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VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **OPIOID THERAPY FOR CHRONIC PAIN**

Department of Veterans Affairs
Department of Defense

Version 1.0

Prepared by:

THE MANAGEMENT OF **OPIOID THERAPY FOR CHRONIC PAIN** Working Group

With support from:

The Office of Quality and Performance, VA, Washington, DC
&
Quality Management Directorate, United States Army MEDCOM

Contractor and Subcontractor:
West Virginia Medical Institute, Inc.
ACS Federal Healthcare, Inc.

Contract Number: V101(93)P-1633

March 2003
Version 1.0

Based on evidence reviewed until June 2002

THE MANAGEMENT OF OPIOID THERAPY FOR CHRONIC PAIN

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VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **OPIOID THERAPY FOR CHRONIC PAIN**

INTRODUCTION

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INTRODUCTION

In a joint statement, twenty-one health organizations and the Drug Enforcement Administration (AAFP et al., ©1996-2002) addressed issues integral to the appropriate management of opioid therapy in patients with chronic pain:

- *Undertreatment of pain is a serious problem in the United States, including pain among patients with chronic conditions and those who are critically ill or near death. Effective pain management is an integral and important aspect of quality medical care, and pain should be treated aggressively.*

- *For many patients, opioid analgesics—when used as recommended by established pain management guidelines—are the most effective way to treat their pain, and often the only treatment option that provides significant relief.*

- *In spite of regulatory controls, drug abusers obtain these and other prescription medications by diverting them from legitimate channels in several ways, including fraud, theft, forged prescriptions, and via unscrupulous health professionals.*

- *Drug abuse is a serious problem. Those who legally manufacture, distribute, prescribe and dispense controlled substances must be mindful of and have respect for their inherent abuse potential. Focusing only on the abuse potential of a drug, however, could erroneously lead to the conclusion that these medications should be avoided when medically indicated—generating a sense of fear rather than respect for their legitimate properties.*

(AAFP et al., ©1996-2002)

Citing the high prevalence and inadequate treatment of chronic pain, the VA identified pain management as a priority in 1998. Chronic pain management is a broad topic and the exact cause of pain is often multifactorial and imprecise. The VA, in partnership with the DoD, has chosen to take a modular approach in developing a guideline for chronic pain focusing on treatment methods. There is panoply of approaches to the management of chronic pain. Pharmacologic (non opioid), physical, cognitive, interventional and spiritual modalities can be considered in formulating the optimal treatment regimen. When such remedies are not effective, the addition of chronic opioid therapy can be considered. This guideline is focused on chronic opioid therapy (opioid therapy for more than one month), and is directed to the clinician who is interested in knowing more about this approach to the management of chronic pain.

The decision to narrow the scope of this guideline to opioid therapy for chronic non-cancer pain, as opposed to chronic pain in general, was debated within the guideline working group. The distinction between "non malignant" or "non cancer" pain and pain in the palliative care setting, where the patient is expected to live less than six months, is somewhat artificial. There is no scientific evidence to suggest that the effects of cancer pain are any worse than non-cancer pain. However, societal aversion to chronic opiate therapy for the population at large dates to the early 1900's and is tempered by the renewed emphasis on the moral imperative to alleviate suffering in the sick. There is a substantial literature on the use of opioids therapy for cancer pain, and in many areas of treatment and follow-up it was possible to apply the same strategies to the patient with non-cancer pain. The workgroup evaluated several suggestions and accepted those that apply to this population, while rejecting those that apply only to the patient with cancer pain.

The use of long-term opioid therapy for patients with chronic pain is increasing. Opioid therapy was once the domain of pain specialists, confined largely to patients with cancer pain. Sales of long-acting opiates have increased by 5 times over the last six years and prescriptions of long-acting opiates are expected to double every 3-4 years. Non-specialists now prescribe opioid therapy, and 95% of long-acting opioids are prescribed for non-cancer pain.

Many practitioners are more comfortable prescribing opioids to patients with "cancer." Despite lack of pain control options in non-cancer patients with pain, some clinicians have been hesitant to prescribe opioids for several reasons:

- The perceived and real legal ramifications of prescribing controlled substances
- Known adverse-effects of opioid therapy
- The need for increasing doses related to tolerance to therapy
- The potential for addiction and abuse of opioids
- The inability to predict when an opioid will be effective
- Incomplete relief when chronic opioids are used to treat non-cancer pain
- Lack of belief in patient subjective reports of pain
- Complexity of having to write monthly prescriptions for controlled substances
- Difficulty dealing with co-morbidities in the chronic pain population

These beliefs form barriers to the use of opioids. To counteract these barriers, respected medical groups and professional societies, recognizing the legitimate place of opioids in medical practice, have issued policy statements. Previous guidelines, such as those developed by the American Pain Society, American Academy of Pain Management, the College of Physicians and Surgeons of Ontario, the Canadian Pain Society, Pain and Policy Group of the World Health Organization, and the Washington State Department of Labor and Industries have also been helpful in breaking down those barriers and form the foundation on which this guideline is built.

