Opiate Analgesics for Chronic Non-Cancer Pain

Recommendations from the Committee on Pain Management and Prescription Drug Abuse

South Dakota State Medical Association

June 2, 2017

Table of Contents:

Executive Summary

When used appropriately, opiate[1] analgesics can be important tools for relieving moderate to severe pain arising from a wide range of conditions, disease states, and medical procedures. These drugs, however, may also be misused and abused, and overprescribing of opiate pain relievers can result in multiple adverse health outcomes, including fatal overdoses. In recent years there has been a shift in thinking among many pain specialists about the use of opiates for chronic non-cancer pain, and legislative efforts to more closely regulate the prescription of opiates are underway in many states, including South Dakota.

Since professional opinions on this topic have evolved, the South Dakota State Medical Association's (SDSMA) Committee on Pain Management and Prescription Drug Abuse has reviewed current literature and existing clinical guidelines in order to articulate an up-to-date set of consensus views for chronic pain management with analgesics. This paper summarizes those findings and provides South Dakota prescribers with clear, evidence-based guidance about the appropriate prescription of opiate analgesics for the treatment of chronic pain outside of active cancer treatment, palliative care, and end-of-life care. These recommendations address: when to initiate or continue opiates for chronic pain; opiate selection, dosage, duration, follow-up, and discontinuation, and assessing risk and addressing harms of opiate use. Although the practices described in these guidelines are intended to apply broadly, they are not intended to establish a "standard of care." Physicians – to include all prescribers - must exercise their own best medical judgment when providing treatment, taking all relevant circumstances into account, including the potential for abuse, diversion and risk for addiction.

The key points of these recommendations include:

- *With respect to chronic pain management, maintenance of clinical and functional goals is key, and the incorporation of opiates should only be used when safer options have been deemed less effective.*

[1] The literature sometimes uses the terms "opiate" and "opioids" interchangeably. As used in this paper, the term "opiates" is intended to include, as applicable, the term "opioids."

- *Opiate analgesics are widely accepted as appropriate and effective for alleviating moderate-to-severe acute pain, pain associated with cancer, and persistent end-of-life pain.*
- *The use of opiates for chronic non-cancer pain is more problematic, and current research on the benefits and/or safety of opiates for this indication is either weak or inadequate.*
- *Opiates should be used for chronic non-cancer pain only when safer options have been deemed ineffective, and continued treatment should be based on maintenance of clinical and functional goals.*
- *Patients should utilize only one provider for the management of chronic pain.*
- *Risks increase with dose. High doses of opiates (greater than 100 morphine-equivalents/day) have been shown to be associated with higher risks for overdose and death and such use should be carefully assessed and monitored.*
- *Extended-release/long-acting opiates should not be used to treat acute pain.*
- *Opiates cause sleep-disordered breathing.*
- *Benzodiazepines and opiates together have clear risk of death from overdose.*
- *Taking other substances/drugs with opiates (e.g., alcohol) or having certain conditions (e.g., sleep apnea, mental illness) increase risk.*
- *Opiates should be used only as prescribed, should be stored securely, and when a course of treatment is altered, discontinued or stopped, any unused opiates should be disposed of properly.*

In addition to these clinical practice recommendations, the Committee came to a consensus on a number of other issues related to responsible opiate prescribing:

- *Expand and strengthen South Dakota's Prescription Drug Monitoring Program (PDMP) to facilitate rapid, accurate patient risk assessment to help improve patient care coordination, and to prevent diversion and/or "doctor shopping."*
- *Create new incentives for continuing medical education for opiate prescribers. Such education should be targeted to specific clinical practice needs, e.g., acute pain = emergency, surgery; long-acting/extended-release = pain management, etc.*
- *Create more safe medication disposal sites and promote their use.*

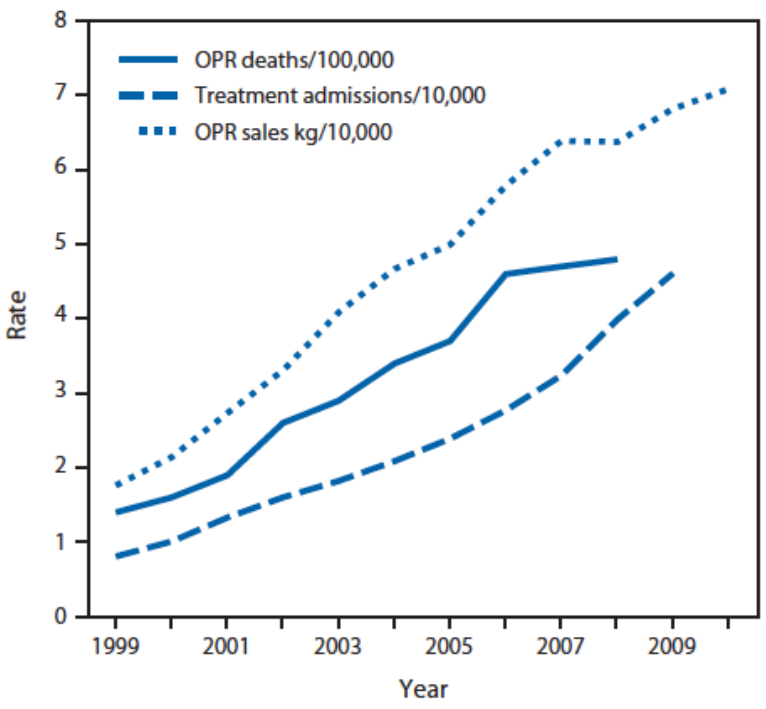
- *Expand patient education about the safe storage and use of opiates and other controlled substances to reduce the diversion of these medications for illicit use.*
- *Increase access to and education on the utilization and administration of opiate-antidote naloxone (Narcan) to reduce morbidity and mortality related to opiate and heroin overdose.*

Scope of the problem

The use of opiate analgesics has risen dramatically in the past 20 years across the U.S., including South Dakota. Between 1999 and 2010, the use of opiates quadrupled.[10] Much of this increase has been for the treatment of pain beyond moderate-to-severe acute pain or intractable end-of-life pain. In the past two decades, opiates have become widely-prescribed for chronic non-cancer conditions, such as back pain, osteoarthritis, fibromyalgia, and headache,[11] despite an evidence base that is much weaker than has been generally appreciated by many ~~physicians~~ health care professionals until recently.[12]

As the number of opiate prescriptions has risen, so, too, have the rates of opiate abuse, addiction, and diversion for non-medical use. The current level of prescription opiate abuse has been described as an "epidemic" by the Centers for Disease Control and Prevention.[10]

Figure 1. Rates* of opiate overdose death, treatment admissions, kilograms sold and in the United States, 1999-2010[10]



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

Despite a 104% increase in opiate 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 opiate users has been demonstrated.[13]

~~Physicians~~ Prescribers must balance an awareness of the ongoing problems of opiate over-prescription and abuse with the equally compelling need to relieve their patients' pain. Pain remains the most common reason people seek health care.[14] 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.[15,16] 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.[17] Pain is also a major cause of work absenteeism, underemployment, and unemployment.[14]

Pain must be treated, but many types of pain treatments exist. Opiate analgesics may – or may not – be the right choice, particularly for those suffering from chronic non-cancer pain. Opiates 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.

Key concepts in pain medicine

Acute and chronic pain. Traditionally, pain has been classified by its duration. In this perspective, "acute" pain is relatively short-duration (lasting for only a matter of days or, at most, a few weeks), arises from obvious tissue injury, and usually fades with healing.[11] "Chronic" pain, in contrast, lasts longer than would be anticipated for the usual course of a given condition. The International Association for the Study of Pain defines this as pain lasting three (3) months or longer.[18] These pain labels, however, provide no information about the biological nature of the pain itself, which is often critically important for optimal treatment.

Nociceptive and neuropathic pain. Pain can also be classified on the basis of its pathophysiology. Nociceptive pain is caused by the activation of nociceptors (pain receptors), and is generally, though not always, short-lived, and associated with the presence of an underlying medical condition. This is "normal" pain: a physiological response to an injurious stimulus.

Neuropathic pain, on the other hand, results either from an injury to the nervous system or from inadequately-treated nociceptive pain. It is an abnormal response to a stimulus caused by abnormal neuronal firing in the absence of active tissue damage. It may be continuous or episodic and varies widely in how it is perceived. Neuropathic pain is complex and can be difficult to diagnose and to manage because available treatment options are limited.

All or almost all neuropathic pain involves sensitization, nociceptive often does but not always. Sensitization is a state of hyperexcitability in either peripheral nociceptors or neurons in the central nervous system. Sensitization may lead to either hyperalgesia (heightened pain from a stimulus that normally provokes pain) or allodynia (pain from a stimulus that is *not* normally painful).[19] 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.[20] Many patients – particularly those with chronic pain – experience pain that has both nociceptive and neuropathic components, which complicates assessment and treatment.

Differentiating between nociceptive and neuropathic pain is critical because the two respond differently to pain treatments. Neuropathic pain can be difficult to treat as it typically responds poorly to non-steroidal anti-inflammatory (NSAID) agents.[21] Neuropathic pain typically responds well to a multidrug class regime of which opiates are included. Other classes of medications, such as anti-epileptics, antidepressants, or local anesthetics, may provide more effective relief for neuropathic pain.[22]

Cancer pain. Pain associated with cancer is sometimes given a separate classification, although it is not distinct, from a pathophysiological perspective. Cancer-related pain includes pain caused

by the disease itself and/or painful diagnostic or therapeutic procedures. The treatment of cancer-related pain may be influenced by the life expectancy of the patient, by co-morbidities, and by the fact that such pain may be of exceptional severity and duration.

