhaps more useful, perspective is to classify pain patho-physiologically. *Nociceptive pain* is caused by the normal activation of nociceptors, and is thus generally, though not always, short-lived and associated with tissue damage, irritation, or inflammation.[16] *Neuropathic* pain arises from nerve injury or neural adaptation to chronic painful stimulation. It may be continuous or episodic and varies widely in its subjective feel (e.g., burning, tingling, sharp, dull).[16]

One form of neural adaptation to chronic painful stimulation is *sensitization*: a state of hyperexcitability in either peripheral nociceptors or spinal cord nerves. Sensitization may lead to either hyperalgesia (increased pain from a painful stimulus) or allodynia (pain from a stimulus that is not normally painful).[17] Sensitization may arise from intense, repeated, or prolonged stimulation of nociceptors, or from the influence of compounds released by the body in response to tissue damage or inflammation.[18] It may also, paradoxically, result from long-term use of opioid analgesics.[19]

Differentiating between nociceptive and neuropathic pain is helpful because neuropathic pain typically responds poorly to non-steroidal anti-inflammatory (NSAID) agents, and, conversely, may respond well to agents that diminish neural hypersensitivity such as anticonvulsants and antidepressants, obviating the need for opioids.[20,21,22] Primary care clinicians should be aware that some patients, particularly those with chronic pain, may experience both nociceptive and neuropathic pain, which complicates assessment and treatment.

Related to the nomenclature of pain are terms commonly used by both patients and clinicians in the context of opioid analgesics. Because these terms are frequently misunderstood, the American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS) have recommended the following definitions:[23]

- **Aberrant drug-related behavior.** A behavior outside the boundaries of an agreed-upon treatment plan.
- **Abuse**. Any use of a drug, or the intentional self-administration of a medication, for a nonmedical purpose such as pleasure-seeking or altering one's state of consciousness.
- **Addiction.** A chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations, characterized by behaviors that include one or more of the following: craving, impaired control over drug use, compulsive use, and continued use despite harm.
- **Chronic opioid therapy.** Daily or near-daily use of opioids for at least 90 days.
- **Diversion.** The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.
- **Misuse.** Use of a medication other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.
- **Physical Dependence.** A state of physical adaptation (tolerance) that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- **Tolerance.** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

BOTTOM LINE: rates of opioid-related overdose deaths are at all-time highs. The unselective use of opioid analgesics for chronic non-cancer pain, promoted for years, is now being reconsidered. Primary care physicians must recognize that some patients and some pain conditions are unlikely to benefit from chronic opioid therapy.

Pain treatment options in primary care

Primary care clinicians can draw upon a wide range of pharmacologic and non-pharmacologic approaches to treating painful conditions. The following general principles can help guide treatment choice and ongoing pain management:

- Identify and treat the source of the pain, if possible, although treatment can begin before the source of the pain is determined
- Select the simplest approach to pain management. This generally means using non-pharmacologic approaches as much as possible and/or trying medications with the least severe potential side effects first, and at the lowest effective doses
- Establish a function-based management plan if treatment is expected to be long-term

These principles will be discussed in greater detail in the following sections devoted to specific treatment options.

Acetaminophen

Acetaminophen, first introduced in the US market in 1953, has been one of the most widely-used over the counter (OTC) medications worldwide. Most acetaminophen is sold OTC (80%), while the remaining 20% is sold in prescription combination products.

Efficacy

While sometimes 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 osteoarthritis (OA), with a small effect size (-0.13; 95% CI: 0.22 to -0.04).[24] Although “extra strength” doses (500 mg x 2) are widely promoted, the bulk of the evidence indicates that doses of 1000 mg are no better than 650 mg in relieving mild to moderate pain, which is significant because higher doses increase the potential for adverse events, especially in combination with other acetaminophen-containing products.

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.[24] 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.[25] 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.

The threshold dose for acetaminophen liver toxicity has not been established, although the FDA recommends that the total adult daily dose should not exceed 4 g/day in patients without liver disease (although a ceiling of 3 g/day is suggested for older adults).[26]

In 2009, the FDA required manufacturers of products containing acetaminophen to revise their product labeling to include warnings about the risks of severe liver damage associated with its use. In 2014, new FDA rules went into effect that set a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g. Vicodin and Percocet) in an attempt to limit liver damage and other ill effects from the use of these products.[26] Despite the new labels and rules, patients are often unaware of the presence of acetaminophen in combination products, and may be unaware, as well, of the dangers of high doses of acetaminophen, hence clinicians should address these issues when discussing such medications with patients.

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 4 g/day, or 3 g/day in patients older than age 65. The drug should be completely avoided in alcoholics, patients with decreased oral intake of food, or those with chronic liver disease.[27, 28] In 2009, an FDA advisory panel recommended that the maximum single dose of acetaminophen should not exceed 650 mg, reserving the 1000 mg dose for prescription use only.

BOTTOM LINE: acetaminophen is modestly more effective than placebo in pain relief, and very safe at recommended doses. No evidence shows that a dose of 1000 mg is significantly more effective than 650 mg, and the total daily dose should not exceed 4 g/day in younger adults and 3 g/day in the elderly (older than age 65). Acetaminophen should be avoided in patients with chronic liver disease or alcoholism, and when fasting. Patient education about the risks of acetaminophen is critical, particularly when combination products are prescribed.

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.[29,30]

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. 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. Of note, aspirin (>325 mg/d), ibuprofen, ketoprofen, naproxen, and other non-COX-selective NSAIDs, are listed as “Potentially Inappropriate Medications” for use in older adults in the American Geriatrics Society 2012 Beers Criteria because of the range of adverse effects they can have at higher doses.[31]

Efficacy

NSAIDs are moderately effective in reducing pain from a variety of conditions. While most studies compare an NSAID with a placebo, no consistent evidence shows 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.[32] In the treatment of chronic low back pain, NSAIDs are also significantly better than placebo, with a mean difference (between groups) in pain scale scores of 12 (on a 100 point scale).[33]

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).[34] A Cochrane review found celecoxib had equivalent analgesic efficacy to non-selective NSAIDs in RA, all of which were superior to placebo.[32] Other meta-analyses have found no evidence of superiority of one NSAID over another in the treatment of low back pain, osteoarthritis (OA) or rheumatoid arthritic (RA).[33,35] 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 (two highly COX-2 selective NSAIDS, valdecoxib and rofecoxib, were withdrawn from the market because of their high cardiac risk). NSAIDS that are more highly COX-1 selective have lower CV risk, but higher risk for gastrointestinal toxicity. The risk of GI bleeding may be mitigated by adding a proton-pump inhibitor (PPI).[36,37]

BOTTOM LINE: all NSAIDs can provide moderate pain relief and are more effective than placebo. 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 is achieve by using celecoxib alone. 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.

Topical agents

Capsaicin

Capsaicin is a naturally-occurring component of hot peppers that locally depletes substance P, and results in modest improvements in painful diabetic neuropathy, post-herpatic neuralgia, and other types of neuropathic pain. 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%).[38]

However, 2 subsequent randomized placebo controlled trials did not find any pain benefit with capsaicin.[39,40] 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 (note: this dose is applied by physicians after first numbing the target region).

Local skin reactions are very common, but tolerable, and usually attenuate over time. Systemic adverse effects are rare.[41] Some have questioned whether the obvious local reactions make it impossible to have a truly blinded randomized trial of these agents. Capsaicin creams are available over the counter, 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 such as musculoskeletal and arthritis pain. A systematic review found only weak evidence that short term use of these agents in acute pain from strains, sprains and sports injuries was more effective than placebo (number needed to treat of 3.2 for acute pain and 6.2 for chronic conditions compared with topical placebo).[42] Side effects were minor and well-tolerated and these preparations are available over the counter at relatively low cost.[43]

Topical NSAIDs

Diclofenac is available in gel and patch form for local pain relief. A meta-analysis found this topical NSAID was less effective than oral NSAIDs for pain relief, although 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 superior efficacy compared to placebo.[44]

Lidocaine

Lidocaine patches reduce discharges in superficial nerves, and have been reported to reduce pain and improve quality of life in patients with post-herpetic neuralgia and painful diabetic neuropathy.[45] Up to 3 patches can be applied at a time for up to 12 hours a day. Each patch is 10cm by 14cm, but can be cut into smaller sizes before application.

BOTTOM LINE: topical capsaicin and salicylates can both be effective for short term pain relief and generally have fewer side effects than oral analgesics, but their long term efficacy is not well studied. Topical NSAIDs and lidocaine have been reported to be effective for short term relief of superficial pain with minimal side effects, although both are more expensive than topical capsaicin and salicylates. None of the topical agents are useful for non-superficial pain.

Antidepressants

Some antidepressants exhibit analgesic properties, possibly via indirect effects on opioid receptors or interactions with NMDA receptors. Their analgesic actions do not depend on antidepressant activity, and antidepressants are equally effective in patients with and without depression.[46] While analgesia may occur at lower doses and sooner than antidepressant activity, maximum efficacy may require high antidepressant doses and treatment of potentially lengthy duration.

Indications and uses

Tricyclic antidepressants (TCAs) such as amitriptyline, nortriptyline, and imipramine, are used to treat a variety of types of chronic and neuropathic pain.[47] Although often considered most effective for continuous burning pain or hypersensitivity conditions, TCAs also may relieve lancinating neuropathic pain.[48]

Table 1: Overview of anti-depressants for pain management

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	None
		venlafaxine: not approved for chronic pain	DM neuropathy polyneuropathy
		milnacipran: FMG	None

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:[49]

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

A systematic review found about a third of all patients treated with a TCA achieved at least a 50% improvement in neuropathic pain.[50] There are no significant differences in efficacy between the different TCAs.[49,51]

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 doses should be titrated cautiously***.

TCAs can also cause cardiac conduction abnormalities and should be avoided in patients with existing cardiac disease.