The increase in the use of opioids is not without its concerns. A recent comprehensive review (Turk 2002) of chronic opioid therapy found that:

The mean pain reduction is approximately 30% (compared to placebo approximately 15%)
The dropout rates due to adverse events are often greater than 30%
Non-compliance, abuse, and addiction average approximately 18%

The body of literature supporting the use of opioids is still small and inconclusive. In their 1998 Guideline, the Canadian Pain Society noted that "Since the early 1980s, a growing number of retrospective case reports have indicated that properly selected and monitored patients with chronic pain can benefit from the use of long term opioid therapy with few adverse effects and a very low risk of addiction." They found, however, only three randomized controlled trials (RCTs) to offer Level I evidence on the efficacy of scheduled oral opioids for chronic pain patients, and even these may give a more favorable impression of the relative benefits of opioid therapy than is warranted. As an example, the relatively long duration of the three trials included the open-label phase, not just the placebo-controlled phase, and may have created a bias favoring opioid therapy. The overall quality of evidence in this guideline is reflected in the small number of "A" recommendations, or recommendations based on high quality evidence, and the preponderance of lower quality recommendations.

Diversion of legitimate prescriptions for non-medical use is a significant issue in many parts of the country. Sensationalization of OxyContin (oxycodone CR) diversion has led to the restriction of this therapy in parts of the country and within health organizations.

The goal of this VA/DoD Clinical Practice Guideline, the Management of Opioid Therapy for Chronic Pain, is to provide a scientific evidence base for practice interventions and evaluations, specifically in the use of opioids to treat chronic non-cancer pain. The guideline was developed to assist facilities in providing care for chronic pain patients that is evidence-based. The guideline builds on the experience, recommendations and guidelines of the following organizations:

- American Academy of Pain Medicine
- American Pain Society
- American Society of Addiction Medicine
- College of Physicians and Surgeons of Ontario
- Canadian Pain Society
- Pain and Policy Group, World Health Organization
- Washington State Department of Labor and Industries; 2000

Clinical algorithms within the guideline provide a model that clinicians can use to determine the best interventions and timing of care for their patients, reduce the incidence of adverse-effects and other undesirable outcomes, and optimize healthcare utilization. If followed, the guideline is expected to have impact on multiple measurable patient outcome domains.

Finally, the members of our guideline development team hope that the elements of care identified in this guideline will provide fruitful ground for clinical research within our DoD/VA healthcare system. Modifications to the guideline will undoubtedly be necessary as a result of new research and practice-based evidence. The developers believe this guideline should always be considered a work in progress.

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American Academy of Family Physicians (AAFP) et al., ©1996-2002. Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act. A Joint Statement From 21 Health Organizations and the Drug Enforcement Administration. Available at http://www.ampainsoc.org/advocacy/promoting.htm.

Turk DC, Loeser JD, Monarch ES. Chronic pain: purposes and costs of interdisciplinary pain rehabilitation programs. TEN: The Economics of Neuroscience, 2002;9:64-69.

KEY POINTS ADDRESSED BY THIS GUIDELINE

1. Use of opioid therapy when other pain therapies are inadequate.
2. Determine goal of therapy with patient and care givers.
3. Opioid therapy for chronic pain has an average decrease in pain score of 30% with a similar incidence of significant adverse effects.
4. Assure safety— do no harm. Optimize therapy through trial and titration based on assessment.
5. Obtain comprehensive assessment of the patient before initiating therapy.
6. Ongoing assessment of adverse effects, adherence to treatment plan, efficacy, and satisfaction.
7. Written opioid therapy agreement to define patient responsibility.
8. Educate patient about therapy, adverse effects and withdrawal.
9. Apply multimodal adjunctive therapy as indicated by the patient and disease process.
10. Accurate documentation of all prescriptions, agreements and assessments.
11. Referral and/or consultation with pain clinic or substance use specialty when needed.
12. Discontinue opioid therapy when it is not indicated.

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VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **OPIOID THERAPY FOR CHRONIC PAIN**