Chronic non-cancer pain. A focus of recent attention by the public, legislators, and ~~physicians~~ health care providers has been chronic pain that is *not* associated with cancer. Such pain may be caused by many kinds of conditions or disease states such as musculoskeletal injury, lower back trauma, dysfunctional healing from a wound or surgery, and persistent pain arising from autoimmune system disorders. With chronic non-cancer pain, the severity of pain experienced by a patient may not correspond well – or at all – to identifiable levels of tissue damage.

Dependence and addiction. The most common error in clinical thinking about opiates is to consider *Addiction* to opiates and *Physical Dependence* on opiates to be the same thing. To help clarify and standardize understanding, 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]

- *Physical Dependence.* A state of adaptation that often includes tolerance and is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, and/or administration of an antagonist. In brief, physical dependence is a physiological/automatic response of the body caused by the lack of or stoppage of treatment.
- *Addiction.* Is a neuroplastic decompensation of the mesocorticolimbic system of the brain. The mesocorticolimbic system includes the ventral tegmental area, the nucleus accumbens, and the medial prefrontal cortex. This system controls complex behaviors such as family nurturing, eating, gambling, spending, risk-for-thrill, and experimenting with drugs and solvents. There is a broad continuum from normal to pathologic mesocorticolimbic behavioral health, upon which any person may be located – simply put, some people have an increased risk for addiction based on complex biopsychosocial factors.

Of note, opiate withdrawal is not physiologically dangerous; however, it is mentally and socially an unpleasant experience that is usually preventable with a slow tapering down of the dosage/intake levels.

Managing chronic non-cancer pain in primary care

Many pharmacologic and non-pharmacologic approaches to treating painful conditions are available to primary care ~~physicians~~providers. These options should be employed by using the following general principles:

- Identify and treat the source of the chronic pain, if possible, although treatment can begin before the source of the chronic pain is determined
- Select the most clinically appropriate approach to chronic 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

In treating chronic pain, clinicians can avail themselves of five basic modalities of chronic pain-management:

1. Cognitive-behavioral approaches
2. Rehabilitative approaches
3. Complementary and alternative therapies
4. Interventional approaches
5. Pharmacotherapy

These options can be used alone or in combinations to maximize pain control and functional gains. Only one of these options involves medications, and opiates are only one of many types of medications with potential analgesic utility. Which options are used in a given patient depends on the type of pain, the duration and severity of pain, patient preferences, co-occurring disease states or illnesses, patient life expectancy, cost, and the local availability of the treatment option.

Throughout assessment and treatment, ~~physicians~~ health care providers should ask themselves two basic questions: 1) who is this person, and 2) what all is going on (with them)? All answers are admissible if they are factors to the presentation and should be used in developing a treatment plan/options. Multidisciplinary treatment needs to be patient-specific and based on the physical ailments of the individual.

Cognitive-behavioral approaches

Psychological therapies of all kinds may be a key element in managing chronic non-cancer pain. Cognitive therapy techniques may help patients monitor and evaluate negative or inaccurate thoughts and beliefs about their pain. For example, some patients engage in an exaggeration of their condition called "catastrophizing" or they may have an overly passive attitude toward their recovery which leads them to inappropriately expect a ~~physician~~ provider to "fix" their pain with little or no work or responsibility on their part. Individual, group, or family psychotherapy may be extremely helpful for addressing this and other psychological issues, depending on the specific needs of a patient. In general, psychological interventions may be best-suited for patients who express interest in such approaches, who feel anxious or fearful about their condition, or whose personal relationships are suffering as a result of chronic or recurrent pain. Unfortunately, the use of psychological approaches to pain management can be hampered by such barriers as provider time constraints, unsupportive reimbursement policies, lack of access to skilled and trained providers, or a lack of awareness on the part of patients and/or ~~physicians~~ providers about the utility of such approaches for improving pain relief and overall functioning.

Rehabilitative approaches

In addition to relieving pain, a range of rehabilitative therapies can improve physical function, alter physiological responses to pain, and help reduce fear and anxiety. Treatments used in physical rehabilitation include exercises to improve strength, endurance, and flexibility, gait and posture training, stretching, and education about ergonomics and body mechanics. Exercise programs that incorporate Tai Chi, swimming, yoga, or core-training work may also be useful. Other noninvasive physical treatments for pain include thermotherapy (application of heat), cryotherapy (application of cold), counter-irritation, and electroanalgesia (e.g., transcutaneous

electrical stimulation). Other types of rehabilitative therapies, such as occupational and social therapies, may be valuable for selected patients.

Complementary and alternative therapies

Complementary and alternative therapies (CAT) of various types are used by many patients in pain, both at home and in comprehensive pain clinics, hospitals, or other facilities. These therapies seek to reduce pain, induce relaxation, and enhance a sense of control over the pain or the underlying disease. Meditation, acupuncture, relaxation, imagery, biofeedback, and hypnosis are some of the therapies shown to be potentially helpful to some patients. CAT therapies can be combined with other pain treatment modalities and generally have few, if any, risks or attendant adverse effects. Such therapies can be an important and effective component of an integrated program of pain management.

Interventional approaches

Although beyond the scope of these guidelines, a wide range of surgical and other interventional approaches to patient-specific pain management exist, including trigger point injections, epidural injections, facet blocks, spinal cord stimulators, laminectomy, spinal fusion, and deep brain implants. Treatments need to be patient-specific and based on the physical ailments of the individual.

Non-opiate analgesics

NSAIDs and acetaminophen

Non-steroidal anti-inflammatory drugs (NSAIDs), which include aspirin and other salicylic acid derivatives, and acetaminophen are used in the management of both acute and chronic pain such as that arising from injury, arthritis, dental procedures, swelling, or surgical procedures. Although they are weaker analgesics than opiates, acetaminophen and NSAIDs do not produce tolerance, physical dependence, or addiction. Acetaminophen and NSAIDs are also frequently added to an opiate regimen for their opiate-sparing effect. Since non-opiates and opiates relieve pain via different mechanisms, combination therapy can provide improved relief with fewer side effects.

These agents are not without risk, however. Adverse effects of NSAIDs include 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.[24] The threshold dose for acetaminophen liver toxicity has not been established; however, the SDSMA recommends that the total adult daily dose should not exceed 3,000 mg in patients without liver disease (although the ceiling may be lower for older adults).[25] In 2014, new Food and Drug Administration (FDA) rules went into effect that set a maximum limit of 325 mg of acetaminophen in prescription combination products (e.g., hydrocodone and acetaminophen) in an attempt to limit liver damage and other ill effects from the use of these products.[32]

Topical agents

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.[26,27] 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

Pain and depression are compounding – improving patient mood and/or controlling pain has a positive impact on the other. Some antidepressants, particularly tricyclics, and SNRIs, exhibit analgesic properties and may be particularly useful for treating neuropathic pain. Their analgesic actions do not depend on antidepressant activity, and antidepressants are equally effective in patients with and without depression.[28] While analgesia may occur at lower doses and sooner than antidepressant activity, maximum efficacy may require high antidepressant doses and trial duration.

Anticonvulsants

Antiepileptic drugs (AEDs) are increasingly used for treating neuropathic pain because they can reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.[29] 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]

Opiates for chronic non-cancer pain

The utility of opiate analgesics for treating chronic non-cancer pain is being increasingly questioned and a broad consensus is developing that these agents are not, in fact, suited for many patients with this type of pain. Clinical guidelines for the use of opiates in chronic non-cancer pain have evolved in recent years to stress the risks of opiates and strengthen procedures that prescribers should use to reduce the risk of addiction and misuse.[30-32]

Little evidence supports or belies the assertion that long-term use of opiates provides clinically significant pain relief or improves quality of life or functioning.[33] The Agency for Healthcare Research and Quality (AHRQ), for example, recently found *no studies* that compare opiate therapy with either a placebo or a non-opiate treatment for long-term (great than 1 year) pain management.[34] A Cochrane review of opiates for long-term treatment of non-cancer pain found that many patients discontinue long-term opiate therapy (especially oral opiates) due to adverse events or insufficient pain relief.[33]

A large – and growing – body of evidence, on the other hand, demonstrates that opiates pose significant risks for adverse effects, abuse, addiction, and accidental overdose leading to death from respiratory depression.

Estimating the risk that patients face of becoming addicted to opiate analgesics is difficult 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 opiate abuse of between 4 to 26 percent.[35-38] Risk rises with higher doses and longer durations.[39]

A 2011 study of a random sample of 705 patients undergoing long-term opiate therapy for non-cancer pain found a lifetime prevalence rate of DSM-5-defined opiate-use disorder of 35 percent.[40] The variability in such results probably reflects differences in opiate 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 opiate for a chronic pain condition.

Caution is also required because a significant portion of patients can be expected not to use an opiate medication as prescribed. Fleming et al., conducted in-depth interviews with 801 patients receiving long-term opiate therapy and found the following:[36]

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

The risk of overdose with opiate analgesics is significant and, as with risk of abuse/dependence, rises with both dose and duration.[41] When prescribing opiates, patient management is critical.