Selective serotonin reuptake inhibitors (SSRIs)

Efficacy

Paroxetine and citalopram appear to be 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.[49,50]

Safety

The SSRIs are associated with weight gain, sexual dysfunction, and a 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 for relieving 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.[52] 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).[53]

Safety

The most common side effects include nausea, somnolence, dizziness, constipation, and decreased appetite. These side effects are dose-dependent, and in clinical trials led to discontinuation of the drug in 16% of patients.[53]

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 daily dose of 150mg to 225mg; no difference was seen between placebo and a 75mg dose of venlafaxine). The NNT to achieve 50% reduction in pain was 4.5.[54] 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.[55]

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).[56,57]

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. Fewer data exist 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.

Anticonvulsants

The increasing use of antiepileptic drugs (AEDs) for neuropathic pain is based on their ability to reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.[58] The exact mechanism of action for their analgesic effects, however, is unclear. It does not appear to be specifically related to their antiepileptic activity. Other drugs that suppress seizures (e.g., barbiturates) do not relieve pain, and some AEDs with effective antiepileptic activity do not necessarily have good analgesic activity.[22]

Indications and uses

AEDs are used to treat neuropathic pain, especially lancinating (i.e., episodic shooting, stabbing, or knife-like) pain from peripheral nerve syndromes.

Table 2: 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 daily dose of 150 mg to be no more effective than placebo, but daily doses of 300-600 mg were significantly better than placebo.[59]

Safety

The most common side effects include peripheral edema, weight gain, and CNS side effects (including dizziness, somnolence, ataxia, and headache). At 600 mg doses:[59]

- somnolence occurs in 15-25% of patients
- dizziness occurs in 27%-46%
- treatment discontinuation occurred in 18%-28%

Gabapentin

Efficacy

Gabapentin effectively reduces diabetic neuropathic pain; 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.[60] 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 1600 mg/day).[61] 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).[62] 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).[63]

Safety

In randomized trials, the frequency of withdrawals due to adverse effects was not significantly different from that seen in control groups.[63] Side effects are primarily neurological. In a randomized trial:[60]

- dizziness occurred in 24% (vs. 5% of placebo)
- somnolence occurred in 23% (vs. 6% of placebo)
- confusion occurred in 8% (vs.1% of placebo).

Carbamazepine

Efficacy

A Cochrane review assessed 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.[64]

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 were nausea, dizziness, and rash.

Others

Lamotrigine, topiramate, valproate, phenytoin, and oxcarbazepine are not FDA-approved for use in any chronic pain syndromes, and all lack adequately-sized randomized controlled trial data to support their use.[65,66,67]

BOTTOM LINE: pregabalin and gabapentin can be effective in the treatment of diabetic neuropathy, post-herpetic neuralgia, and fibromyalgia. Limited data 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.

Cannabis

Efficacy

Cannabis sativa has been used for centuries to treat ailments ranging from nausea to glaucoma. Its leaves or flower buds can be smoked, vaporized, or taken by mouth (by blending into food products or put into blank capsules). However, evidence assessing the medicinal value of cannabis is limited due to legal restrictions on the clinical research that could be performed on these products.[135]

Cannabinoids act, at least in part, through an opioid receptor mechanism that increases dopamine concentrations in the nucleus accumbens.[68] 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.[69] However, the individual studies were small (sample size ranging from 10-177), short-term (mean duration 25 days) and of overall poor methodological 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. No significant differences for dysphoria were observed between cannabis and placebo. Side effects of cannabis included euphoria, alterations in perception, events relating to cognitive function, and events concerning motor function.

Lynch et al., in a 2011 systematic review of RCTs of cannabinoids for CNCP, found 15 of 18 trials demonstrated "significant analgesic effects compared to placebo."[70] Adverse effects in this review were generally well-tolerated, and cannabinoids were found to be "moderately effective" in neuropathic pain.

Cannabis has been used to help stabilize patients on methadone maintenance treatment and cannabis use has been associated with modest reductions in opioid withdrawal symptoms for such patients.[71] Cannabis use has also been associated, on a state-wide level, with reduced rates of opioid overdose. Bachhuber et al., in a time-series analysis, found that between 1999 and 2010 states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI: −37.5% to −9.5%; p=0.003) compared with states without medical cannabis laws.[72]

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).[73]

Opioids

Opioid mechanisms of action

Opioid analgesics work by binding to one or more of the three major types of opioid receptors in the brain and body: mu, kappa, and delta receptors. Opioids inhibit both ascending transmission of nociceptive information as well as descending pain control circuits. The most common opioid pain medications are "mu agonists" because they bind to and activate mu opioid receptors. Mu agonists include morphine, codeine, hydromorphone, and hydrocodone. The partial agonist buprenorphine has high affinity, but low efficacy, at the mu receptor and is also a kappa receptor antagonist, which contributes to its utility as an abuse deterrent.[74] Pentazocine, nalbuphine, and butorphanol are agonist/antagonists with poor mu receptor efficacy but which are full agonists for kappa receptors. These agents thus have a ceiling whereby increasing dose leads to increasing side effects with minimal effects on analgesia. The antagonists naloxone and naltrexone competitively bind to opioid receptors, blocking or disrupting agonists without causing the receptor to respond.

The binding of mu agonist opioids to receptors in various body regions results in both therapeutic effects (such as pain relief) and side effects (such as constipation). Tolerance develops for some effects of opioids,

but not others. For example, some tolerance develops to respiratory suppressant effects within 5-7 days of continuous use, whereas tolerance to constipating effects never occurs. Tolerance to analgesia may develop early, requiring an escalation of dose, but tolerance may lessen once an effective dose is identified and administered regularly, as long as the associated pathology or condition is stable.[75]

General considerations in opioid selection

Opioids as a class include many specific agents available in a wide range of formulations and routes of administration, including:

- Oral (e.g., tablets, capsules, solutions, lollipops)
- Transdermal
- Transmucosal
- Rectal
- Intrathecal

Little evidence exists that specific analgesic formulations or dosing schedules affect efficacy or addiction risk, so selection of agent should be based on the patient's pain complaint, lifestyle, and preferences.[76] Generally, if opioids are used at all, it is better to offer short-acting opioids PRN. Long-acting (LA) or extended-release (ER) opioids may be helpful for patients who have difficulty managing an "as needed" regimen, or who are physically dependent on opioid analgesics and require continued use to maintain their functioning.

Scheduled long-acting opioids have the advantage of producing a steady state, without the cycling effect of pain relief and withdrawal associated with short-acting opioids, which could, theoretically, lead to problematic behavior patterns.[77] With LA/ER agents, however, patients may end up using more drug than is actually needed, and adaptations to the steady state may ultimately decrease efficacy.[78] Clinicians should warn patients that oral ER/LA opioids should not be broken, chewed, or crushed, and patches should not be cut or torn prior to use, since this may lead to rapid release of the opioid and could cause overdose or death.

Table 3: Long acting and Immediate release opioids

Long acting opioids	Immediate release opioids
Buprenorphine patch (Butrans)	Codeine (generics)
Fentanyl patch (Duragesic)	Fentanyl – transmucosal (Abstral, Actiq, Fentora, Lazanda, Onsolis, Subsys)
Hydrocodone (Zohydro ER)	Hydrocodone+acetaminophen (generics, Norco, Vicodin, Xodol)
Hydromorphone ER (generics, Exalgo)	Hydromorphone (generics, Dilaudid)
Methadone (generics, Dolophine, Methadose)	Levorphanol (generics)
Morphine ER (generics, Avinza, Kadian, MS Contin)	Meperidine (generics, Demerol, Meperitab)
Oxycodone (Oxycontin)	Morphine (generics)
Oxymorphone ER (generics, Opana ER)	Oxycodone (generics, Roxicodone)
Tapentadol (Nucynta ER)	Oxymorphone (generics, Opana)
Tramadol ER (generics, ConZip, Ultram ER)	Tapentadol (Nucynta)
	Tramadol (generics, Ultram)

Prescribers considering ER/LA opioid products should consider carefully the general characteristics, toxicities, and drug interactions for these agents. [For detailed information on current ER/LA opioid analgesics, see the FDA Blueprint for Prescriber Education, available at: er-la-opioidrems.com]. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for safer administration of opioid analgesics. Methadone can be an effective opioid, but it must be prescribed carefully and with full knowledge of its highly variable pharmacokinetics and pharmacodynamics.

Combination products join an opioid with a non-opioid analgesic, usually for use in patients with moderate pain. Using a combination product when dose escalation is required risks increasing adverse effects from the non-opioid co-analgesic, even if an increase of the opioid dose is appropriate. In such cases, using a pure opioid is preferable. Care, in particular, must be given to not exceed maximal daily doses of acetaminophen.

Abuse-deterrent formulations

Concern about opioid misuse and abuse has spurred efforts to create abuse-deterrent opioid formulations. Two agents are currently available, which are co-formulated with an antagonist: Targiniq ER (oxycodone and naloxone) and Embeda ER (morphine and naltrexone). The abuse-deterrent forms of long-acting oxycodone also contain a polymer that makes the pill difficult to crush, snort, or melt for injection. Transdermal opioid formulations were thought to be less vulnerable to misuse, but such formulations *can* be abused.[79] Abuse-deterrent opioid formulations do not prevent users from simply consuming too much of a medication or using it without a prescription.

Opioids as scheduled substances

The Controlled Substances Act of 1970 places all substances which were in some manner regulated under existing federal law into one of five schedules (with the exceptions of alcohol and tobacco). This placement is based upon the substance's perceived medical use, potential for abuse, safety, and risk of inducing dependence. Schedule I drugs are deemed to have a high potential for abuse and no accepted medical use in the U.S. Schedule II drugs have a high potential for abuse but *do* have an accepted medical use. Schedule II drugs require written or electronic prescriptions meeting DEA requirements, and automatic refills are not allowed. Schedules III through IV are drugs posing, respectively, lower risks of abuse or dependence, and refills are permitted, although not for more than 5 refills in 6 months.

Table 4: Common opioids by schedule

Schedule	Opioid
Schedule I	Heroin Cocaine
Schedule II	Hydrocodone Oxycodone Morphine Hydromorphone Tapentadol
Schedule III	Buprenorphine Codeine + acetaminophen
Schedule IV	Tramadol

Patient education

Whenever an opioid is prescribed, the patient should be thoroughly educated about the safe use, storage, and disposal of opioid medications. This can be done by a non-physician, if desired, and the key points can be included in patient/provider agreements or treatment plans. Safe use means following clinician instructions about dosing, not using concurrent alcohol or sedatives, not sharing medications, not breaking, chewing, or crushing medicines, and not using transdermal products if they are broken or torn.