ALGORITHM & ANNOTATIONS

Version 1.0

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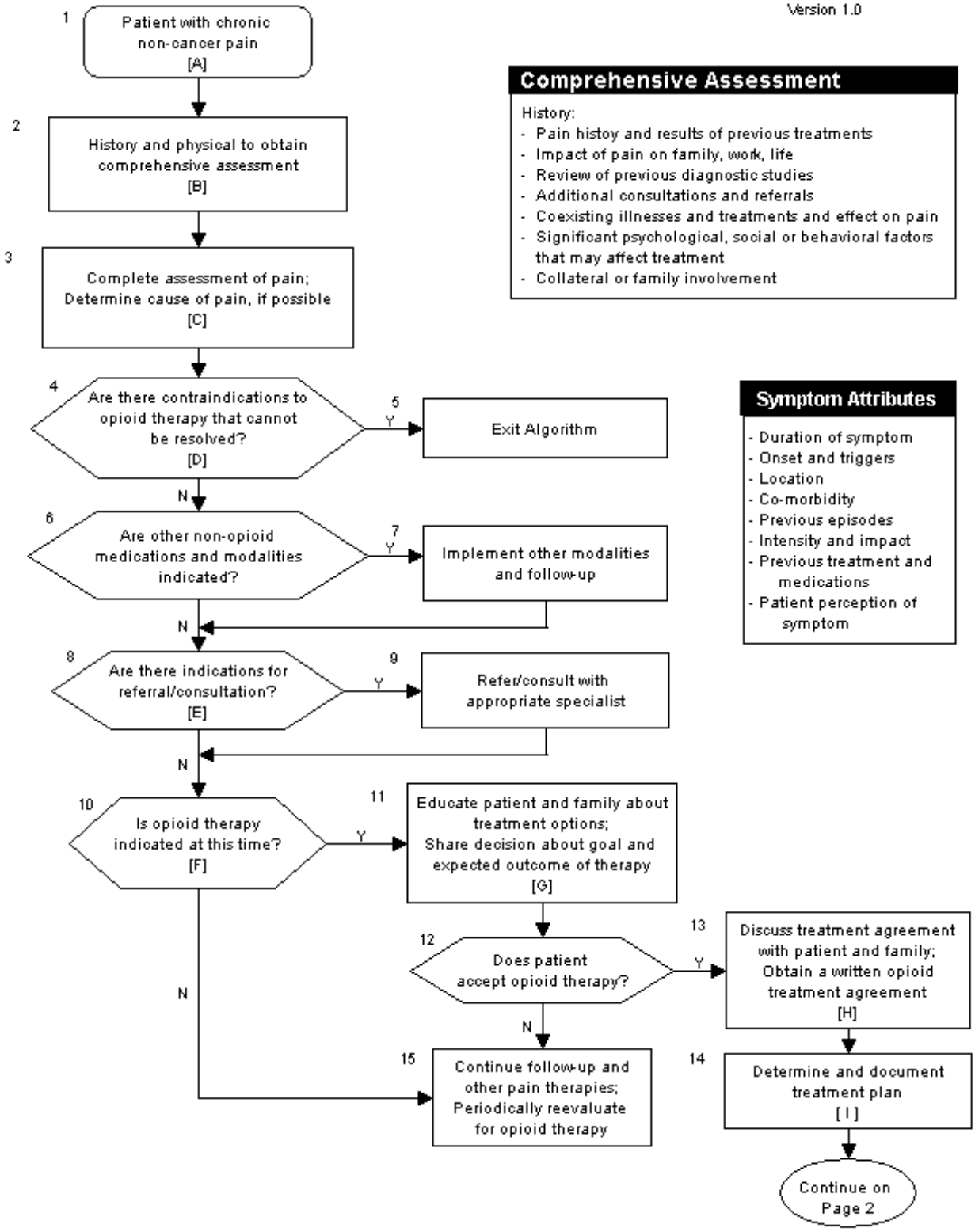

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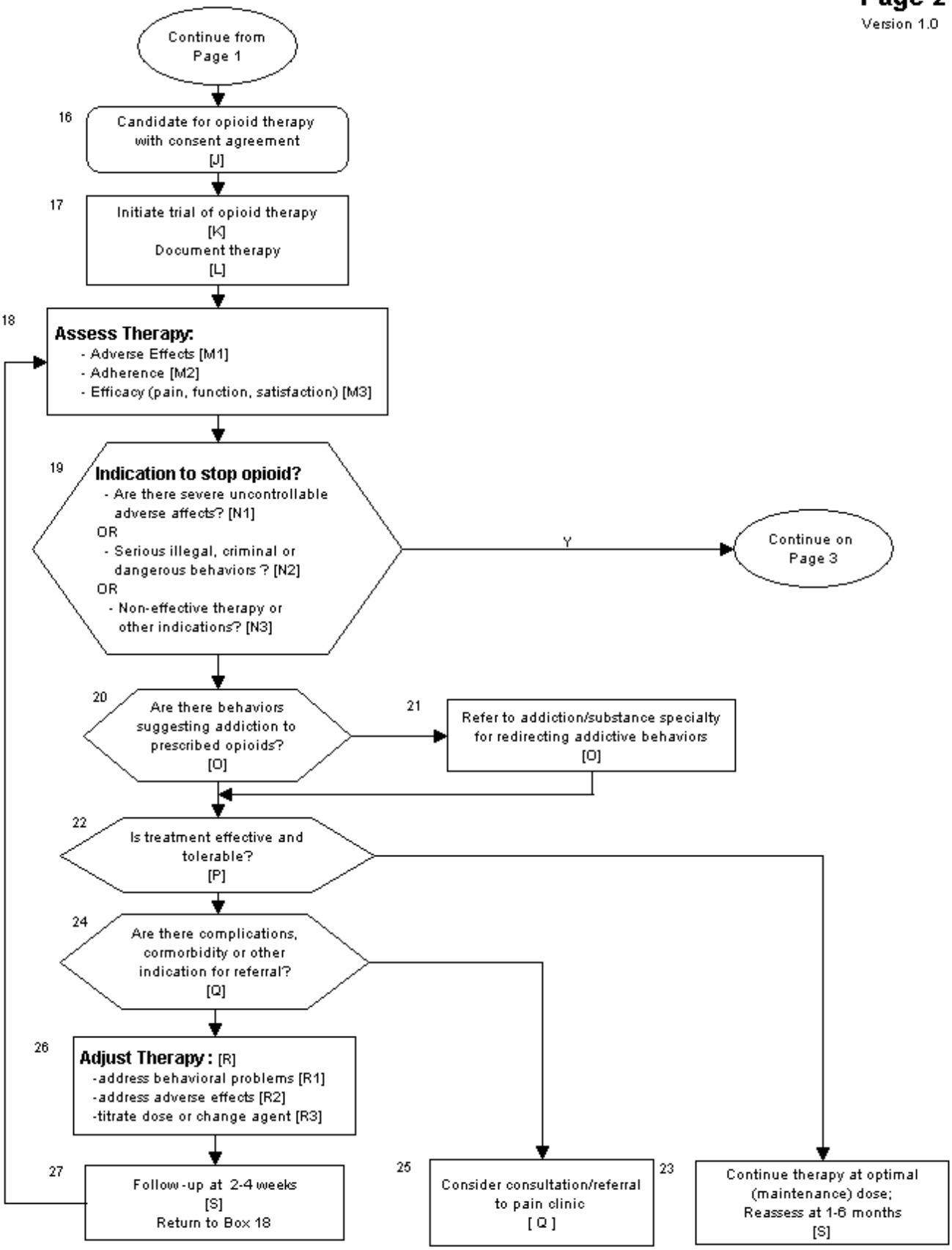