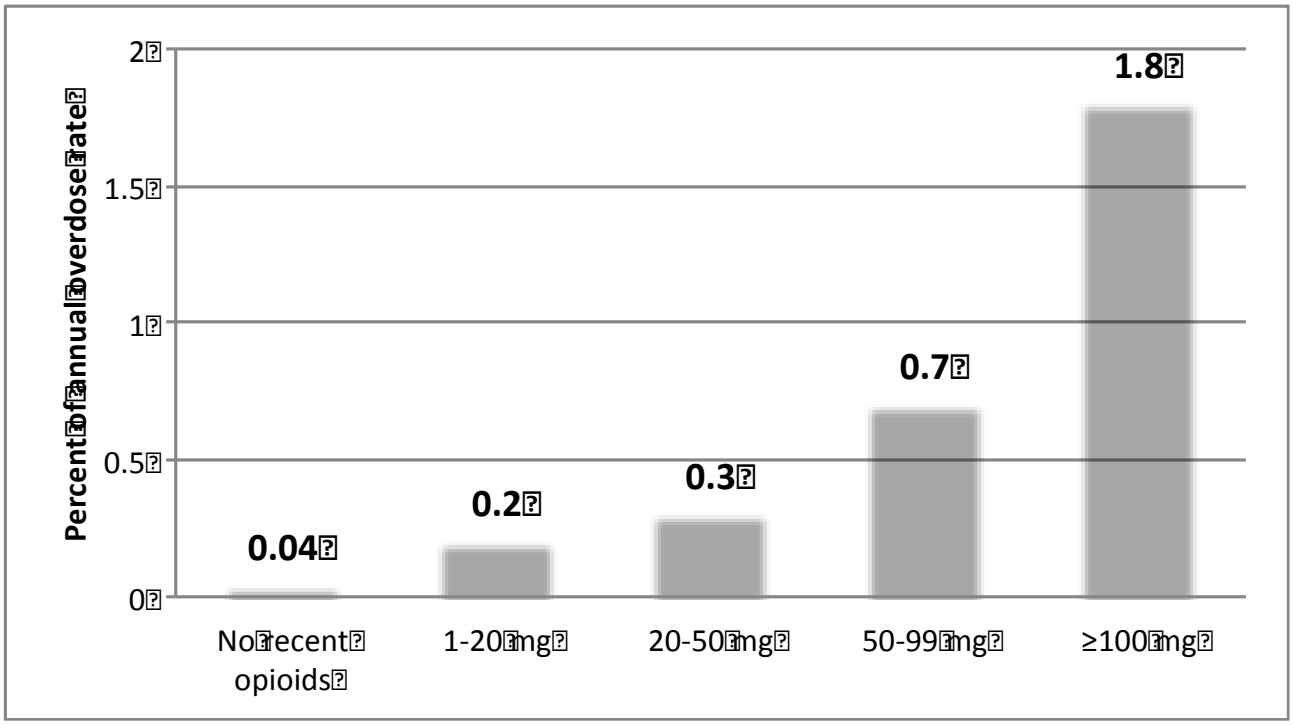


Figure 2. Percent of annual overdose rates rises with daily opiate dose[41]

In addition to the risks for misuse, addiction, and overdose, opiates can exert 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 opiates, 50 to 80 percent of patients report a side effect, and about 25 percent withdraw due to an adverse event.[33,42,43]

Although less common, there is also a dose-dependent increase in risk of fractures in opiate users compared to non-users, with risk highest in the period following initiation, particularly for short-acting opiates.[44,45]

An area of potential concern is the possibility that chronic opiate use may have immunosuppressive effects. Evidence from cell cultures and animal models is suggestive, and this is an area requiring further investigation.[46] Dublin et al. in a population-based case-control study, found a significantly higher risk of pneumonia in immunocompetent older adults who were prescribed opiates.[47] The risk was particularly high for adults taking long-acting opiates.[47]

Guidelines for responsible opiate prescribing

Given the limited evidence and risks, prescribing opiates for long-term non-cancer chronic pain should be carefully evaluated and only initiated in certain situations. For example, an opiate 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.[11] In these cases, clinicians can take many steps to maximize the chances that the opiate will be effectively used with minimal risk to the patient and to society at large. This section reviews these steps in detail.

Patient selection and risk stratification

Prior to initiating opiate 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.[11] A risk-benefit evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented both before a decision to treat is made, and on an ongoing basis if opiate treatment is begun.[11]

Patients or pain conditions unlikely to benefit from opiate therapy

Although the available evidence base is limited, professional guidelines suggest that the following patient characteristics and pain conditions are unlikely to benefit from opiate analgesics:[11]

- 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[2]

[2] Some evidence suggests that early treatment with opioids in this population may delay recovery and a return to work. Conflicts of motivation may also exist in patients on workers' compensation, such as if they don't want to return to an unsatisfying, difficult, or hazardous job.

Opiates must be used with extreme caution in patients with:[11]

- 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. 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[48]
- Brief Pain Inventory[49]
- McGill Pain Questionnaire (short-form available)[50]

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.[51]

Instruments such as the Depression Anxiety & Positive Outlook Scale (available at www.dapos.org), the Generalized Anxiety Disorder assessment (GAD-7, available at http://www.patient.co.uk/doctor/generalised-anxiety-disorder-assessment-gad-7), and the Patient Health Questionnaire (www.phqscreeners.com) can facilitate a thorough psychosocial history.

These are brief (i.e., less than 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 a clinician's expertise.

Evaluating patients for risk of opiate dependence or abuse

Given the demonstrated risks of abuse and addiction associated with opiate 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.[52] 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.[11] Some studies also show that younger age and the presence of psychiatric conditions are associated with aberrant drug-related behaviors.[11]

Relatively brief, validated tools can help formalize assessment of a patient's risk of having a substance misuse problem (Table 1) and these should be considered for routine clinical use.[11] For more information on risk reduction strategies, a free online CME is available at www.opioidprescribing.com. The use of a Prescription Drug Monitoring Program may also provide some helpful information about a patient's risk of dependence or abuse (see section on PDMPs on page 27).

Table 1. 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

Function-based opiate 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 opiate pain medication.[11] Additionally, routine screening should be considered by clinicians and medical systems for identification and brief intervention, if required. Of note, agreements should be written and signed by the provider and the patient, and should include the elements listed in Table 2.

Table 2. Components of an opiate medication agreement

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

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).[53] 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 (a sample agreement is provided in Appendix I of this document).

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."[54]

Since pain itself cannot be measured objectively, opiate 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 can allow for functional improvements.[55] 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 opiate management plan is that the resulting data can help differentiate patients who are addicted to an opiate 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.[31]

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."

Opiates for acute pain

Although the focus of this paper is on chronic non-cancer pain, opiates are widely used for acute pain as well, and a brief overview of recommended practice is appropriate here.

Cautious use of opiates for moderate or severe acute pain 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 one week. Opiates should be used only as one part of a comprehensive pain care plan, and extended release opiates should be avoided in acute pain patients.[3]

Studies show that physicians routinely over-prescribe opiates 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.[4] Another study found that 72 percent of people who had been prescribed an opioid had leftover medication.[5] This guideline recommends that no more than a one-week supply be prescribed following surgery.

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 opiates, or any other analgesic, will be needed beyond 90 days from initiation of treatment. Research shows that after 90 days of continuous opioid use, treatment is more likely to become life-long.[6-9] The 90-day mark, therefore, should be considered a "red flag" point at which use should be re-evaluated.

Informed consent

Informed consent is a fundamental part of any medical treatment plan, but it is critically important when considering long-term opiate therapy, given the potential risks involved. Four key questions clinicians may ask when obtaining informed consent in the context of opiate treatment are:[56]

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 may best be incorporated into an opiate management agreement.

Initiating opiates

Before prescribing any opiate, clinicians may consider whether:

- Other treatment options have been exhausted – nonpharmacologic and nonopiate pharmacologic therapies are preferred for chronic pain
- The patient's physical and psychosocial condition has been fully assessed
- Level of opiate tolerance has been determined or estimated (see below)
- Informed consent has been obtained and a management plan is in place
- Treatment goals have been established – to include realistic goals for pain and function
- Opiates will be continued after reassessment – opiates should only be continued if benefits outweigh risk and there is clinically meaningful improvements in pain and function

When initiating opiates, clinicians should prescribe the lowest effective dosage, and should only prescribe the quantity needed for the expected duration of pain severe enough to require opiates – three days or less will often be sufficient; more than seven days will rarely be needed.

Opiate selection, initial dosing, and titration must be individualized to the patient's health status, previous exposure to opiates, and treatment plan.[11] Patients who are opiate-naïve or have modest previous opiate exposure should be started at a low dose, generally of a short-acting opiate because these confer a lower risk of overdose, and titrated slowly upward to decrease the risk of opiate-related adverse effects.[11] If it is unclear whether a patient has recently been using

The Special case of methadone

Methadone has some unique safety issues. It 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.

opiates (either prescribed or non-prescribed), the clinician should assume that the patient is opiate-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.

A decision to continue opiate therapy should be based on careful review of the trial outcomes. Outcomes to consider include:[31]

- 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 opiate tolerance in the patient
- Identification of aberrant behaviors, misuse, or diversion

Patient education

Before starting and periodically during opiate therapy, providers should discuss known risks and benefits of opiate therapy, and patient and provider responsibilities for managing therapy. Given the potentially serious risks of long-term opiate therapy, providers should ensure patients are aware of potential benefits, harms, and alternatives to opiates before starting or continuing opiate therapy. Providers are encouraged to have open and honest discussions with patients to form mutual decisions about whether to start or continue opiate therapy. Important considerations include the following:

- Be explicit and realistic about expected benefits – explaining that while opiates can reduce pain during the short-term, there is no conclusive evidence that opiates improve pain or function with long-term use, and that complete pain relief is unlikely.
- Emphasize improvement in function as a primary goal and that function can improve even while pain in present.
- Advise patients about serious adverse effects to include potentially fatal respiratory depression and development of an opiate use disorder.
- Advise patients of common effects of opiates, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opiates.