Safe storage means reminding patients that pain medications are sought-after by many people, and, thus it is best if opioids are stored in a locked cabinet or other secure storage unit. If a locked unit is not available, patients should, at least, not keep opioids in a place that is obvious to, or easily accessed by others, since theft by friends, relatives, and guests is a known route by which opioids become diverted.[80] Storage areas should be cool, dry, and out of direct sunlight. Proper disposal means getting rid of unused medications by: returning the medications to a pharmacy, health center, or other organization with a take-back program; flushing them down a toilet (unless this is specifically forbidden by state law); or mixing the medication with an undesirable substance and putting it in the trash. (Note: in 2014, the DEA loosened regulations to allow pharmacies, hospitals, clinics, and other authorized collectors to serve as drop-off sites for unused prescription drugs).

BOTTOM LINE: opioids comprise many specific agents and routes of administration, so selection of agent should be based on the patient's pain complaint, lifestyle, and preferences. In general, ER/LA opioids taken around-the-clock should be reserved for patients who have difficulty managing an "as needed" regimen, or have become dependent on opioid analgesia. Patients should be educated to use opioids only as prescribed, to store them as securely as possible, and to dispose of un-used opioids responsibly.

Evidence for opioid efficacy

A meta-analysis of 41 randomized controlled trials of opioids in chronic pain found that both "weak" (e.g., tramadol, codeine) and "strong" (e.g., morphine, oxycodone) opioids 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).[81] Similar results were found in a systematic review of elderly patients with chronic pain.[82] A Cochrane review of opioids versus controls in the treatment of hip or knee osteoarthritis found smaller effect sizes for pain relief (-0.28; 95% CI: -0.35 to -0.20), and functional improvement (-0.26; 95% CI: -0.35 to -0.17).[83] These studies must be interpreted cautiously because the duration of the trials was very short (median treatment duration was 4 weeks, with a range of 3 days to 6 months).[83] The relevance of these studies to chronic opioid treatment is highly questionable. As noted above, with prolonged opioid use, analgesic tolerance may develop, and short clinical trials do not capture this dynamic or any of the other potentially dire effects of long-term therapy.

A Cochrane review of opioids for long-term treatment of non-cancer pain found that many patients discontinue long-term opioid therapy (especially oral opioids) due to adverse events or insufficient pain relief.[84] Overall, little evidence supports the assertion that long-term use of opioids provides clinically significant pain relief and improves quality of life or functioning.[84] Similarly, no high-quality evidence shows that any one opioid will be significantly more effective than another for any given patient.[85,86]

Clinicians should be aware of the significant gaps in our knowledge about the efficacy of opioids for chronic non-cancer pain (CNCP), gaps recently highlighted in a report by the Agency for Healthcare Research and Quality (AHRQ), which found *no studies* addressing the following key questions:[87]

- Efficacy of long-term (>1 year) opioid therapy vs. placebo/no opioid therapy
- Efficacy of opioids versus non-opioid therapies (pharmacological or non-pharmacological) on outcomes
- Efficacy of opioids *plus* non-opioid interventions (pharmacological or non-pharmacological) versus opioids or non-opioid interventions alone on outcomes

Evidence for opioid risks

Although opioids can be effective pain relievers, they also pose many significant risks for adverse effects, abuse, addiction, and accidental overdose leading to death from respiratory depression. It is currently impossible to quantify the degree of addictive risk associated with opioid analgesics, either for an individual patient or the population of pain patients in general, because rigorous, long-term studies of these risks in patients without co-existing substance-use disorders have not been conducted.[5] A few surveys conducted in community practice settings, however, estimate rates of prescription opioid abuse of between 4% to 26%.[88,89,90,91] Risk rises with higher doses and longer durations.[92]

A 2011 study of a random sample of 705 patients undergoing long-term opioid therapy for non-cancer pain found a lifetime prevalence rate of DSM-5-defined opioid-use disorder of 35%.[93] The variability in such results probably reflects differences in opioid treatment duration, the short-term nature of most studies, and disparate study populations and measures used to assess abuse or addiction. Nonetheless, the levels of risk suggested by these studies are significant enough to warrant extreme caution in the prescription of any opioid for a chronic pain condition.

Table 5: Summary of odds ratios of developing opioid abuse or dependence by dose and duration[92]

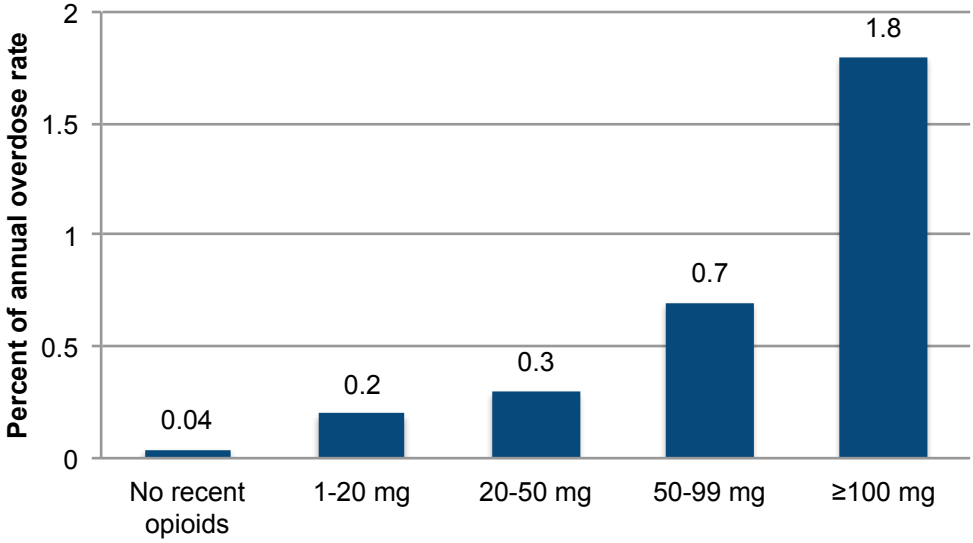
Daily Opioid Dose	Acute (0-90 days) OR (CI)	Chronic (>90 days) OR (CI)
Low (1 - 36mg)	3.03 (2.32 - 3.95)	14.92 (10.38 - 21.46)
Medium (36 - 120mg)	2.80 (2.12 - 3.71)	28.69 (20.02 - 41.13)
High (>120mg)	3.10 (1.67 - 5.77)	122.45 (72.79 - 205.99)

Caution is also required because a significant portion of patients can be expected not to use an opioid medication as prescribed. Fleming et al., conducted in-depth interviews with 801 patients receiving long-term opioid therapy and found the following:[89]

- 39% of patients increased their dose without direction from a health care provider
- 26% engaged in purposeful over-sedation
- 20% drank alcohol concurrent with opioid use
- 18% used opioids for purposes other than pain relief
- 12% hoarded their pain medications
- 8% obtained extra opioids from other doctors

The risk of overdose with opioid analgesics is significant and, as with risk of abuse/dependence, rises with both dose and duration.[94]

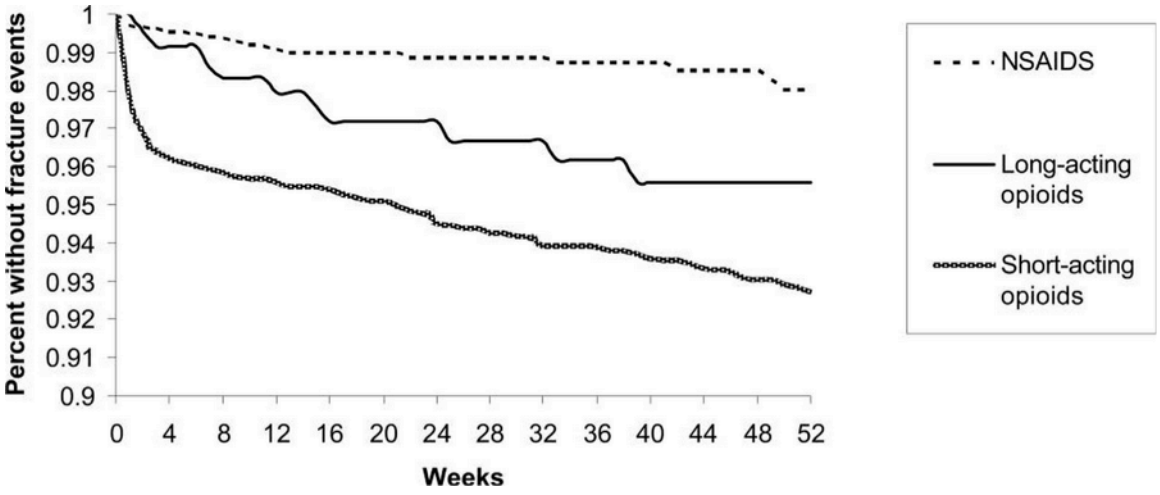
Figure 2: Percent of annual overdose rates rises with daily opioid dose[94]



In addition to the risks for misuse, addiction, and overdose, opioids can cause a wide range of uncomfortable or harmful adverse effects, the most common of which are neurologic (somnolence, dizziness), endocrine (hypogonadism), gastrointestinal (nausea, vomiting, and constipation), sexual (erectile dysfunction), and cutaneous (pruritus). In randomized trials of opioids, 50%-80% of patients reported a side effect, and about 25% withdrew due to an adverse event.[84,95,96]

Although less common, there is also a dose-dependent increase in risk of fractures in opioid users compared to non-users (RR 1.4; 95% CI: 1.2 to 1.7), with the risk highest in the period following initiation, particularly for short-acting opioids.[97,98]

Figure 3: Fracture risk over time[98]



An area of potential concern is the possibility that chronic opioid use may have immunosuppressive effects. Evidence from cell cultures and animal models is suggestive, and this is an area requiring further investigation.[99] Dublin et al., in a population-based case-control study, found a significantly higher risk of pneumonia in immunocompetent older adults who were prescribed opioids (OR 1.88; 95% CI: 1.26 to

1.79).[100] The risk was particularly high for adults taking long-acting opioids (OR 3.43; 95% CI: 1.44 to 8.21).[100]

An association between a higher risk for myocardial infarction and chronic opioid use has also been reported, though the mechanism of action for such cardiac effects is unclear.[101,102]

BOTTOM LINE: although opioids can reliably relieve short-term pain, little evidence supports claims that they can relieve pain effectively or increase function when used long-term. Much evidence, on the other hand, shows that opioids pose serious risks to patients of addiction, overdose, misuse, and a wide range of adverse effects including hypogonadism, erectile dysfunction, and fractures.