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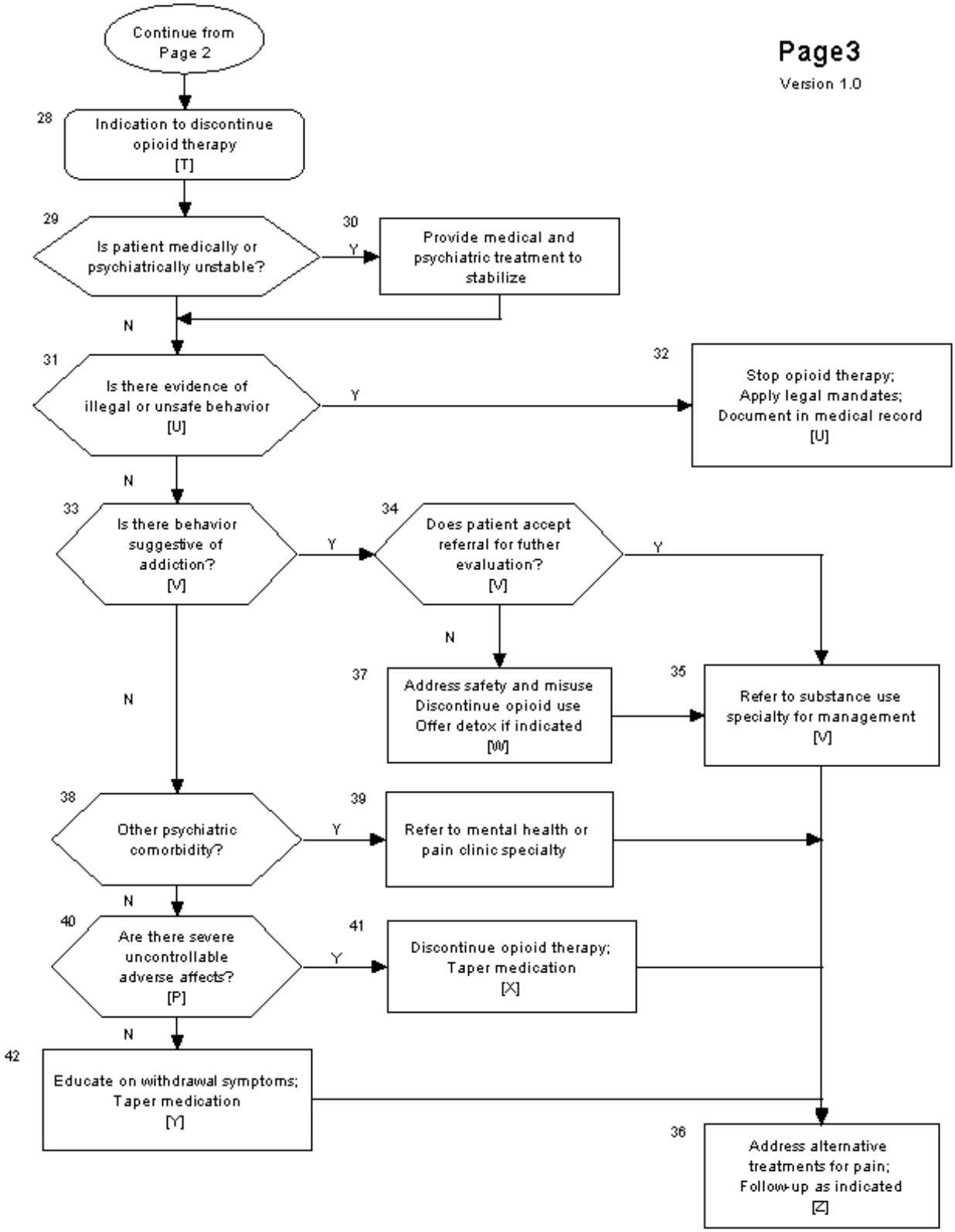


ANNOTATIONS

A. Patient with Chronic Non-cancer Pain

The patient managed within this guideline suffers from chronic non-cancer pain. The patient has been previously assessed and treated, over a period of time, with non-opioid therapy or non-pharmacologic pain therapy. Because the response to treatment has not provided adequate pain relief, the patient is considered to be a candidate for a trial of opioid therapy.