- Discuss effects that opiates might have on one's ability to operate a vehicle, particularly when opiates are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol are used concurrently.
- Discuss increased risks for opiate use disorder, respiratory depression, and death at higher dosages, along with taking only the amount that is prescribed – not taking more or taking them more often.
- Review increased risks for respiratory depression when opiates are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opiates.
- Discuss risks to household members and other individuals if opiates are intentionally or unintentionally shared with others from whom they are not prescribed.
- Discuss the importance of periodic reassessment to ensure that opiates are helping to meet patient goals and to allow opportunities for opiate discontinuation and consideration of additional nonpharmacologic or nonopiate pharmacologic treatment options of opiates are not effective or are harmful.
- Discuss planned use of precautions to reduce risks. Consider including a discussion of naloxone use for overdose reversal.
- Consider whether cognitive limitations might interfere with management of opiate therapy, and if so, determine whether a caregiver can responsibly co-manage opiate therapy. Discuss the importance of reassessing safer medication use with both patient and caregiver.

In addition, whenever an opiate is prescribed, the patient should be thoroughly educated about the safe storage and disposal of opiate 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, reviewing and avoiding potentially dangerous drug interactions with other drugs, and assuring full understanding of how the medication should be consumed or, in some cases applied.

Safe storage means reminding patients that pain medications are sought after by many people, and, thus it is best if opiates are stored in a locked cabinet or other secure storage unit. If a locked unit is not available, patients should, at least, not keep opiates 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 opiates become diverted.[57] Storage areas should be cool, dry, and out of direct sunlight.

Proper disposal means getting rid of unused medications. Patients should:

- Follow any specific disposal instructions on the prescription drug labeling or patient information that accompanies the medication. Do not flush medicines down the sink or toilet unless this information specifically instructs to do so;
- Return medications to a pharmacy, health center, or other organization with a take-back program; or
- Mix the medication with an undesirable substance (e.g., coffee grounds or kitty litter) and putt it in the trash.

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.

Opiate selection

Opiate analgesics are available in a wide range of formulations and routes of administration (i.e., oral, transdermal, transmucosal, rectal, intrathecal). Little evidence exists that specific analgesic formulations affect efficacy or addiction risk, so selection of agent should be based on the patient's pain complaint, lifestyle, and preferences.[58] Generally, if opiates are used at all, it is better to offer short-acting opiates used on an as-needed basis. Extended-release (ER) or long-acting (LA) opiates produce a more steady state of analgesia without the cycling effect of pain relief and withdrawal associated with short-acting opiates, which may be helpful for certain patients.[59] With ER/LA agents, however, patients may end up using more drug than is actually needed, and physiological adaptations to the steady state may ultimately decrease analgesic efficacy.[60] In addition, ER/LA opiates pose a higher risk for being abused. Clinicians should warn patients that oral ER/LA opiates should not be broken, chewed, or crushed. Patches should not be cut or torn prior to use, since this may lead to rapid release of the opiate and could cause overdose or death. ER/LA agents should not be used to treat acute pain.

Prescribers should educate themselves about the general characteristics, toxicities, and drug interactions for ER/LA opiate products. For detailed information on current ER/LA opiate

analgesics, see the FDA Blueprint for Prescriber Education, available at: http://www.er-la-opioidrems.com.

Combination products join an opiate with a non-opiate 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-opiate co-analgesic, even if an increase of the opiate dose is appropriate. In such cases, using a pure opiate is preferable. Care, in particular, must be given to not exceed maximal daily doses of acetaminophen.

Periodic review and monitoring

Regarding duration of use, patients can experience tolerance and loss of effectiveness of opiates over time. Patients who do not experience clinically meaningful pain relief early in treatment (i.e., within one (1) month) are unlikely to experience pain relief with longer-term use. Providers should evaluate benefits and harms with patients within 1 to 4 weeks of starting opiate therapy for chronic pain or dose escalation.

If an opiate medication appears to be helpful (as determined by the functional goals outlined in the management plan) and therapy is continued, regular review and monitoring should be performed for the duration of treatment. Exactly what constitutes "regular" 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 against 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.

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

Those who are taking other medications that may interact with an opiate

If benefits do not outweigh harms of continued opiate therapy, clinicians should optimize other therapies and work with patients to taper opiates to lower dosages or to taper and discontinue opiates.

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.[61] Prescribing high-dose opiate therapy (greater than or equal to 120 mg morphine equivalents/day) may not be appropriate, and in such cases, referral to a provider with specialized skill or experience in dealing with high-risk patients may be prudent. A recent cohort study of 9,940 patients receiving opiate 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 opiates per day.[41] No randomized trials show long-term effectiveness of high opiate doses for chronic non-cancer pain. Many patients on high doses continue to have substantial pain and related dysfunction.[61] As noted earlier, higher doses of opiates are associated with increased risks for adverse events and side effects including overdose, fractures, hormonal changes, and increased pain sensitivity.

Table 3. 100 MED equivalents*

100 morphine equivalents =	**Dose of Opiate**
	42 mcg/hr fentanyl transdermal
	100 mg hydrocodone
	25 mg hydromorphone
	67 mg oxycodone
	33 mg oxymorphone

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

Urine drug screens

Urine drug testing is an imperfect science, but such testing can be a helpful component of responsible opiate prescribing. Drug testing should be conducted in a consensual manner as part of an agreed-upon opiate 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 compliance with the treatment plan

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[62] (a guide for dealing with suspected adulteration of a urine sample or patients suspected of misusing a prescription is available to members of the SDSMA).

Prescribers should be familiar with the metabolites associated with each opiate 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 opiates).[11]

Protecting against opiate-induced adverse events

The Veterans Administration/Department of Defense clinical practice guideline outlines a number of evidence-based strategies to reduce opiate-related adverse effects, summarized in Table 4.[63] Prophylaxsis for constipation, which is the most common opiate-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.

Table 4: Recommendations for preventing or treating opiate-induced side effects[63]

Constipation	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	Consider prophylactic antiemetic therapy Add or increase non-opiate pain control agents (e.g., acetaminophen) If analgesia is satisfactory, decrease dose by 25 percent Treat based on cause
Sedation	Determine whether sedation is due to the opiate Eliminate nonessential CNS depressants (such as benzodiazepines) If analgesia is satisfactory, reduce dose by 10-15 percent Add or increase non-opiate or non-sedating adjuvant for additional pain relief (such as NSAID or acetaminophen)so the opiate can be reduced Add stimulant in the morning (such as caffeine) Change opiate
Pruritus	Consider treatment with antihistamines Change opiate
Hallucination or dysphoria	Evaluate underlying cause 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 opiates is particularly problematic since these agents act synergistically to depress respiratory functioning.

Opiate rotation

Switching from one opiate 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.

Opiate 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 opiate 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.[64] 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 opiates because of differences in the receptors or receptor sub-types to which different opiates bind. Do not simultaneously switch both an agent *and* a route of administration or type of release (e.g., ER/LA)

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 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.[31]

Non-opiate 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 opiate 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 opiate medications for pain flares.

Using prescription monitoring programs

Potential benefits of prescription drug monitoring programs (PDMPs) and urine drug testing include the ability to identify patients who might be at higher risk for opiate overdose or opiate use disorder, and help determine which patients may benefit from great caution and increased monitoring or interventions when risk factors are present. Research indicates that most fatal overdoses could be identified retrospectively on the basis of two pieces of information – multiple prescribers and high total daily opiate dosage – both of which are available to prescribers through the South Dakota PDMP.

South Dakota's PDMP offers point-of-care access to pharmacy dispensing records of controlled substances from prescribers. From these, clinicians can quickly assess patterns of prescription drug use that can be helpful in confirming or refuting suspicions of aberrant behaviors.

Information from the PDMP may also reveal that a patient is being prescribed medications whose combinations are contraindicated. By reviewing the PDMP each prescriber can identify other prescribers involved in the care of their patient. This can be especially useful for new patients to a practice on high dose opiates, with suspect or concerning behaviors.
Pharmacies and practitioners that dispense any Schedule II, III, or IV controlled substances in South Dakota, or to an address in South Dakota, must report such dispensing to the PDMP.