Treating acute pain

Rapid and effective treatment of acute pain is needed not only to reduce suffering, but also to reduce or prevent adverse physiologic and psychological consequences (e.g., excessive stress response, progression to chronic pain, inability to comply with rehabilitation).[103] The management goals and strategies for acute pain can be summarized as:[104]

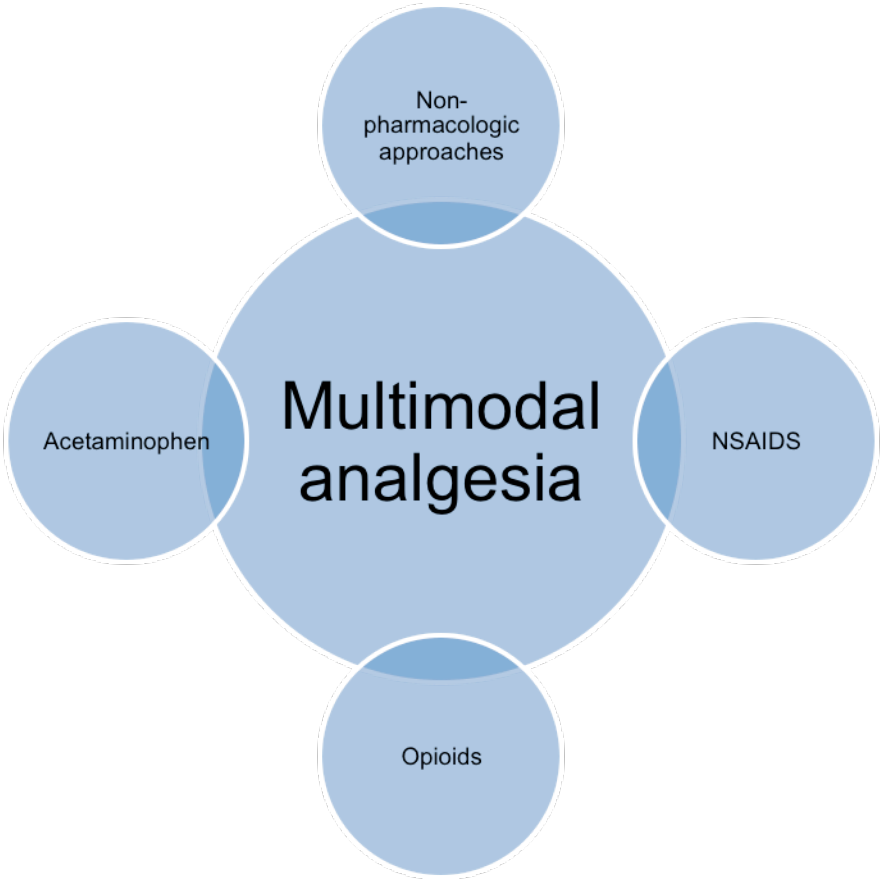
- Accurate pain assessment using validated tools or scales
- Early intervention, with prompt adjustments in treatment for inadequately controlled pain
- Working collaboratively with patients to create a pain management plan
- Facilitating recovery from underlying disease, injury, or surgery
- Avoiding, or minimizing, use of opioids

Non-pharmacologic approaches and/or analgesic drugs may be used to treat acute pain, with the selection of treatment plan components guided by pain intensity, patient preferences, and drug side effect profiles.

In general, for mild-to-moderate acute pain, non-pharmacologic approaches should be tried first (e.g., rest, ice, compression, elevation, heat/cold, electroanalgesia, relaxation training), with oral non-opioids (e.g., acetaminophen, NSAIDs, topical agents) added as needed.

For severe acute pain (e.g., post-surgical pain), evidence supports using a multimodal treatment approach.[105,106,107] Non-pharmacological approaches should be combined, as appropriate, with analgesics of different potencies (Figure 4).

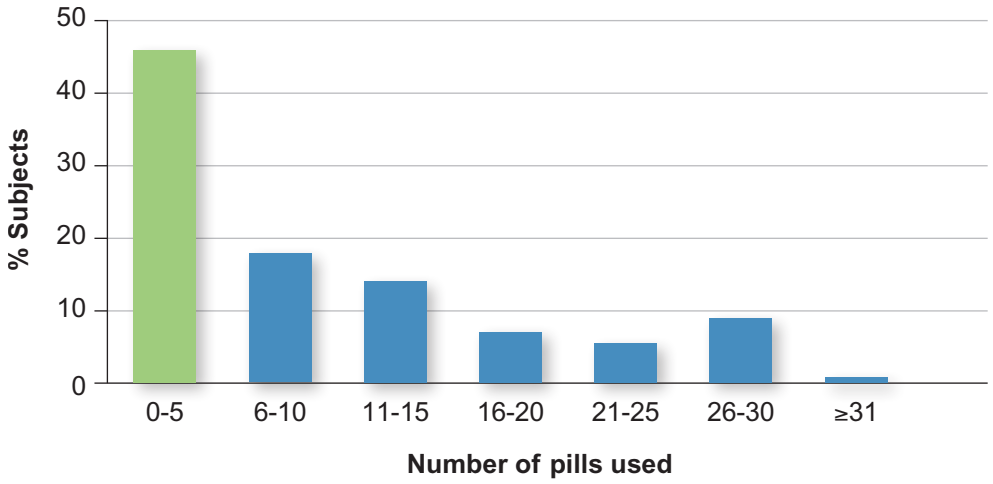
Figure 4: Multimodal approach to severe acute pain



For moderate to severe acute pain, cautious use of opioids may be considered for carefully-selected patients whose pain is not controlled with acetaminophen or NSAIDs, or for whom such medications are contraindicated. The opioid should be used at a minimum effective dose, and for a limited period of time, usually less than 2-3 days. Opioids should be used only as one part of a comprehensive pain care plan, and extended release opioids should be avoided in acute pain patients.[108]

Whenever opioids are prescribed for acute pain, the amount of drug dispensed should be limited to prevent the spread of opioids beyond those for whom they have been prescribed. Data from Utah, which may be representative of the nation, show that in 2009, 72% of people who had been prescribed an opioid had leftover medication, and 71% of those kept the medication rather than returning it or disposing of it.[109] Other studies confirm that patients routinely receive many times more opioids than they will use for acute pain. For example, Rodgers et al., found that after outpatient orthopedic surgery, most patients were prescribed 30 pills of an opioid analgesic, although the mean patient consumption of those analgesics was only 10 pills.[110]

Figure 5: Opioid pills consumed following outpatient upper extremity surgery.[110]



By definition, treatment of acute pain should not last longer than the time required for the healing or resolution of the trauma or condition. Hence, it is unlikely that opioids, or any other analgesic, should be needed beyond 90 days from initiation of treatment. But it bears noting that research shows that after 90 days of continuous opioid use, treatment is more likely to become life-long.[111,112,113,114] The 90-day mark, therefore, should be considered a "red flag" point at which use should be re-evaluated.

BOTTOM LINE: acute pain generally responds well to opioids, but opioids should be reserved for severe pain. Many safer options work well for mild to moderate pain, including both non-pharmacologic treatments, and drugs such as NSAIDs and acetaminophen. If opioids are needed, they should be used at a minimum effective dose, for a limited period of time, usually less than 2-3 days. Quantities prescribed should be limited to what can realistically be expected to be consumed. 90 days of continuous use of an opioid is a "red flag" point at which use should be re-evaluated

Treating chronic non-cancer pain

Explore non-opioid options first

Before an opioid analgesic is considered as a possible treatment for CNCP, all other potential therapies should be tried—or at least considered. A wide range of non-opioid therapies exist, most of which pose significantly less risk than opioids:

- Physical therapy, exercises, and other rehabilitative therapies
- Complementary therapies (e.g., yoga, mindfulness-based interventions)
- Psychotherapy
- Non-opioid analgesics

Some of these options can be combined, and they can also be used concurrently with an opioid. Many factors govern which options are appropriate for a given patient, including patient preferences, comorbid

physiological or psychological conditions, patient life expectancy, cost, local availability of the treatment option, and the type, duration, and severity of the pain.

A full discussion of all these options is beyond the scope of this document, although two examples illustrate some of the evidence showing that non-pharmacologic approaches can have significant positive effects. A systematic review and meta-analysis of yoga for low back pain by Cramer et al., found strong evidence for short-term effectiveness (SMD -0.48; 95% CI: -0.65 to -0.31; p<0.01) and moderate evidence (SMD -0.35; 95% CI: -0.55 to -0.15; p<0.01) for long-term pain relief.[115] A systematic review and meta-analysis by Veehof et al., of mindfulness-based interventions found significant reductions in pain (SMD -0.37; 95% CI: -0.20 to -0.53), depression (SMD -0.32; 95% CI: -0.13 to -0.50), and anxiety (SMD -0.40; 95% CI: -0.07 to -0.73).[116]

Non-opioid analgesic medicines, particularly acetaminophen, anticonvulsants, and antidepressants, should also be tried prior to initiating an opioid for chronic pain. NSAIDs are generally not recommended for chronic pain because long-term use raises risks of gastrointestinal problems (e.g., stomach upset, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., antiplatelet effects), kidney dysfunction, hypersensitivity reactions, and cardiovascular concerns, particularly in the elderly.[31] Long-term use of acetaminophen may also entail risk: liver damage can occur with doses in excess of 4 gram per day. Particular caution must be given to the use acetaminophen alongside opioid combination products (e.g. Vicodin and Percocet) that also contain acetaminophen to ensure that the maximum daily dose is not exceeded.[26]

The table below lists examples of therapies with evidence showing effectiveness in some common pain conditions. These should be explored before prescribing an opioid for chronic pain.