In addition, because of the regulatory restrictions on the prescription of controlled substances, the guideline addresses the special considerations and documentation issues that are required for the safe and effective management of opioid therapy.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP, 1994). The perception of pain is influenced by physiological, psychological, and social factors. The human reaction to the sensory experience, suffering, takes an added dimension in patients who have chronic, non-cancer pain. Some of these patients may have, in addition to the persistent pain, overriding affective components and learned responses that can lead to severe psychological disability and a pattern of repeated interaction with the health care system.

B. History and Physical Examination to Obtain Comprehensive Assessment

OBJECTIVE

Obtain clinical data required to manage the patient with chronic non-cancer pain.

BACKGROUND

Most of the information needed to develop an effective pain therapy is contained in a routine history and physical examination. Management of opioid therapy requires a thorough assessment before initiation of treatment. A patient with chronic pain may have physical, psychological, social and/or behavioral contributors to suffering that require special attention in an evaluation. Optimal management involves a comprehensive assessment leading to an individualized treatment approach using a combination of treatment options. Multiple factors may determine the effectiveness of opioid therapy for a particular patient. The clinician should also be aware of relative and absolute contraindications to opioid therapy for particular patients.

Note: A specific diagnosis will help direct adjunctive therapy. The assessment should help to distinguish between nociceptive and neuropathic pain and this may, in turn, guide the intervention. For some patients, however, it may not be possible to narrow down the diagnosis further than "chronic pain."

RECOMMENDATIONS

1. A comprehensive patient assessment should be completed to identify clinical conditions that may interfere with the appropriate and safe use of chronic opioid therapy.

   The comprehensive assessment should include:

   - Age, Sex
   - History of present illness, including a complete pain assessment (see Annotation C)
   - Pain-related history (pain-related fear, pain interference with function, prior pain treatment)
   - Past Medical and Surgical history
   - Past Psychiatric history (including depression, anxiety, other emotional disorders)
   - Substance use history

- Family history
- Social history (including employment, cultural background, social network, marital history, and legal history, other behavioral patterns (i.e. impulse behaviors))
- Review of systems
- Medications
- Allergies
- Physical examination
- Mental Status Examination
- Review of diagnostic studies and assessments
- Evaluation of occupational risks and ability to perform duty

2. Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.

3. Consider the use of a urine drug screen (UDS) or other laboratory tests to screen for the presence of illegal drugs, unreported prescribed medication or unreported alcohol use.

DISCUSSION

History of Present Illness Including Complete Pain Assessment—A comprehensive pain assessment is required for initial evaluation of patients with pain (see Annotation C). The components of a comprehensive pain assessment vary, but for the purposes of evaluating the patient being considered for chronic opioid therapy, it should include several areas.

Pain-related History—Should include the following:

- **Prior Pain Treatment**—Since in many cases opioids may be recommended only after alternative pain control methods have been attempted, information regarding an individual's response to past pain treatment efforts is essential. Of particular relevance is any information regarding past opioid treatment, including adherence, adverse effects, and outcomes, as previous opioid therapy failure may be a contraindication to additional trials.

  Other drugs co-administered with opioids may result in adverse drug interactions. For example, concurrent sedative use may cause cognitive deficits in patients on opioid therapy (Canadian Pain Society, 1998). Cognitive deficits may worsen on opioid therapy; therefore caution is advised.

- **Pain-Related Fear**: Although there is no evidence linking levels of pain-related fear to the effectiveness of opioids, there is evidence that pain-related fear is associated with decreased function. Individuals with high fear levels may experience greater pain-related impairment and less improvement following treatment (Crombez et al., 1999; Vlaeyen et al., 1999; Vlaeyen et al., 2001).

- **Pain Interference with Function**: Pain at higher levels of intensity is more likely to interfere with individuals' daily life activities (Serlin et al., 1995). Pain interference may have important implications for individuals' quality of life.

Medical History—Certain medical conditions require caution with opioid use. COPD patients may have decreased respiratory drive with opioid therapy. This is not an absolute contraindication as opioids are used to successfully treat air hunger in the palliative care setting. Sleep apnea patients who do not use CPAP are at increased risk of further desaturation with the use of opioids. Renal failure and liver failure may alter the recommended dosing of opioids.

Psychiatric History—Should include the following:

- Depression: Patients with chronic pain may have co-morbid depression, which can complicate treatment. In these patients screening and concurrent treatment of depression may lead to improved results. Patients with depression who are treated with MAOIs should not be treated with opioid therapy. Although there are no studies that specifically address the issue of active suicidality and chronic pain treatment, prudent practice mandates that the risk of harmful behavior be addressed.
- Anxiety Disorders: Significant anxiety disorders may complicate pain treatment and may necessitate ancillary treatment.
- Other Emotional Disorders: Affective disorders, personality disorders, and/or active psychosis warrant close association with the mental health provider network in the assessment process prior to any determination to initiate opioid therapy.
- Personality Disorder: A personality or character disorder is a very enduring pattern of behavior and interpersonal tendency that deviates markedly from the individual's culture. These patterns are often pervasive, ingrained and inflexible, usually starting in adolescence. DSM-IV notes three clusters under the Axis II diagnostic category: (1) odd or eccentric; (2) dramatic, emotional or erratic; and (3) anxious or fearful. The presence of a personality disorder can be associated with patient management issues including manipulation, noncompliance, impulsiveness and emotional reactivity. Some disorders are not immediately apparent but will declare themselves over time. Careful attention should be given to their detection.