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.[31] 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

For persistent non-compliance, options include one or more of the following:

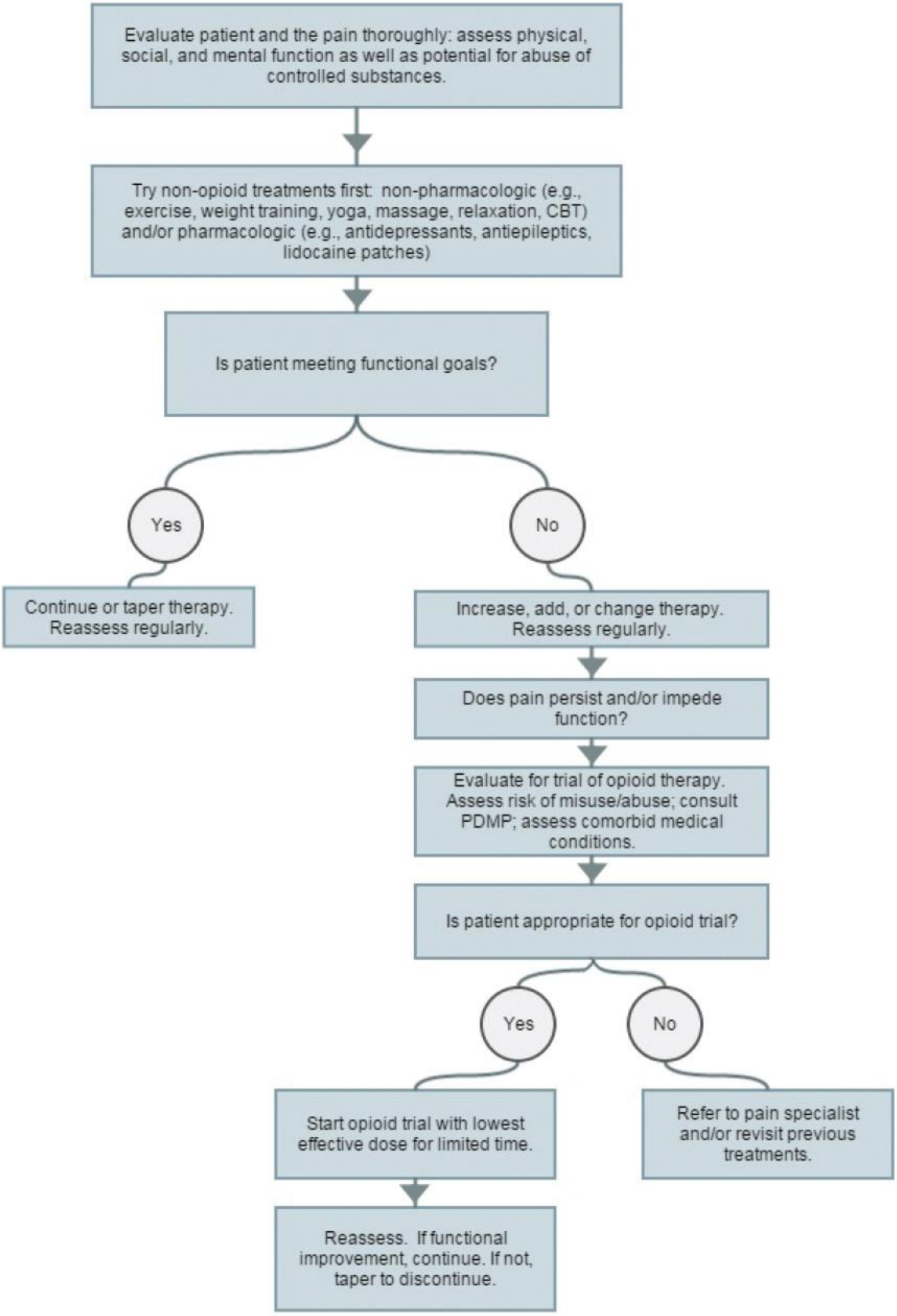
- Tapering drug therapy over several weeks to avoid withdrawal; consider incorporating non-opiate pain treatments.
- Referral to specialists, e.g., pain specialist, for evaluation of continued controlled substance prescribing
- Referral to an addiction management program

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. A Legal Brief on Reporting Patient Drug Use or Diversion is available from the SDSMA and provides more detailed information on this topic.

Roadmap for responsible opiate prescribing

The algorithm on the following page summarizes the guidance presented in this section. It emphasizes the need to pursue non-opiate therapies first, to rigorously assess patients, and to work within a function-based paradigm of care.

Figure 3. Algorithm for pain management



Discontinuing opiate therapy

Discontinuation of an opiate 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 opiate 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 the primary care ~~physicians~~provider. In such cases, referral to a provider with specialized skill or experience in dealing with high-risk patients may be prudent.

Stopping long-term opiate therapy is often more difficult than starting it[65] and it is important to understand what triggers withdrawal in people is highly variable. For most patients, the opiate dose may be tapered by 20 to 50 percent of the current dose per week; however, if time allows, a ~~physician~~ provider may go considerably slower to give every possible chance for success. The longer the patient has been on the drug, and the higher the initial dose, the slower the taper should be.[63] A taper of 10 percent every two weeks may provide the patient an opportunity to learn and deal with an increase in pain as the dosage of opiates is reduced. Of note, if diversion is in question, it may be appropriate to stop writing immediately with the recommendation that the patient report to the emergency room if they go into withdrawal.

Opiates and pregnancy

Current American Pain Society-American Academy of Pain Medicine (APS-AAPM) guidelines suggest that clinicians should avoid prescribing opiates during pregnancy unless the potential benefits outweigh risks.[11] Some data suggest an association between the use of long-term opiate 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.[11] Exposure to these medications has also been associated with birth defects in some studies. Opiate withdrawal can be expected in up to half of newborns of opiate-dependent mothers (neonatal abstinence syndrome).[11] If a mother is receiving long-term opiate therapy at or near the time of delivery, a professional experienced in the management of neonatal withdrawal should be available – per ASAM, ACOG, and AAP, neonatal abstinence can be effectively treated with no long-term, harmful effects on mom or baby.

Reducing the risk of overdose

Opiate overdose is reversible through the timely administration of the medication naloxone (trade name Narcan). Narcan is a prescription drug, but it is not a controlled substance and has no abuse potential. It is regularly carried by medical first responders and, as of July 1, 2015, such use became legal in South Dakota.

As an opiate antagonist, naloxone can quickly restore normal respiration to a person whose breathing has slowed or stopped as a result of heroin or prescription opiate overdose. As of 2010, programs that distribute naloxone to nonmedical personnel had reported more than 10,000 overdose reversals nationwide since 1996.[66] As of November 2014, 23 states have statutes that allow for "third-party" prescriptions of naloxone (i.e., the prescription can be written to friend, relative or person in a position to assist a person at risk of experiencing an opiate overdose). This kind of prescription has not yet been legalized in South Dakota.

Given the effectiveness of naloxone in overdose reversal, the FDA has encouraged innovations in more user-friendly naloxone delivery systems such as auto-injectors, made particularly for lay use outside of health care settings. The FDA approved such an auto-injector in 2014.

Special populations

A full discussion of the many non-opiate pain treatment modalities, and how those modalities can be employed to manage pain across all disease states and conditions is beyond the scope of these guidelines, which focus primarily on the use of opiates. But a brief review of pain management recommendations in some common patient populations is warranted, since these often involve decisions about whether to use opiates and, if so, how they can most optimally be prescribed.

Emergency department, urgent, and acute care patients

Pain is a frequent complaint of emergency room (ER) patients, and ER physicians are among the higher prescribers of opiates to patients ages 10-40.[67] ER, urgent and acute care ~~physicians~~providers, however, face considerable challenges in determining a patient's appropriateness for opiate therapy. A medical history is often lacking, and the ~~physician~~ provider seldom knows the patient personally. Time constraints, as well, can preclude the kinds of careful assessment and evaluation recommended for responsible opiate prescribing. Because of this, current guidelines from the American College of Emergency Physicians (ACEP) include the following recommendations:[68]

1. For the patient being discharged from the emergency department (ED), urgent or acute care setting with acute pain, the ~~physician~~ provider should ascertain whether non-opiate analgesics and non-pharmacologic therapies will be adequate for initial pain management
2. Given a lack of demonstrated evidence of superior efficacy of either opiate or non-opiate analgesics and the individual and community risks associated with opiate use, misuse, and abuse, opiates should be reserved for more severe pain or pain refractory to other analgesics rather than routinely prescribed.
3. If opiates are indicated, the prescription should be for the lowest practical dose for a limited duration (e.g., less than 1 week), and the prescriber should consider the patient's risk for opiate misuse, abuse, or diversion.

For patients presenting to the ED, urgent or acute care setting with an acute exacerbation or non-cancer chronic pain, the SDSMA recommends the following:

1. Opiates are appropriate to treat acute illness or injury; however, ~~physicians~~ providers should avoid the routine prescribing of outpatient opiates for a patient with an acute exacerbation of chronic non-cancer pain seen in the ED, urgent or acute care settings
2. If opiates are prescribed on discharge, the prescription should be limited to the amount needed until follow-up, and should not exceed seven (7) days. In prescribing, the prescriber should consider the patient's risk for opiate misuse, abuse, or diversion
3. A patient should not receive narcotic prescriptions from multiple doctors. Emergency, urgent and acute care ~~physicians~~ providers should not prescribe additional narcotics for a

condition previously treated in the ED, urgent or acute care setting or by another ~~physician~~ provider unless there are extenuating circumstances

4. Patients with chronic non-cancer pain should not receive injections of opiates in the ED, urgent or acute care setting
5. Emergency, urgent and acute care ~~physicians~~ providers should not prescribe long acting narcotic agents such as oxycontin, extended release morphine or methadone. Oxycodone (ex. Percocet), hydrocodone (ex. Vicodin) and hydromorphone (Dilaudid) have high abuse potential and the ~~physician~~ provider should consider using alternative agents
6. Emergency, urgent and acute care ~~physicians~~ providers should not replace lost or stolen prescriptions for controlled substances
7. Emergency, urgent and acute care ~~physicians~~ providers should not fill prescriptions for patients who have run out of pain medications. Refills are to be arranged with the primary provider or specialty prescribing physician
8. Narcotic pain medication is discouraged for certain conditions including:
    a. Back pain – whether acute or chronic
    b. Routine dental pain
    c. Migraines
    d. Chronic abdominal or pelvic pain and gastroparesis
9. Patients with suspected substance abuse behavior should be referred to appropriate resources
10. Prior to prescribing, the emergency, urgent and acute care providers ~~physician~~ should consider accessing the state's prescription drug monitoring program
11. Patients identified with multiple ED, urgent and/or acute care visits for pain, problematic or dishonest behavior (abusive, altering prescriptions, false reports) or use of multiple hospitals for pain should be reviewed by the ~~physician~~ health care leadership team – which should consider the following actions
    a. Sending a certified letter stating the patient will no longer be provided opiates in the ED, urgent and/or acute care setting
    b. Adding an internal code (ex. 555) identifying probable drug seeking behavior into their medical record.