Table 6: Potential therapeutic interventions for selected pain conditions

Condition	Intervention
Neuropathies (e.g., diabetic, post-herpetic)	Antidepressants (TCAs, SNRIs) Anticonvulsants Percutaneous electrical nerve stimulation
Osteoarthritis	Exercise/strength training [117,118] Weight loss (combined with exercise)[119] Tai Chi [120] Electromagnetic stimulation[121] Braces and insoles [122]
Fibromyalgia	Cognitive behavioral therapy [123] Exercise/strength training [124] Tai Chi [125]
Low back pain	Yoga[115] Exercise/strength training [126] Spinal manipulation [127] Massage [127] Cognitive behavioral therapy [128]
Trigeminal neuralgia	Anticonvulsants[129]
Rheumatoid arthritis	Disease-modifying antirheumatic medication[130]
Polymyalgia rheumatica	Corticosteroid medications[131]
Migraine	Abortive and prophylactic therapies (e.g., triptans)[3]

The pharmacologic options for treating CNCP are the same as those reviewed above for acute pain, although the risks associated with analgesic medications rises considerably when used long-term. For example, prolonged use of NSAIDs leads to increased risk of side effects, which significantly limits their role in treating CNCP. Acetaminophen needs to be limited to <4 g/day, or much lower doses for elderly patients (i.e. 3 g/day) or patients with liver disease or risk of liver disease (i.e., <2 g/day). And the use of opioids in CNCP is not supported by strong evidence.[4]

BOTTOM LINE: many non-pharmacologic interventions, particularly exercise and strength-training, can be effective in relieving pain, improving function, or both in chronic pain conditions. These options, along with the use of non-opioid medications, should be explored prior to prescribing an opioid for CNCP.

Patient selection and risk stratification

Prior to initiating opioid treatment for a chronic pain condition, clinicians should conduct a history, physical examination, appropriate testing, and an assessment of the patient's risk of substance abuse, misuse, or addiction.[3] An opioid may be appropriate for chronic pain in certain limited circumstances, such as: when the pain is severe and refractory to other treatments; when it adversely impacts function or quality of life; and when the potential therapeutic benefits outweigh, or are likely to outweigh, potential harms.[3]

Patients or pain conditions unlikely to benefit from chronic opioid therapy

Although the available evidence base is limited, professional guidelines suggest that the following patient characteristics and pain conditions are unlikely to benefit from opioid analgesics:[3]

- Poorly-defined pain conditions
- Daily headache
- Fibromyalgia
- A likely or diagnosed somatoform disorder
- Patients with unresolved workers compensation or legal issues related to pain or injury

Opioids must be used with extreme caution in patients with:[3]

- Pre-existing constipation, nausea, pulmonary disease, or cognitive impairment
- A history of drug or alcohol abuse

Pain assessment tools

Unidimensional pain scales (e.g., numeric or "faces") are seldom useful for guiding a decision to treat chronic pain because such pain is variable and scores from pain assessment tools are highly subjective. Multidimensional tools provide more information, such as the effects of pain on daily life and functional roles. These tools can typically be administered in an office, examination room, or other clinical setting by either a physician or another health care professional, or they could be filled out by the patient, if appropriate. Examples of some multidimensional tools include:

- Initial Pain Assessment Tool[132]
- Brief Pain Inventory[133]
- McGill Pain Questionnaire (short-form available)[134]

Psychosocial evaluation

Because life stressors often underlie or co-exist with chronic pain and may warrant intervention, it is critical to assess the patient's psychosocial functioning. A thorough history should include questions about a patient's functioning at work and home, as well as how their pain might be affecting their significant relationships, sexual functioning, and recreational activities. Clinicians should be alert for signs of depression or anxiety (common in patients with chronic pain) as well as for suicidal thoughts since the risk of suicide is roughly double for patients with chronic pain.[135]

Instruments such as the Depression Anxiety & Positive Outlook Scale (available at: dapos.org), the Generalized Anxiety Disorder assessment (GAD-7, available at: patient.co.uk/doctor/generalised-anxiety-disorder-assessment-gad-7), and the Patient Health Questionnaire (phqscreeners.com) can facilitate a thorough psychosocial history. These are brief (i.e. <5 min.) questionnaires filled out and scored by a clinician. The results can guide next steps, which may include pursuing a course of treatment, further questioning, use of additional short tools if a particular issue is uncovered (e.g., suicidality), or referral to a mental-health professional if the patient has active psychological issues that are beyond the treating clinician's expertise.

Evaluating patients for risk of opioid dependence or abuse

Given the demonstrated risks of abuse and addiction associated with opioid analgesics, clinicians must assess patients for their potential vulnerability to these risks. Such assessment is not completely objective, and opinions differ about which patients should be more rigorously assessed. Some favor a "universal precautions" approach, in which all pain patients are considered to have some degree of vulnerability to abuse and addiction and, hence, all patients are given the same screenings and diagnostic procedures.[136] Some patient characteristics, however, do appear to be predictive of a potential for drug abuse, misuse, or other aberrant behaviors, particularly a personal or family history of alcohol or drug abuse.[3] Some studies also show that younger age and the presence of psychiatric conditions are associated with aberrant drug-related behaviors.[3]

Table 7: Risk factors for aberrant opioid behavior[3]

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)

Relatively brief, validated tools can help formalize assessment of a patient's risk of having a substance misuse problem (Table 8) and these should be considered for routine clinical use.[3] For more information on risk reduction strategies, a free online CME is available at: opioidprescribing.com.

Table 8: Tools for Patient Risk Assessment

Tool	Who Administers?	Length
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Clinician	7 items
Opioid Risk Tool (ORT)	Clinician or patient self-report	5 yes/no questions
Screener and Opioid Assessment for Patients with Pain, Version 1 and Revised (SOAPP, and SOAPP-R)	Patient self-report	24 items

BOTTOM LINE: opioids may not be appropriate for many patients. Before starting an opioid analgesic for a chronic pain condition, conduct a history, physical examination, appropriate testing, and an assessment of the patient's risk of substance abuse, misuse, or addiction. A variety of fast, easy-to-use tools can help clinicians assess patient risk for adverse effects or addiction, and these should be used regularly.

Function-based opioid management plans

A "medication agreement" or "management plan" can serve many useful functions, including patient education, clarification of expectations, and goal-setting, all of which may help a patient adhere to a regimen of opioid pain medication.[3] These agreements should be written and signed by the provider and the patient, and should include the elements listed in Table 9. (See Appendix 2 for a sample medication agreement).

Table 9: Components of an opioid 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)
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** opioids (lack of efficacy, pain resolution, aberrant behavior)

In crafting a management plan, clinicians should avoid framing the agreement in terms of punishments for possible future misbehaviors or difficulties, and should take care to avoid using language that is stigmatizing, dominating, or pejorative. Since written agreements must be clearly understood by the patient, they should be written at the sixth- to seventh-grade level, and translated into the patient's language, if possible (in-person translators may also be used).[137] Time must be allowed for patients to ask questions, and for

prescribers to ensure patients understand what they are being told. Some, or all, of these tasks may be handled by trained personnel (or staff members) rather than physicians.

Clinicians should be aware that although the terms “agreement” or “plan” are more patient-friendly than the word “contract,” from a legal standpoint, any written or oral agreement between a prescriber and a patient may be considered a binding “contract.”[138]

Since pain itself cannot be measured objectively, opioid management plans should not be framed solely in terms of pain relief; functional goals are preferable. Chronic pain often impairs functioning in daily life, such as the ability to be physically active, mentally focused, and well-rested. Even relatively modest reductions in pain (e.g., a 20% reduction on a pain score) can allow for significant functional improvements.[139] Framing treatment goals in terms of improved functioning allows prescribing decisions (or decisions to terminate treatment) to be based on objective data such as attendance at physical therapy appointments, sleeping in a bed instead of a chair, or walking a designated distance or number of steps. Another key benefit of a function-based opioid management plan is that the resulting data can help differentiate patients who are addicted to an opioid from patients who are not addicted but are nonetheless seeking an increased dose: addiction typically leads to *decreased* functioning, while effective pain relief typically *improves* functioning.[140]

Functional treatment goals should be realistic and tailored to each patient. Because patients with long-standing chronic pain are frequently physically deconditioned, progress in achieving functional goals can be slow or interrupted with “setbacks.” It is better to set goals slightly too low than slightly too high. Raising goals after a patient has “succeeded” is preferable—and more motivational—than lowering goals after a patient has “failed.”

Informed consent

Informed consent is a fundamental part of any medical treatment plan, but it is critically important when considering long-term opioid therapy, given the potential risks involved. Clinicians should ask themselves four key questions when obtaining informed consent in the context of opioid treatment:[141]

1. Does the patient understand the various options for treatment?

2. Has the patient been informed of the potential benefits and risks associated with each of those options?

3. Is the patient free to choose among those options, and free from coercion by the health care professional, the patient’s family, or others?

4. Does the patient have the capacity to communicate his or her preferences—verbally or in other ways (e.g., is the patient deaf or cognitively impaired)?

Documented informed consent can be incorporated into an opioid management plan.

BOTTOM LINE: function-based pain management plans can help patients and clinicians by clarifying expectations, goals, procedures, and terminology. Pain reduction itself is not the only goal—it is simply one component of the larger effort to improve functioning. Pain management plans and informed consent documents should be written at a level, and in a language, that patients can understand.

Initiating opioids

Before prescribing any opioid, confirm that:

- Other treatments with more optimal risk-benefit profiles have been explored
- The patient's physical and psychosocial condition has been fully assessed
- Level of opioid tolerance has been determined or estimated (see below)
- Informed consent has been obtained and a management plan is in place

Opioid selection, initial dosing, and titration must be individualized to the patient's health status, previous exposure to opioids, and treatment plan.[3] Patients who are opioid-naïve or have modest previous opioid exposure should be started at a low dose, generally of a short-acting opioid because these confer a lower risk of overdose, and titrated slowly upward to decrease the risk of opioid-related adverse effects.[3] If it is unclear whether a patient has recently been using opioids (either prescribed or non-prescribed), the clinician should assume that the patient is opioid-naïve (i.e., not tolerant) and proceed as just described. Some patients, such as frail older persons or those with comorbidities, may require an even more cautious therapy initiation.