Substance Use History—Patients with a substance abuse history are at special risk of developing an addiction problem when treated with opioids. Physicians should be especially cautious about prescribing controlled substances to these patients. The degree of risk in opioid use forms a continuum in terms of both the type of addiction and its history. For example, a patient with a distant history of substance use would be less at risk than a patient with a recent history of substance use. Consultation with an addiction specialist for evaluation or co-management may be useful, as well as involvement of the patient's family.

Social History—Should include the following:

- Employment: Pain may have significant impact on the patient's employment status. Patients with occupations that require a high level of cognitive function may require special considerations. Consultation to occupational health providers and review of industry guidelines may be necessary (see Annotation E). Accommodations to the workplace environment and/or role may have already been considered or instituted. If continued employment is a goal of the patient, employment information should be obtained in the assessment. One of the goals of opioid therapy may be the improvement of functional status and return to full employment status. Research literature supports the prompt return to employment for acute back pain. Disability compensation for pain may prognosticate poor response to opioids.

- Cultural Background: In general, cultural factors are not an issue in response to opioid therapy. Only one clinical study addressed cultural variation in the use of opioid therapy. Caraco (1999) reports a study of codeine with/without quinidine in Caucasian and Chinese patients. Chinese patients with a particular form of an enzyme (CYP2D6) were less likely to convert codeine to morphine, resulting in reduced analgesic effects.

- Family Support: Concurrent interviewing (in person or via phone contact) of involved family members is warranted (if available) to complete the patient assessment.

- Legal History: There are no trials relating opioid therapy to legal issues. Some reports indicate that pending legal issues decrease the likelihood of pain treatment success.

Physical Examination—A physical examination should be part of every comprehensive patient assessment.

Mental Status Examination (MSE)—evaluation of cognitive function, anxiety, depression and other psychiatric disorders.

Age—Patient age is of special concern when prescribing opioids. Older patients are more likely to experience difficulty with common adverse effects of opioids such as constipation and respiratory depression. In a literature review, Herr (2002) cautions caregivers to be particularly aware of adverse effects that may be more severe in older patients. This may be due to the fact that older patients often have multiple medical conditions and multiple medications. In older patients the potential is high for drug-drug interactions and drug-disease interactions. Older patients are more prone to constipation, nausea, vomiting, sedation, respiratory depression, urinary retention, intestinal obstruction, delirium and cognitive impairment. Morphine has a specific warning against use in older patients secondary to its variable half-life. Some older patients benefit from short-acting agents rather than long acting agents due to the accumulation of metabolites (Pappagallo, 1999). Although older patients have increased incidence of cognitive impairment and sedation, there is no evidence that there is an increased incidence of falls in the older patient on opioids (Leipzig et al., 1999). However, opioids have been associated with hip fractures in the elderly. (Guo et al., 1998; Shorr et al., 1992)

Gender—Zacny (2001), in a literature review of six studies, analyzed the differences in the subjective effects of morphine in women and men. He found that females report higher ratings of feeling "spaced out," "heavy/sluggish," and dry mouth. No differences in psychomotor or physiological effects of morphine emerged in this study.

Allergies—True allergy to opioids is uncommon. In patients reporting adverse reaction to opioid therapy, a careful history of the nature of the reaction should be undertaken to determine if it is a true allergy or a manageable adverse effect. In patients with true allergy to an opioid, an opioid of a different chemical class can be tried with caution.

Review of Diagnostic Studies—Patients should have a complete assessment of their prior evaluations to include consultations, laboratory data and imaging studies. If the assessment is found to be incomplete, the studies should be completed prior to the initiation of chronic opioid therapy.

Evaluation of Occupational Risks and Ability to Perform Duty—Patients with occupations that require a high level of cognitive function or personal reliability (e.g. pilots) require special consideration. When possible, consult with their occupational physician or industry guidelines about allowed medical therapies.

Urine Drug Screen (UDS)—Consider UDS or other laboratory tests as part of a comprehensive patient assessment. Presence of illicit metabolites may warrant referral to a substance abuse/addiction consultant. Clinicians should be aware of the type of drugs tested, and the sensitivity and specificity of their facility's UDS assay because detection of synthetic opioids and newer benzodiazepines may not be part of routine screens. The goal should be to check for the presence of drugs in any amount. Most UDS, however, have cut-off levels below which the test result is reported as negative.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Complete assessment for every patient	Canadian Pain Society, 1998 Working Group Consensus	III III	Poor	C
2	Assess age	Herr, 2002 Leipzig et al., 1999 Pappagallo, 1999	III III III	Poor	I
3	Assess gender	Zacny, 2001	II-1	Fair	B
4	Consider a Urine Drug Screen (UDS)	Canadian Pain Society, 1998 Working Group Consensus	III III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

C. Complete Assessment of Pain; Determine Cause of Pain, If Possible

OBJECTIVE

Obtain pain-related data required to manage the pain intervention.