Cancer pain

Pain is one of the most common symptoms of cancer, as well as being one of the most-feared cancer symptoms. Pain is experienced by about 30 percent of patients newly diagnosed with cancer, 30 to 50 percent of patients undergoing treatment, and 70 to 90 percent of patients with advanced disease.[16] Unrelieved pain adversely impacts motivation, mood, interactions with family and friends, and overall quality of life. Survival itself may be positively associated with adequate pain control.[69] Opiate pain medications are the appropriate to consider for cancer patients with moderate or severe pain, regardless of the known or suspected pain mechanism.[70] ER/LA opiate formulations may optimize analgesia and lessen the inconvenience associated with the use of short-acting opiates. Patient-controlled analgesia with subcutaneous administration using an ambulatory infusion device may provide optimal patient control and effective analgesia.[71] The full range of adjuvant medications covered earlier should be considered for patients with cancer pain, with the caveat that such patients are often on already complicated pharmacological regimens, which raises the risk of adverse reactions associated with polypharmacy. If cancer pain occurs in the context of a patient nearing the end of life, other treatment and care considerations may be appropriate. In these cases, patient integrated with a specialist in palliative care medicine may be advisable.

Pain at the end of life

Pain management at the end of life seeks to improve or maintain a patient's overall quality of life. This focus is important because sometimes a patient may have priorities that compete with, or supersede, the relief of pain. For some patients mental alertness sufficient to allow lucid interactions with loved ones may be more important than physical comfort. Optimal pain management, in such cases, may mean lower doses of an analgesic and the experience, by the patient, of higher levels of pain.

Since dying patients may be unconscious or only partially conscious, assessing their level of pain can be difficult. Nonverbal signs or cues must sometimes be used to determine if the patient is experiencing pain and to what degree an analgesic approach is effective. In general, even ambiguous signs of discomfort should usually be treated, although caution must be exercised in interpreting such signs.[72] Reports by family members or other people close to a patient should

not be overlooked. In the Study to Understand Prognosis and Preference for Outcomes and Risks of Treatment (SUPPORT) , surrogates for patients who could not communicate verbally had a 73.5 percent accuracy rate in estimating presence or absence of the patient's pain.[73]

Opiates often are useful to providing effective analgesia at the end of life, and they are available in such a range of strengths, routes of administration, and duration of action that an effective pain regimen can be tailored to nearly each patient. No specific opiate is superior to another as first-line therapy. Rectal and transdermal routes of administration can be valuable at the end of life when the oral route is precluded because of reduced or absent consciousness, difficulty swallowing, or to reduce the chances of nausea and vomiting.[74] When selecting an opiate, clinicians should also consider cost, since expensive agents can place undue burden on patients and families.

Fear of inducing severe or even fatal respiratory depression may lead to clinician under-prescribing and reluctance by patients to take an opiate medication.[28] Despite this fear, studies have revealed no correlation between opiate dose, timing of opiate administration, and time of death in patients using opiates in the context of terminal illness.[75] A consult with a specialist in palliative medicine in these situations may be advisable.

Older Adults

The prevalence of pain among community-dwelling older adults has been estimated between 25 and 50 percent.[76] The prevalence of pain in nursing homes is even higher. Unfortunately, managing pain in older adults is challenging due to underreporting of symptoms; presence of multiple medical conditions; polypharmacy; declines in liver and kidney function; problems with communication, mobility, and safety; and cognitive and functional decline in general. Acetaminophen is considered the drug of choice for mild-to-moderate pain in older adults because it lacks the gastrointestinal, bleeding, renal toxicities, and cognitive side-effects that have been observed with NSAIDs in older adults (although acetaminophen may pose a risk of liver damage). Opiates must be used with particular caution, and clinicians should "start low, go slow" with initial doses and subsequent titration. Clinicians should consult the American

Geriatrics Society *Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults* for further information on the many medications that may not be recommended.[31] The many challenges of pain management in older adults, only sketched here, suggest that early referral and/or consultation with geriatric specialists or pain specialists may be advisable.

Conclusions

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

When used for severe acute pain in time- and dose-limited ways, or for the relief of cancer and end-of-life pain, opiates can be uniquely valuable and the risks of addiction and abuse are low. The benefits of using opiates 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 opiates with other respiratory depressants such as alcohol or benzodiazepines.

These guidelines have outlined an evidence-based strategy for identifying patients for whom the benefits of long-term opiate therapy might outweigh the risks. It is intended neither as an exhaustive review nor a standard of care. Rather, it summarizes established methods for appropriately prescribing opiate analgesics. Appropriate prescribing of opiates can be challenging, but it is not inherently different from the challenges ~~physicians~~ health care providers face when using any other treatment option that carries significant risks of harm. It is both feasible and necessary for clinicians to treat pain effectively while minimizing risk.

Resources

American Academy of Pain Medicine
www.painmed.org

Depression Anxiety & Positive Outlook Scale
www.dapos.org

Drug Enforcement Administration Diversion Control Program
www.DEAdiversion.usdoj.gov

FDA Blueprint for Prescriber Education
http://www.er-la-opioidrems.com

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

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

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

Patient Health Questionnaire
www.phqscreeners.com

PainLaw.org
www.painlaw.org

Risk reduction strategies (free online CME)
www.opioidprescribing.com

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

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

Appendix I: Sample Patient/Provider Agreement

[Directions for Use – it is it is recommended that the provider create a pre-printed form with the provider's name inserted anywhere the words "your health care provider" are used; doing so should help avoid confusion and will otherwise make the form more user-friendly for both the patient and the provider.]

Opiate Pain Medication

Treatment Agreement and Informed Consent

Safe and effective treatment with opiate pain medications requires your understanding and your cooperation as is outlined below. Please read each item and check the box if you understand and agree to comply with the statement. If you do not understand the statement, or if you do not agree to it, please discuss the item with your healthcare provider.

Examples of opiate pain medications include, but are not limited to morphine, hydrocodone, oxycodone, hydromorphone, fentanyl and methadone.

I the patient understand and agree as follows:

Agreement Basics.

☐ 1. Your routine opiate pain medications need to be prescribed only by **your health care provider, Dr._____,** or another healthcare provider that he/she may choose and name in writing. Do not ask for or accept opiate pain medications from other health care providers.

☐ 2. You may only get your opiate pain medications from one designated pharmacy. You have selected _____. Your pharmacy choice can be changed by notifying **your health care provider** in advance.

☐ 3. Do not take opiate pain medications at a larger dose or more often than has been prescribed. If I take too much pain medication or more often than prescribed, I understand that I could have complications and I could die. If I am not satisfied with my treatment, I am to call my **health care provider**.

☐ 4. Do not give or sell your opiate pain medications to anyone. Do not take opiate pain medications prescribed or otherwise obtained from any source except **your health care provider**. Do not take drugs from non-medical sources. Do not take illegal drugs.

☐ 5. You must give an honest and complete past medical history, including prior opiate treatment, current medications (including over-the-counter medications), current and past non-medical drug use, chemical dependency treatment, and psychiatric diagnoses and treatment. You should consent to communication among your current and past health care providers.

☐ 6. Inform any other healthcare provider who treats you that you have an Opiate Pain Medication Treatment Agreement with **your health care provider**.

☐ 7. Contact **your health care provider** before taking any outpatient opiate pain medication that may be prescribed by an emergency room or at hospital discharge. Contact **your health care provider** when you have been treated with opiate pain medications in an emergency room. This Agreement does not prevent you from being treated with opiate pain medications in an emergency room or when you have been admitted to a hospital.

☐ 8. You are required to undergo laboratory drug testing promptly when asked. This may include urine, blood or hair. This request may come at the start of treatment, randomly, or from time-to-time when requested by **your health care provider**.

☐ 9. Chronic pain treatment requires full and cooperative patient participation. Besides routine office visits, this may include physical therapy, counseling, and chemical dependency assessment. Frequent late arrivals, cancelling less than 24 hours before a scheduled appointment and/or not showing up for appointments is not acceptable.

☐ 10. You must accept and cooperate with **your health care provider's** prescription writing and renewal practices. This may include only receiving prescriptions at scheduled, in-person appointments.

☐ 11. Tell **your health care provider** if you are pregnant or may become pregnant.

☐ 12. The goal of opiate pain medication is to assist with pain control in order to allow for improved function and successful living. Relief of 100 percent of pain is usually not possible or necessary. Your health care provider may stop your opiate medication if your function does not improve.

Prescription and medication management safety.

☐ 13. Do not lose your prescription form. Immediately filling your prescription at your pharmacy of choice may be best. Do not lose or damage your pills.

☐ 14. Prescription form or pill loss may cause you to lose your access to opiate pain medications. Lost prescription forms or pills will not necessarily be replaced.

☐ 15. If your behavior causes **your health care provider** to become concerned about a chemical dependency problem, referral for a chemical dependency assessment may be made.

☐ 16. Keep your medications in a lock box. Do not give others access to your key or combination to your lock box. Take out a daily medication supply each day and keep it in your personal possession.