Methadone has a long and unpredictable half life and accounts for a higher proportion of accidental overdoses than any other opioid.[1] 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.

A decision to continue opioid therapy should be based on careful review of the trial outcomes. Outcomes to consider include:[140]

- Progress toward meeting functional goals
- Presence and nature of adverse effects
- Changes in the underlying pain condition
- Changes in medical or psychiatric comorbidities
- Degree of opioid tolerance in the patient
- Identification of aberrant behaviors, misuse, or diversion

Opioid maintenance therapy

Periodic review and monitoring

If an opioid medication appears to be helpful (as determined by the functional goals outlined in the management plan) and therapy is continued, periodic review and monitoring should be performed for the duration of treatment. Exactly what constitutes "review and monitoring" is determined by the needs and characteristics of each patient. A physical examination, for example, may or may not be required at each follow-up visit. Clinicians must evaluate progress towards agreed-upon treatment goals for both pain relief and function, assess for physical and behavioral adverse effects, and confirm adherence to prescription regimens.

The intensity and frequency of monitoring is guided, in part, by the clinician's assessment of the patient's risk for abuse, diversion, or addiction. Tools and techniques similar or identical to those used during an initial

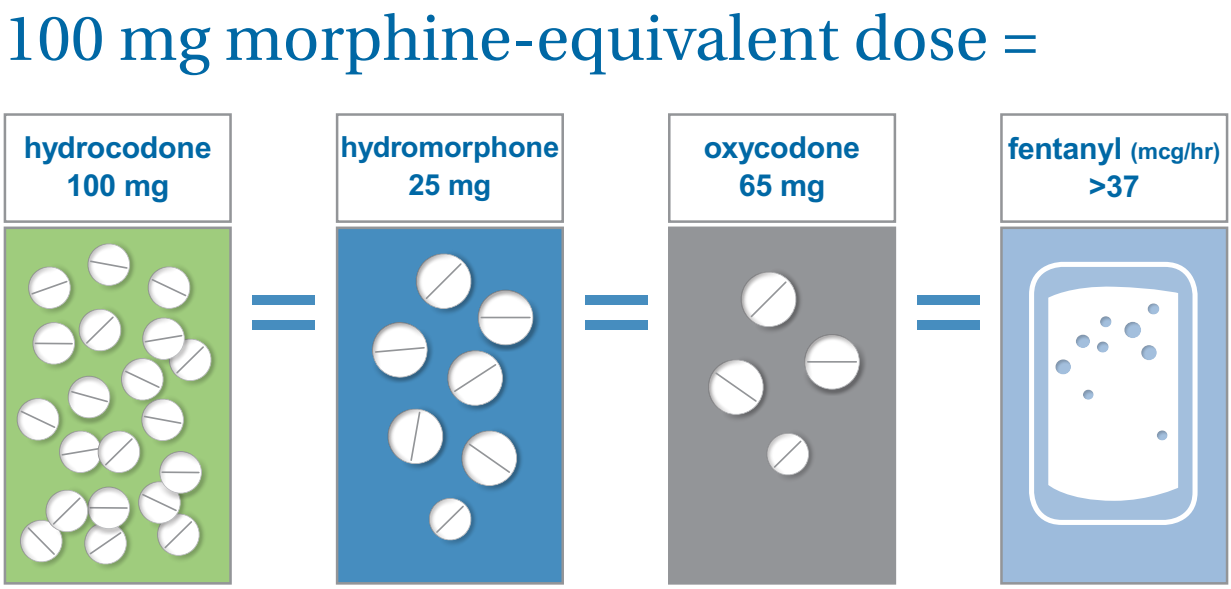
assessment of a patient's risk can be used to re-assess or monitor risk on an on-going basis. State and federal laws may mandate, or suggest, intervals for follow-up visits when a patient is prescribed medications in schedules II or III, so clinicians should consult with their state medical board or another trusted source to ensure compliance. Although federal law allows for a 90-day supply of prescriptions for patients receiving schedule II drugs (who are otherwise deemed safe to have this amount), state law can vary from 30 days to 6 months.[142] In cases where state and federal law conflict, the most restrictive rule prevails.[142] Patients who may need more frequent or intense monitoring include:

- Those with a prior history of an addictive disorder, past substance abuse, or other aberrant use
- Those in an occupations demanding mental acuity
- Older adults
- Patients with an unstable or dysfunctional social environment
- Those with comorbid psychiatric or medical conditions

Caution about dose escalation

When treating chronic pain, dose escalation has not been proven to reduce pain or increase function, but it *can* increase risks.[143] Prescribing high-dose opioid therapy (≥120 mg morphine equivalents/day) is not supported by strong evidence, and, indeed, a recent cohort study of 9940 patients receiving opioid analgesics for chronic non-cancer pain found that patients receiving 100 mg or more per day had an 8.9-fold increase in overdose risk compared to patients receiving 1-20 mg. of opioids per day.[94] The state of Washington has set a level of 120 mg morphine equivalents/day as a threshold dose that should not be exceeded without either demonstrated improvement in function and pain, or obtaining a consultation from a pain management specialist.[144] No randomized trials show long-term effectiveness of high opioid doses for chronic non-cancer pain. Many patients on high doses continue to have substantial pain and related dysfunction.[143] As noted earlier, higher doses of opioids are associated with increased risks for adverse events and side effects including overdose, fractures, hormonal changes, and increased pain sensitivity (hyperalgesia).

Figure 6: What does 100 MED look like?*



*This is not a chart for opioid conversion. See below regarding considerations for conversion or opioid rotation.

Urine drug screens

Urine drug testing is an imperfect science, but such testing can be a helpful component of responsible opioid prescribing. Drug testing should be conducted in a consensual manner as part of an agreed-upon opioid management plan and with the idea that such testing benefits both the patient and the provider. The potential benefits of urine drug testing include:

- Serving as a deterrent to inappropriate use
- Providing objective evidence of abstinence from drugs of abuse
- Monitoring response to treatment
- Helping patients allay concerns by family members, employers, or law-enforcement
- Demonstrating to regulatory authorities a clinician's dedication to "best practices"

In primary care settings, unobserved urine collection is usually acceptable, however, clinicians should be aware of the many ways in which urine specimens can be adulterated. Specimens should be shaken to determine if soap products have been added, for example. The urine color should be noted on any documentation that accompanies the specimen for evaluation, since unusually colored urine could indicate adulteration. If possible, urine temperature and pH should be measured immediately after collection.[142]

Prescribers should be familiar with the metabolites associated with each opioid that may be detected in urine, since the appearance of a metabolite can be misleading. A patient prescribed codeine, for example, may test positive for morphine because morphine is a codeine metabolite. Similar misunderstandings may occur for patients prescribed hydrocodone who appear positive for hydromorphone or oxycodone and oxymorphone. In the event of an abnormal urine drug screen, prescribers should consider a differential diagnosis that includes: drug abuse or addiction; self treatment of poorly-controlled pain; psychological issues; or diversion (which may be suggested by absence of prescribed opioids).[3]

Protecting against opioid-induced adverse events

The Veterans Administration/Department of Defense (VA/DoD) clinical practice guideline outlines a number of evidence-based strategies to reduce opioid-related adverse effects, summarized in Table 10.[145] Prophylaxis for constipation, which is the most common opioid-induced adverse event, has been facilitated by the recent approval of methylnaltrexone (Relistor) subcutaneous administration and naloxegol (Movantik) oral administration for patients with chronic non-cancer pain. For Relistor, this was an extension of an existing indication from opioid-induced constipation in palliative care.

Table 10: Recommendations for preventing or treating opioid-induced side effects[145]

Constipation	Reduce dose Methylnaltrexone or naloxegol 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	If analgesia is satisfactory, decrease dose by 25% Consider prophylactic antiemetic therapy Add or increase non-opioid pain control agents (e.g. acetaminophen) Treat based on cause
Sedation	Determine whether sedation is due to the opioid Eliminate nonessential CNS depressants (such as benzodiazepines) If analgesia is satisfactory, reduce dose by 10-15% Add or increase non-opioid or non-sedating adjuvant for additional pain relief (such as NSAID or acetaminophen)so the opioid can be reduced Add stimulant in the morning (such as caffeine) Change opioid
Pruritus	If analgesia is satisfactory, decrease dose by 25% Consider treatment with antihistamines Change opioid
Hallucination or dysphoria	Evaluate underlying cause Reduce dose Eliminate nonessential CNS acting medications
Sexual dysfunction	Reduce dose Testosterone replacement therapy may be helpful (for men) Erection-enhancing medications (e.g., sildenafil)

The concurrent use of benzodiazepines and opioids is particularly problematic since these agents act synergistically to depress respiratory functioning.

BOTTOM LINE: clinicians should monitor patients on a chronic opioid regimen by evaluating progress against agreed-upon treatment goals for both pain relief and function, assessing for physical and behavioral adverse effects, and confirming adherence to prescription regimens. Dose escalation above 100-120 mg morphine equivalents/day raises risks for side effects, adverse events, and addiction, and little evidence supports efficacy in terms of either pain relief or function beyond

this point. Urine drug testing can provide helpful data to guide treatment decisions, but clinicians need to educate themselves about how to interpret test results and how to conduct urine tests so as to reduce the chance of adulteration.

Opioid rotation

Switching from one opioid to another may be needed for a variety of reasons: to better balance analgesia and side effects; lack of efficacy (often related to tolerance); bothersome or unacceptable side effects; need for dose increases that exceed recommended limits (e.g., dose limitations of co-compounded acetaminophen); or inability to absorb the medication in its present form.