BACKGROUND

Assessment and documentation of pain in a systematic and consistent manner guides the identification of unrelieved pain and the evaluation of treatment-related change. Since the goal of therapy is to alleviate pain and improve function, the assessment should focus on pain and functional status.

Nociceptive pain is usually due to continuous stimulation of specialized pain receptors in such tissues as the skin, bones, joints and viscera. It is often indicative of ongoing tissue damage. Typical examples include osteoarthritis and chronic pancreatitis. Neuropathic pain is due to nerve damage or abnormal processing of signals in the peripheral and central nervous system. Examples include postherpetic neuralgia, phantom limb pain, and pain resulting from spinal cord injuries. Most chronic pain syndromes involve one or both of the above mechanisms (Canadian Pain Society, 1998).

RECOMMENDATIONS

1. Pain intensity should be evaluated at each visit.
   - Intensity of pain should be measured using a numerical rating scale (0-10 scale) for each of the following:
     - Current pain
     - Least pain in last week
     - "Usual" or "average" pain in the last week

   - The patient's response to current pain treatments should be assessed at each visit using the following questions:
     (Note: some interventions may temporarily increase pain, so it may not be appropriate to ask these questions.)
     - "What is your intensity of pain after taking (use of) your current treatment/medication?"
     - "How long does your pain relief last after taking your medication?"

   - Other attributes of pain should be assessed as part of the comprehensive pain assessment:
     - Onset and Duration
     - Location
     - Description (Quality)
     - Aggravating and alleviating factors
     - Behavioral manifestations of pain
     - Impact of pain
     - Current and past treatments for pain
     - Patients' expectations for pain relief

   - If possible, determine type of pain:
     - Differentiate between nociceptive and neuropathic pain
     - Consider further evaluation if needed (such as EMG or consultation)

2. Assessment of function should include:
   - Cognitive function (attention, memory, and concentration)
   - Employment
   - Enjoyment of life

- Emotional distress (depression and anxiety)
- Housework, chores, hobbies, etc.
- Sleep
- Mobility
- Self-care behaviors
- Sexual function

3. Information from the pain history and physical exam should be reviewed to ensure that the patient has had an adequate trial of non-opioid therapy.

DISCUSSION

There are advantages to using a numeric rating scale (NRS) for assessing pain and function. The NRS has been found to be valid and reliable, and to be sensitive to changes in acute, cancer, and chronic pain (Breivik & Skoglund, 1998; De Conno et al, 1994; Paice & Cohen, 1997). Research indicates that "least" and "usual" pain ratings provide the best estimate of actual pain intensity (Jensen et al., 1992). Assessment of goal attainment and treatment-related changes can be helpful in clinical decision making (Serlin et al., 1995).

In a 30-day study of 167 patients with moderate to severe osteoarthritis, Caldwell et al. (1999) compared opioid treatment to placebo (all patients were allowed to maintain baseline NSAID therapy). The study results demonstrated that global quality of sleep improved in the active treatment group compared to the placebo cohort. Peloso et al. (2000) compared controlled release codeine to placebo in a 4-week study of 103 patients with osteoarthritis of the hip or knee. They reported an improvement in physical function in the codeine group.

Roth et al. (2000) report that patient self-evaluations of general activity, sleep, enjoyment of life, and mood improved during treatment with controlled-release oxycodone therapy versus placebo in a group of elderly patients with moderate osteoarthritis. Improvement was sustained for up to 18 months of follow-up.

NOTE: The VA Pain Outcomes Toolkit includes several optional instruments for functional status assessment.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Evaluate pain intensity using 0-10 scales	Breivik & Skoglund, 1998 De Conno et al, 1994 Jensen et al, 1996 Ogon et al., 1996 Serlin et al., 1995	II-2	Fair	B
2	Evaluate function related to pain	Caldwell et al., 1999 Jensen et al., 1992 Peloso et al, 2000 Roth et al., 2000	I III I I	Good	A
3	If possible, determine type of pain	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

D. Are There Contraindications to Opioid Therapy That Cannot Be Resolved?

OBJECTIVE

Avoid inappropriate or harmful therapy.

BACKGROUND

Although there are few absolute contraindications to the use of opioids in chronic pain, many factors must be considered prior to initiating therapy. The clinician must carefully weigh risks and benefits of chronic opioid therapy, and should discuss them with the patient and family/care giver where appropriate. Patients with relative contraindications pose a higher risk of legal and clinical problems.

RECOMMENDATIONS

1. Opioid therapy should not be used in the following situations (absolute contraindications):

    - Allergy to opioid agents (may be resolved by switching agents)
    - Co-administration of drug capable of inducing life-limiting drug-drug interaction
    - Active diversion of controlled substances (providing the medication to someone for whom it was not intended)

2. Opioid therapy should be used only after careful consideration of the risks and benefits (relative contraindications):

    - Acute psychiatric instability or high suicide risk
    - History of intolerance, serious adverse effects, or lack of efficacy of opioid therapy
    - Meets DSM-IV criteria for current substance use disorder (DSM IV, 1994)
    - Inability to manage opioid therapy responsibly (e.g., cognitively impaired)
    - Unwillingness or inability to comply with treatment plan
    - Unwillingness to adjust at-risk activities resulting in serious re-injury
    - Social instability
    - Patient with sleep apnea not on CPAP
    - Elderly patients
    - COPD patients

3. Consider consultation with an appropriate specialist if legal or clinical problems indicate that more intensive care related to opioid management is indicated. A patient with substance use problem should be referred to a substance use specialty for concurrent treatment of substance use.