☐ 17. Do not handle your opiate pain medication by a sink or toilet. Only open your lock box after placing it on a table.

☐ 18. Some people do not tolerate opiates well and as a result may feel tired or not as alert as normal. Temporary periods of drowsiness may occur when drugs are new or when dose has been increased. In any event, there should be **no driving or operating powered machinery or equipment if there is any question of your ability to do so safely and alertly.** Discussion and agreement among you, a household or family member, and **your health care provider** is best.

☐ 19. Do not consume alcohol while taking opiate pain medications.

Opiate information.

☐ 20. Opiate medicine shouldn't be stopped suddenly. Another way of saying this is to say that routine use of opiates may cause physical dependence. Suddenly stopping opiates after prolonged routine use may cause a feeling of withdrawal over the course of several days or more. Opiate withdrawal is not dangerous, but it can be a miserable experience for some patients. Usually, it is preventable with a slow taper-down of the medication. Withdrawal symptoms can include increased pain, anxiety, sweating, yawning, difficulty sleeping, tearing, and loose stools.

☐ 21. Addiction is completely unrelated to physical dependence. Addiction, also called chemical dependency, is a short-circuit of the reward system of the brain. Instead of feeling good on account of family, career, religion, and recreation, people with chemical dependency substitute a drug for their reward. In a well-structured opiate prescribing program, the chance of developing a new chemical dependency problem is low.

☐ 22. Any of your healthcare providers can find out from the South Dakota Prescription Drug Monitoring Program (the "Program") about all opiate medications you fill at pharmacies in South Dakota and surrounding states. **Your health care provider** is obligated to report your prescriptions to the Program. Doctor shopping is a crime in South Dakota.

☐ 23. Routine opiate use may suppress the pituitary gland. This is most significant in men. An annual testosterone blood level test can monitor for this in men. Decreased testosterone can cause sweating, depression, decreased libido, and it can have an adverse effect on bone health. Tapering down or off opiates returns pituitary function to normal.

☐ 24. Opiates can cause or aggravate sleep apnea.

☐ 25. Opiates do not damage organs. They do not cause stomach, liver, kidney, blood vessel, or nerve injury.

☐ 26. Opiates must be used cautiously if you have chronic obstructive lung disease. Opiates can cause respiratory depression if a large dose is given to someone whose body is inexperienced with opiates.

☐ 27. Nausea, itching and hives occur, and are more common at the beginning of treatment. Constipation is common with opiates, and must be managed on an ongoing basis. Dry mouth is occurs occasionally and is very bad for dental health. Difficulty initiating urination in men seems more common with morphine, and may be a reason to not use that drug.

☐ 28. What benefit opiates are providing to any individual remains under ongoing review. Establishing a correct dose at the beginning of treatment must be done by a slow taper-up. Determining what this is needed after a period of success is done by slow taper-down. High-dose opiates with poor pain control and functional result may be an indication for taper-down.

I the patient acknowledge and agree to the contents of this document and consent to treatment with opiate pain medication as proposed by **my health care provider.**

Patient Name: _____

Patient Signature: _____ Date_____

Doctor Name: _____

Doctor Signature: _____ Date_____

Checklist for Prescribing Opiates for Chronic, Non-Cancer Pain

The following checklist is designed to aid primary care providers who use opiates to improve function in patients with chronic pain. Specifically, this checklist is for treating adults (18+) with chronic pain > 3 months, excluding cancer, palliative, and end-of-life care.

CHECKLIST

When CONSIDERING long-term opiate therapy

- ☐ Review patient's medical and psychosocial history.
- ☐ Review results of all physical examinations and laboratory tests, including screening assessments.
- ☐ Check that non-opiate therapies tried and optimized.
- ☐ Evaluate risk of harm or misuse.
  - Confirm that the appropriate state prescription drug monitoring program (PDMP) has been accessed.
  - Check urine drug screen.
- ☐ Obtain an informed consent.
  - Discuss benefits and risks (eg, addiction, overdose) with patient.
- ☐ Assess baseline pain and function (eg, PEG scale).
- ☐ Set realistic goals for pain and function based on diagnosis (eg, walk around the block).
- ☐ Prescribe short-acting opiates using lowest dosage on product labeling; match duration to scheduled reassessment.
- ☐ Set criteria for stopping or continuing opiates.
- ☐ Schedule initial reassessment within 1-4 weeks.

If RENEWING without a patient visit

- ☐ Check that return visit is scheduled ≤ 3 months from last visit. Schedule visit earlier than 3 months if patient is requesting a prescription refill earlier than prescription instruction/dosage.

Continuation versus Initiation - REASSESSING at return visit

- ☐ Check that non-opiate therapies optimized.
- ☐ Assess pain and function (eg, PEG); compare results to baseline.
- ☐ Evaluate progress against agreed-upon treatment for pain relief and function.
  - **Continue opiates only after confirming clinically meaningful improvements in pain and function without significant risks or harm.**
- ☐ Evaluate risk of harm or misuse:
  - Observe patients for signs of over-sedation or overdose risk. If yes – taper dose.
  - Check PDMP.
  - Check for opiate use disorder if indicated (eg, difficulty controlling use). If yes – refer for treatment.
- ☐ Determine whether to continue, adjust, taper, or stop opiates, and document reasoning in clinic record.
- ☐ Calculate opiate dosage morphine milligram equivalent (MME).
  - If ≥ 50 MME/day total (≥ 50mg hydrocodone; ≥ 33mg oxycodone), increase frequency of follow-up; consider offering naloxone.
  - Avoid ≥ 100 MME/day total (≥ 100 mg hydrocodone; ≥ 66mg oxycodone), or carefully justify; consider specialist referral.
- ☐ Schedule reassessment at regular intervals (< 3 months).
- ☐ Patients who may need more frequent or intense monitoring include:
  - Those with a prior history of an addictive disorder or past substance abuse;
  - Those in occupations demanding mental acuity;
  - Older adults;
  - Patients with an unstable or dysfunctional social environment;
  - Those with comorbid psychiatric or medical conditions;
  - Those who are taking benzodiazepines; and
  - Those who are taking other medications that may interact with an opiate – to include at-risk alcohol consumers.

REFERENCE

EVIDENCE ABOUT OPIATE THERAPY

- *Benefits of long-term therapy for chronic, non-cancer pain is not well supported by evidence.*
- *Short-term benefits small to moderate for pain; inconsistent for function.*
- *Insufficient evidence for long-term benefits in low back pain, headache, and fibromyalgia.*

NON-OPIATE THERAPIES

- Use alone or combined with opiates as indicated:
- Non-opiate medications (eg, NSAIDS, TCAs, SNRIs, anti-convulsants).
- Physical treatments (eg, exercise therapy, weight loss).
- Behavioral treatment (eg, CBT).
- Procedures (eg, intra-articular corticosteroids).

EVALUATING RISK OF HARM OR MISUSE

Known risk factors include:

- Illegal drug use; prescription drug use for nonmedical reasons.
- History of substance use disorder or overdose.
- Mental health conditions (eg, depression, anxiety).
- Sleep-disordered breathing.
- Concurrent benzodiazepine use.
- At-risk alcohol consumption (eg, binge drinking).

ASSESSING PAIN AND FUNCTION USING PEG SCALE

- **PEG** score = average 3 individual question scores
- 30% improvement from baseline is clinically meaningful

Q1: What number from 0 - 10 best describes your pain in the last week?
0 = "no pain," 10 = "worst you can imagine"

Q2: What number from 0 - 10 describes how during the past week, pain has interfered with your enjoyment of life?
0 = "not at all," 10 = "complete interference"

Q3: What number from 0 - 10 describes how, during the past week, pain has interfered with your general activity?
0 = "not at all," 10 = "complete interference"

NOTE: Always document assessments as required by applicable law, including any applicable administrative rules or regulations.

SOUTH DAKOTA STATE MEDICAL ASSOCIATION
Values. Ethics. Advocacy.

Acknowledgements

The South Dakota State Medical Association would like to acknowledge the contributions and guidance of the California Medical Association (CMA). Portions of this paper are based on a 2014 whitepaper, *Prescribing Opioids: Care amid Controversy. Recommendations from the California Medical Association's Council on Scientific Affairs* with CMA's permission.

References

1. Centers for Disease Control & Prevention. Increases in poisoning and methadone-related deaths: United States, 1999-2005. *NCHS Health & Stats.* February, 2008 2008.
2. Goodnough A, Zezima K. When children's scribbles hide a prison drug. *New York Times.* May 26, 2011.
3. Goertz M, Thorson D, Bonsell J, et al. *Adult acute and subacute low back pain.* Bloomington, MN: Institute for Clinical Systems Improvement; November 2012 2012.
4. Rodgers J, Cunningham K, Fitzgerald K, Finnerty E. Opioid consumption following outpatient upper extremity surgery. *The Journal of hand surgery.* Apr 2012;37(4):645-650.
5. Centers for Disease C, Prevention. Adult use of prescription opioid pain medications - Utah, 2008. *MMWR. Morbidity and mortality weekly report.* Feb 19 2010;59(6):153-157.
6. Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: results from the TROUP study. *J Pain.* Nov 2008;9(11):1026-1035.
7. Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. *The Clinical journal of pain.* Jul-Aug 2008;24(6):521-527.
8. Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *Journal of general internal medicine.* Dec 2011;26(12):1450-1457.
9. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain.* Apr 2009;142(3):194-201.
10. Centers for Disease Control & Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR. Morbidity and mortality weekly report.* Nov 4 2011;60(43):1487-1492.
11. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain.* Feb 2009;10(2):113-130.
12. Von Korff M, Kolodny A, Deyo RA, Chou R. Long-term opioid therapy reconsidered. *Annals of internal medicine.* Sep 6 2011;155(5):325-328.
13. Sites BD, Beach ML, Davis MA. Increases in the use of prescription opioid analgesics and the lack of improvement in disability metrics among users. *Regional anesthesia and pain medicine.* Jan-Feb 2014;39(1):6-12.
14. Fox CD, Berger D, Fine P, et al. *Pain assessment and treatment in the managed care environment: a position statement from the American Pain Society.* Glenview, IL: American Pain Society;2000.
15. NCHS. *Health, United States, 2006 with Chartbook on trends in the health of Americans.* Hyattsville, MD: U.S. Department of Health and Human Services;2006.
16. American Cancer Society. *Cancer Facts and Figures, 2012.* Atlanta, GA: American Cancer Society;2012.
17. Becker N, Bondegaard Thomsen A, Olsen AK, Sjogren P, Bech P, Eriksen J. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. *Pain.* Dec 1997;73(3):393-400.

18. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain. Supplement.* 1986;3:S1-226.
19. Alexander J, Black A. Pain mechanisms and the management of neuropathic pain. *Current opinion in neurology and neurosurgery.* Apr 1992;5(2):228-234.
20. Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature.* Nov 28 1996;384(6607):360-364.
21. Arner S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain.* Apr 1988;33(1):11-23.
22. Covington EC. Anticonvulsants for neuropathic pain and detoxification. *Cleveland Clinic journal of medicine.* 1998;65 Suppl 1:SI21-29; discussion SI45-27.
23. American Society of Addiction Medicine. *Definitions related to the use of opioids for the treatment of pain. Consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American society of Addiction Medicine.* 2001.
24. American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* Apr 2012;60(4):616-631.
25. Food and Drug Administration. Prescription drug products containing acetaminophen; actions to reduce liver injury from unintentional overdose. Federal Register. 2011;76(10):2691-2697. http://www.gpo.gov/fdsys/pkg/FR-2011-01-14/html/2011-709.htm. 2011.
26. Paice JA, Ferrans CE, Lashley FR, Shott S, Vizgirda V, Pitrak D. Topical capsaicin in the management of HIV-associated peripheral neuropathy. *J Pain Symptom Manage.* Jan 2000;19(1):45-52.
27. Low PA, Opfer-Gehrking TL, Dyck PJ, Litchy WJ, O'Brien PC. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. *Pain.* Aug 1995;62(2):163-168.
28. Max MB PR, Edwards WT, et al.,. *Principles of analgesic use in the treatment of acute pain and cancer pain. 4th Edition.* Glenview, IL: American Pain Society; 1999.
29. Macdonald RL, Kelly KM. Mechanisms of action of currently prescribed and newly developed antiepileptic drugs. *Epilepsia.* 1994;35 Suppl 4:S41-50.
30. California Medical Association. *Prescribing Opioids: Care amid Controversy. Recommendations from the California Medical Association's Council on Scientific Affairs.* March, 2014.
31. Fishman SM. *Responsible Opioid Prescribing: A Clinician's Guide, 2nd Ed.* Washington, DC: Waterford Life Sciences; 2012.
32. Washington State Department of Labor & Industries. *Guideline for prescribing opioids to treat pain in injured workers.* Office of the Medical Director;2013.
33. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *The Cochrane database of systematic reviews.* (1):CD006605.
34. Agency for Healthcare Research and Quality. The effectiveness and risks of long-term opioid treatment of chronic pain. 2014.
35. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of internal medicine.* Jan 16 2007;146(2):116-127.
36. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain.* Jul 2007;8(7):573-582.
37. Banta-Green CJ, Merrill JO, Doyle SR, Boudreau DM, Calsyn DA. Opioid use behaviors, mental health and pain--development of a typology of chronic pain patients. *Drug and alcohol dependence.* Sep 1 2009;104(1-2):34-42.
38. Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain medicine.* May-Jun 2008;9(4):444-459.
39. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *The Clinical journal of pain.* Jul 2014;30(7):557-564.

40. Boscarino JA, Rukstalis MR, Hoffman SN, et al. Prevalence of prescription opioid-use disorder among chronic pain patients: comparison of the DSM-5 vs. DSM-4 diagnostic criteria. *Journal of addictive diseases.* Jul-Sep 2011;30(3):185-194.

41. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of internal medicine.* Jan 19 2010;152(2):85-92.

42. American Pain Society. Guideline for the use of chroni opioid therapy in chronic noncancer pain. 2009.

43. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther.* 2005;7(5):R1046-1051.

44. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf.* 2007;30(2):171-184.

45. Miller M, Sturmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. *J Am Geriatr Soc.* Mar 2011;59(3):430-438.

46. Brack A, Rittner HL, Stein C. Immunosuppressive effects of opioids--clinical relevance. *Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology.* Dec 2011;6(4):490-502.

47. Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. *J Am Geriatr Soc.* Oct 2011;59(10):1899-1907.

48. McCaffery M, Pasero C. Assessment: underlying complexities, misconceptions, and practical tools. In: McCaffery M, Pasero C, eds. *Pain Clinical Manual, 2nd Ed.* St. Louis, MO: Mosby Inc.; 1999:35-102.

49. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* Oct 1983;17(2):197-210.

50. Melzack R. The short-form McGill Pain Questionnaire. *Pain.* Aug 1987;30(2):191-197.

51. Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. *Psychological medicine.* May 2006;36(5):575-586.

52. Gourlay D, Heit H. Universal precautions: a matter of mutual trust and responsibility. *Pain medicine.* Mar-Apr 2006;7(2):210-211; author reply 212.

53. Roskos SE, Keenum AJ, Newman LM, Wallace LS. Literacy demands and formatting characteristics of opioid contracts in chronic nonmalignant pain management. *J Pain.* Oct 2007;8(10):753-758.

54. Fishman SM, Mahajan G, Wilsey B. Author response to: The trilateral opioid contract: bridging the pain clinic and the primary care physician through the opioid contract. *J Pain Symptom Manage.* 2003;25(5):403.

55. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Annals of the Academy of Medicine, Singapore.* Mar 1994;23(2):129-138.

56. Payne R, Anderson E, Arnold R, et al. A rose by any other name: pain contracts/agreements. *The American journal of bioethics : AJOB.* Nov 2010;10(11):5-12.

57. Levine DA. "Pharming": the abuse of prescription and over-the-counter drugs in teens. *Current opinion in pediatrics.* Jun 2007;19(3):270-274.

58. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med.* Nov 13 2003;349(20):1943-1953.

59. Young SS, Ballantyne JC, Domino FJ, Wetterau NW. *Balancing clinical and risk management considerations for chronic pain patients on opioid therapy: CME monograph.* American Academy of Family Physicians;2008.

60. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain.* Jun 2007;129(3):235-255.

61. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. *The Clinical journal of pain.* Nov-Dec 2009;25(9):743-751.

62. Webster LR, Dove B. *Avoiding opioid abuse while managing pain.* North Branch, MN: Sunrise River Press; 2007.

63. VA/DoD. The management of opioid therapy for chronic pain working group. VA/DoD clinical practice guidelines for the management of opiod therapy for chronic pain. 2003(contract number: V101 (93)).

64. Webster LR, Fine PG. Overdose deaths demand a new paradigm for opioid rotation. *Pain medicine.* Apr 2012;13(4):571-574.

65. Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM. A Clinical Trial Comparing Tapering Doses of Buprenorphine with Steady Doses for Chronic Pain and Co-existent Opioid Addiction. *Journal of addiction medicine.* Sep 2010;4(3):140-146.
66. Centers for Disease Control and Prevention. Community-based opioid overdose prevention programs providing naloxone—United States, 2010. MMWR. 2012;61(6):101–105.
67. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. *Jama.* Apr 6 2011;305(13):1299-1301.
68. Cantrill SV, Brown MD, Carlisle RJ, et al. Clinical policy: critical issues in the prescribing of opioids for adult patients in the emergency department. *Annals of emergency medicine.* Oct 2012;60(4):499-525.
69. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med.* Mar 3 1994;330(9):592-596.
70. Cherny NI, Thaler HT, Friedlander-Klar H, et al. Opioid responsiveness of cancer pain syndromes caused by neuropathic or nociceptive mechanisms: a combined analysis of controlled, single-dose studies. *Neurology.* May 1994;44(5):857-861.
71. Bader P ED, Fonteyne V, et al. . *Guidelines on pain management.* 2010.
72. Forrow L SH. Pain management in end of life: palliative care. In: Warfield CA BZ, ed. *Principles & Practice of Pain Medicine*. 2nd ed. New York, NY: McGraw-Hill; 2004.
73. Desbiens NA, Mueller-Rizner N. How well do surrogates assess the pain of seriously ill patients? *Critical care medicine.* May 2000;28(5):1347-1352.
74. Mercadante S. Intravenous morphine for management of cancer pain. *The Lancet. Oncology.* May 2010;11(5):484-489.
75. Morita T, Tsunoda J, Inoue S, Chihara S. Effects of high dose opioids and sedatives on survival in terminally ill cancer patients. *J Pain Symptom Manage.* Apr 2001;21(4):282-289.
76. Ferrell BA. Pain management in elderly people. *J Am Geriatr Soc.* Jan 1991;39(1):64-73.