Opioid rotation must be done cautiously because of the many pharmacokinetic and pharmacodynamic variables involved.[31] An equianalgesic chart should be used when changing from one opioid to another or from one route of administration to another. Such charts must be used carefully, however. A high degree of variation has been found across the various charts and online calculators, and may account for some overdoses and fatalities.[146] The optimal dose for a specific patient must be determined by careful titration and appropriate monitoring, and clinicians must remember that patients may exhibit incomplete cross-tolerance to different types of opioids because of differences in the receptors or receptor sub-types to which different opioids bind. Do not simultaneously switch both an agent *and* a route of administration or type of release (e.g. LA/ER)

Managing Pain Flare-ups

Pain is dynamic, and pain intensity may sometimes rise to the point that it is not controlled by a given steady-state dose. Providing patients with either paper or electronic pain diaries can help them track such pain episodes and spot correlations between the flare-ups and variables in their lives. If specific triggers are identified, patients may be able to make changes that will reduce the prevalence of episodes without recourse to increased medication.[140]

Non-opioid methods of dealing with pain flare-ups (e.g., cold or warmth, massage, yoga, acupuncture, meditation, electrical stimulation) should be tried—or at least considered—before the dose of an opioid is increased. As with the management of the underlying chronic pain condition, clinicians should use an agreed-upon set of functional goals as a way to monitor, and if necessary, adjust, the use of as-needed opioid medications for pain flares.

Using Prescription Monitoring Programs (PMPs)

PMPs offer point-of-care access to state-specific pharmacy dispensing records of controlled substances. The information from a PMP can help clinicians quickly assess prescribing patterns to confirm or refute suspicions of aberrant behaviors. Information from a PMP may also reveal that a patient is being prescribed medications whose combinations are contraindicated. PMPs can be used as a platform for discussion with patients and other care providers. By reviewing a PMP each prescriber can identify other prescribers involved in the care of their patient. This can be especially useful when patients on high dose opioids present to a new practice or other clinical setting.

Some states send reports to providers based on patient thresholds of “doctor shopping.” Each state manages their own PMP, with some (e.g., Kentucky’s KASPER system) mandating a review at initiation of opioid therapy and periodically throughout continuous therapy. Regardless of state-specific details, using a PMP can help to identify emerging patterns of behavior in advance of developing problems of abuse.[147] One

of the largest challenges regarding PMPs is the timeliness of information reported, which can range from as short as 72 hours to as long as a week or more. Also, federal health care groups, such as Veterans Affairs, Department of Defense and Indian Health Service, do not report to state PMPs.[148]

Little uniformity, information-sharing, or cooperation currently exists among state PMPs, but efforts are under way to improve this situation. An advisory committee of the Council of State Governments has endorsed the formation of an interstate PMP compact, and legislation to accomplish this goal is currently being drafted.

Addressing concerns about prescription activity

Suspicion that a patient is non-adherent to a prescription or is engaging in aberrant drug-related behaviors should prompt a thorough investigation of the situation, including an honest evaluation of the patient/provider relationship, which may be strained by such behaviors.[140] Possible reasons for non-adherence include:

- Inadequate pain relief
- Misunderstanding of the prescription
- Misunderstandings related to lack of fluency with English
- Attempts to "stretch" a medication to save money
- Cultural or familial pressure not to take a medication
- Stigma about taking a pain medication
- Patient fears about addiction

Listed below are some possible steps to take in response to concerns about a patient's prescription activity:

- Discuss the situation with the patient: express concern over the pattern of behavior; discuss how drug abuse begins; and emphasize its negative consequences on health, employment, finances, friends and family, etc.
- Clarify expectations (e.g., receiving controlled medications from only one prescriber, using only one pharmacy) and review existing patient/provider agreements
- Increase the intensity of patient monitoring (e.g., urine toxicology, pill counts and early refills) and establish limits on refills or lost medications

The National Institute on Drug Abuse has freely-available short and longer-form validated questionnaires that can help clinicians assess a patient's use of alcohol, cigarettes, and other drugs (see Appendix 3).

For persistently problematic patterns of use, options include one or more of the following:

- Tapering drug therapy over several weeks to avoid withdrawal; consider incorporating non-opioid pain treatments.
- Referral to specialists, e.g., pain specialist, for evaluation of continued controlled substance prescribing
- Referral to an addiction management program

Patients with addictive disorders and/or complex chronic pain problems should maintain a relationship with a primary care provider, even if the management of the pain and/or addiction will be conducted by specialists. Providers are not required to take action that they believe to be contrary to the patient's best interests. If the provider believes that a crime has been committed, such as misrepresenting oneself to obtain controlled substance prescriptions, it is the right of the provider or staff to contact law enforcement and/or other providers. In criminal matters HIPAA restrictions generally do not apply. Legal input in difficult cases may be helpful.

BOTTOM LINE: state PMPs allow prescribers to quickly assess patterns of prescription drug use that can be helpful in confirming or refuting suspicions of aberrant behaviors and should be used whenever possible. If non-compliant behaviors are suspected, clinicians should proceed cautiously and begin by discussing the concerns directly with the patient, since there may be many factors involved in an apparent problem. If concerns are confirmed, primary care physicians must decide whether to continue treatment using heightened monitoring. Strongly consider referral to a specialist in pain management and/or substance abuse in these cases.

Discontinuing opioid therapy

Discontinuation of chronic opioid treatment may be necessary for a variety of reasons, including the healing of an injury or condition, an inability to achieve adequate analgesia, the lack of progress toward functional goals, the experience of intolerable side effects, or evidence of abuse, addiction or aberrant behaviors. If inappropriate use of a prescription medication is discovered, treatment must usually be suspended, although provisions should be in place for continuation of some kind of pain treatment and/or referral to other professionals or members of a pain management team.

Some clinicians may be willing and able to continue a regimen of opioid therapy even after the discovery of aberrant behavior, although this would require intensified monitoring, patient counseling, and careful documentation of all directives. This level of vigilance and risk management, however, may exceed the abilities and resources of primary care physicians. In such cases, referral to a provider with specialized skill or experience in dealing with high-risk patients may be prudent.

Stopping long-term opioid therapy is often more difficult than starting it.[149] For most patients, the opioid dose should be tapered by 20% to 50% of the current dose per week. The longer the patient has been on the drug, and the higher the initial dose, the slower should be the taper.[145]

BOTTOM LINE: stopping long-term opioid therapy is often more difficult than starting it, but may be necessary for a variety of reasons. Opioids should be tapered slowly to minimize withdrawal effects, and, if a patient is transferred to another provider, provision should be made for adequate access to the prescribed medication until care is picked up by the new provider.

Opioids and pregnancy

Current American Pain Society-American Academy of Pain Medicine (APS-AAPM) guidelines suggest that clinicians should avoid prescribing opioids during pregnancy unless the potential benefits outweigh risks.[3] Some data suggest an association between the use of long-term opioid therapy during pregnancy and adverse outcomes in newborns, including low birth weight and premature birth, though co-related maternal factors may play a role in these associations and causality is not certain.[3] Exposure to these medications has also been associated with birth defects in some studies. Opioid withdrawal can be expected in up to half of newborns of opioid-dependent mothers (neonatal abstinence syndrome).[3] If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available.

Driving and work safety

Driving while using opioid medications remains a controversial issue. Particularly at the initiation of therapy, opioid medications may cause sleepiness, clouded thinking, decreased concentration, slower reflexes, or incoordination, all of which may pose a danger to the patient and others when driving or operating machinery. A number of epidemiologic studies, however, have failed to show an association between long-term opioid use and motor vehicle accidents, fatalities, or citations for impaired driving.[150,151] Since at least some of the cognitive and motor-impairing effects of opioids resolve with steady use and a consistent dose, some activities or driving may be allowable at the discretion of the clinician's medical judgment and in the absence of signs of impairment.

Current APS-AAPM guidelines recommend that patients initially prescribed opioid medications, or those who have their dose increased, be advised not to drive or engage in potentially dangerous work or other activities.[3] No consensus exists on exactly how long they should abstain from driving. Patients should be educated about the increased risk of impairment when starting opioid therapy, when increasing doses, and when taking other drugs or substances that may exacerbate cognitive and motor impairment. Clinicians should be aware that certain professions (i.e., school bus drivers and pilots) may be subject to restrictions in the use of opioid medications.

BOTTOM LINE: clinicians should avoid prescribing opioids during pregnancy unless the potential benefits outweigh risks. If a mother is receiving long-term opioid therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available. Driving or operating potentially dangerous equipment should be avoided at the initiation of opioid therapy or after a dose escalation, although engaging in such activities once a patient has achieved a steady dose is not absolutely contraindicated.

Putting it all together

The soaring use of opioid analgesics to treat a wide range of chronic pain conditions has led to escalating rates of opioid diversion, abuse, addiction, and overdose. The clinical evidence base supporting this widespread use is much weaker than is often assumed, however, while the evidence for the many risks involved in long-term use of opioids is accumulating.

Opioids can produce compelling subjective feelings of euphoria, relaxation, and disinhibition which, combined with the dysphoria of withdrawal symptoms, can be powerfully reinforcing. When used for severe acute pain in time- and dose-limited ways, or for the relief of cancer and end-of-life pain, opioids can be uniquely valuable and the risks of addiction and abuse are low. The benefits of using opioids outside of these realms, however, seldom outweigh their risks. These risks are amplified among older adults; those with impaired renal or hepatic function; individuals with COPD, cardiopulmonary disorders, sleep apnea, or mental illness; and in patients who are likely to combine opioids with other respiratory depressants such as alcohol, sedative-hypnotics, benzodiazepines, or barbiturates.

Clinical guidelines for the use of opioids in chronic non-cancer pain have shifted in recent years to stress the risks of opioids and strengthen procedures that prescribers should use to reduce the risk of addiction and misuse.[152,140,153] These guidelines can be summarized as:

- Use opioids only for patients whose chronic pain is severe, in whom it might improve function and quality of life, and who have failed other analgesics and non-pharmacological treatment options
- Before opioid initiation, assess the patient's risk of addiction and misuse by using a validated screening tool such as the SOAPP-SF
- Create and use a written opioid management plan that outlines patient rights and responsibilities and includes clear information about potential risks
- For those at high risk, monitor drug use closely or refer the patient to a chronic pain specialist
- Prescribe generics whenever possible so that patients can afford their medications
- Be mindful of expected side effects, and act preventively when appropriate (e.g., laxatives when starting an opioid)
- Institute a monitoring plan that includes regular assessments of pain levels, activities of daily living, adverse events, and aberrant behavior.
- Do not use LA/ER agents for acute pain
- Use the lowest dose possible to achieve adequate pain relief. Higher opioid dose is associated with higher risk of accidental overdose and a wide range of adverse effects
- For patients who do not achieve functional goals, or who show signs of aberrant behavior, refer to a chronic pain or addiction specialist for management advice

Questions for family physicians

Before you take on the challenges of opioid prescribing in your practice or with a particular patient, the authors of an American Academy of Family Physicians monograph suggest you ask yourself the following:

1. Do I have the time and interest to thoroughly evaluate, properly monitor, and follow these patients?

2. Does my office have the appropriate systems in place to support the management of patients on opioid therapy? This may include the availability of frequent appointments for patients on opioid therapy and time allotted for physician-patient phone consultations.

3. Do I have access to a consultant who can support me and my patient during opioid therapy and who can accept referrals when necessary? This consultant may specialize in pain and/or addiction or be certified to prescribe buprenorphine/naloxone (Suboxone).

Adapted from: Young SS, et al. Balancing clinical and risk management considerations for chronic pain patients on opioid therapy; CME Monograph. American Academy of Family Physicians. 2008.

Appendix 1: SOAPP-SF[155]

(Screener and opioid assessment for patients with pain – short form)

How often do you have mood swings?

How often do you smoke a cigarette within an hour after you wake up?

How often have you taken medication other than the way it was prescribed?

How often have you used illegal drugs in the past 5 years (marijuana, cocaine)?

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: Sample patient agreement[154]

Pain Treatment with Opioid Medications: Patient Agreement*

I,_____, understand and voluntarily agree that (initial each statement after reviewing):

_____I will keep (and be on time for) all my scheduled appointments with the doctor and other members of the treatment team.

_____I will participate in all other types of treatment that I am asked to participate in.

_____I will keep the medicine safe, secure and out of the reach of children. If the medicine is lost or stolen, I understand it will not be replaced until my next appointment, and may not be replaced at all.

_____I will take my medication as instructed and not change the way I take it without first talking to the doctor or other member of the treatment team.

___I will not call between appointments, or at night or on the weekends looking for refills. I understand that prescriptions will be filled only during scheduled office visits with the treatment team.

_____I will make sure I have an appointment for refills. If I am having trouble making an appointment, I will tell a member of the treatment team immediately.

_____I will treat the staff at the office respectfully at all times. I understand that if I am disrespectful to staff or disrupt the care of other patients my treatment will be stopped.

_____I will not sell this medicine or share it with others. I understand that if I do, my treatment will be stopped.

_____I will sign a release form to let the doctor speak to all other doctors or providers that I see.

_____I will tell the doctor all other medicines that I take, and let him/her know right away if I have a prescription for a new medicine.

_____I will use only one pharmacy to get all on my medicines:_ Pharmacy name/phone#

_____I will not get any opioid pain medicines or other medicines that can be addictive such as benzodiazepines (klonopin, xanax, valium) or stimulants (ritalin, amphetamine) without telling a member of the treatment team **before I fill that prescription**. I understand that the only exception to this is if I need pain medicine for an emergency at night or on the weekends.

_____I will not use illegal drugs such as heroin, cocaine, marijuana, or amphetamines. I understand that if I do, my treatment may be stopped.

___I will come in for drug testing and counting of my pills within 24 hours of being called. I understand that I must make sure the office has current contact information in order to reach me, and that any missed tests will be considered positive for drugs.

_____I will keep up to date with any bills from the office and tell the doctor or member of the treatment team immediately if I lose my insurance or can't pay for treatment anymore.

_____I understand that I may lose my right to treatment in this office if I break any part of this agreement.

Pain Treatment Program Statement

We here at____are making a commitment to work with you in your efforts to get better. To help you in this work, we agree that:

We will help you schedule regular appointments for medicine refills. If we have to cancel or change your appointment for any reason, we will make sure you have enough medication to last until your next appointment.

We will make sure that this treatment is as safe as possible. We will check regularly to make sure you are not having bad side effects.

We will keep track of your prescriptions and test for drug use regularly to help you feel like you are being monitored well.

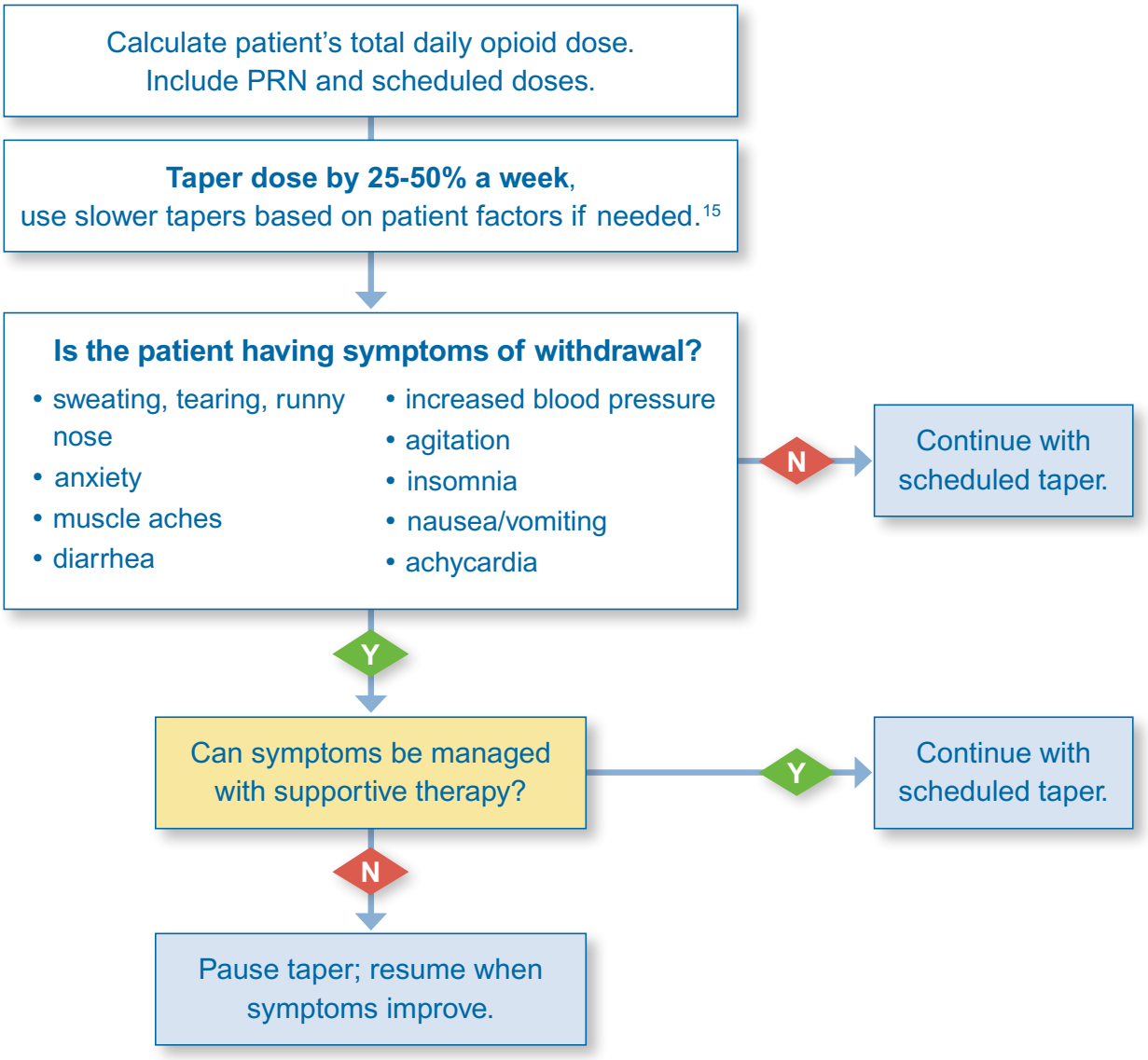
We will help connect you with other forms of treatment to help you with your condition. We will help set treatment goals and monitor your progress in achieving those goals.
We will work with any other doctors or providers you are seeing so that they can treat you safely and effectively.

We will work with your medical insurance providers to make sure you do not go without medicine because of paperwork or other things they may ask for.

If you become addicted to these medications, we will help you get treatment and get off of the medications that are causing you problems safely, without getting sick.

Patient signature	Patient name printed	Date
Provider signature	Provider name printed	Date

Appendix 3: Algorithm for tapering opioids[145]



Appendix 4: Resources

American Academy of Pain Medicine
painmed.org

Depression Anxiety & Positive Outlook Scale
dapos.org

Drug Enforcement Administration Diversion Control Program
DEAdiversion.usdoj.gov

FDA Blueprint for Prescriber Education
er-la-opioidrems.com

Generalized Anxiety Disorder assessment (GAD-7)
patient.co.uk/doctor/generalised-anxiety-disorder-assessment-gad-7

National Institute on Drug Abuse
Clinical resources: prescription opioids
www.drugabuse.gov/nidamed-medical-health-professionals/tool-resources-your-practice/opioid-prescribing-resources

National Institute on Drug Abuse
Short and longer-form validate questionnaires
drugabuse.gov/sites/default/files/pdf/nmassist.pdf

The National Association of State Controlled Substances Authorities (NASCSA)
nascsa.org

Patient Health Questionnaire
phqscreeners.com

PainLaw.org
painlaw.org

Risk reduction strategies (free online CME)
opioidprescribing.com

University of Wisconsin Pain & Policy Studies Group
painpolicy.wisc.edu

Veterans Administration opioid clinical practice guidelines
www.healthquality.va.gov/guidelines/Pain/cot/

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About this publication

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

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This material was produced by Brian Bateman, M.D., M.Sc., Assistant Professor of Anesthesia, Jerry Avorn, M.D., Professor of Medicine, Michael A. Fischer, M.D., M.S., Associate Professor of Medicine, Niteesh K. Choudhry, M.D., Ph.D., Associate Professor of Medicine, all at Harvard Medical School; Eimir Hurley, BSc (Pharm), MBiostat, Program Director, Ellen Dancel, PharmD, MPH, Director of Clinical Material Development, both at the Alosa Foundation. Drs. Avorn, Bateman, Choudhry, and Fischer are all physicians at the Brigham and Women's Hospital in Boston. None of the authors accepts any personal compensation from any drug company.

Medical writer: Stephen Braun.