DISCUSSION

Absolute contraindications

1. *Allergy to opioid agents*

    Morphine causes the release of histamine, frequently resulting in itching, but this is not an allergic reaction. True allergy to opioid agents (e.g. anaphylaxis) is not common but does occur. Generally, allergy to one opioid agent does not mean the patient is allergic to other opioids; also switching to an agent in another opioid drug class may be effective. For example, if a patient has a hypersensitivity to a phenanthrene, then a diphenylheptane drug may be tried. (See table below.) When patients report an "allergy" to all but one agent (such as meperidine), the presence of a substance use disorder should be considered. Consultation with an allergist may be helpful to resolve these issues.

Table 1. Classes of Opioid Medications

Phenanthrenes	**Diphenylheptanes**	**Phenylpiperidine**
Codeine	Methadone	Fentanyl
Hydrocodone	Propoxyphene	Meperidine [a]
Hydromorphone		
Levorphanol		Other
Morphine		Tramadol
Oxycodone		

[a] Meperidine is not recommended for chronic pain because of the potential for accumulation of the neurotoxic metabolite, normeperidine, and a potentially fatal drug interaction with monoamine oxidase inhibitors (MAOIs).

2. *Co-administration of a drug capable of inducing life limiting drug-drug interaction*

Providers should carefully evaluate potential drug interactions prior to initiating opioid therapy, (such as MAOI with concurrent meperidine use, or propoxyphene and alcohol and other CNS depressants). (Note: meperidine is not recommended for chronic pain because of this potentially fatal drug interaction and the potential for accumulation of the neurotoxic metabolite, normeperidine, with regular dosing.)

3. *Active diversion of controlled substances*

Diversion should be suspected when there are frequent requests for early refills, atypically large quantities are required, when purposeful misrepresentation of the pain disorder is suspected, or when a urine drug screen (UDS) is negative for the substance being prescribed, in the absence of withdrawal symptoms. Routine UDS often does not detect synthetic and semi-synthetic opioids (methadone, oxycodone, fentanyl, hydrocodone, meperidine or hydromorphone). Verified diversion is a crime and constitutes a strong contraindication to prescribing additional medications, and consultation with a pain specialist, psychiatrist, or addiction specialist may be warranted.

Relative contraindications

4. *Acute psychiatric instability*

Current serious suicidality, severe depression, or unstable bipolar disorder or psychotic disorder precludes safe use of opioids, unless the patient is closely monitored and professional staff or family members administer the medication (Harden, 2002).

5. *Intolerance, serious adverse effects or history of inadequate clinical response to opioids (lack of efficacy)*

Although generally well tolerated, opioids have potential adverse effects that may cause significant morbidity.

6. *Meets DSM-IVR criteria for current substance use disorder (SUD) other than nicotine dependence*

Current substance abuse or dependence increases the risk of drug-drug interactions, addiction to prescribed opioids, and diversion. However, use of a substance, whether legal or illegal, does not in itself constitute a substance use disorder. A medical diagnosis of a SUD should be made according to the Diagnostic and Statistical Manual-Version IV, Revised (DSM-IV). A diagnosis of SUD requires that substance use is maladaptive and results in clinically significant impairment or distress. Chronic and appropriate use of prescribed opioids will cause physiologic dependence and may result in tolerance. However, appropriate use of opioids for chronic pain that results in improved function and quality of life does not constitute a SUD. The term "pseudoaddiction" describes prescription of an inadequate dose of opioids, leading to attempts by the patient to seek additional pain relief through additional medication. The proper response to pseudoaddiction is to adjust the dose of opioids to provide effective pain relief.

It is not clear whether a history of a SUD in sustained remission (> 12 months) is predictive of increased risk for development of addiction in the context of opioid therapy. However, prudence dictates that the provider consider the stability of remission, including the patient's insight, participation in recovery activities such as self-help groups, and social support. Providers should consider consultation with an addiction specialist when the patient has a more recent history of a SUD, when remission is unstable, or for

patients with a history of prior opioid addiction, intravenous drug use, or prescription drug abuse or dependence (Large & Schug, 1995; Becker et al., 2000).

Substance Dependence (or addiction) refers to a condition characterized by a presentation of three or more of seven specific symptoms, defined in DSM-IV. Psychological dependence or drug addiction is different from physiologic dependence. Substance dependence requires a higher level of intervention and management than substance abuse.

7. *Inability to manage opioid therapy responsibly*

Patients may repeatedly "lose" medication, may be unable or unwilling to store the medication in a safe place, or may repeatedly run short and ask for early refills, or obtain medication from more than one physician or pharmacy. The likelihood of these problems can be minimized by clearly specifying expectations prior to initiating therapy through the use of the written contract agreement (See Appendix C). Many patients respond to reminders and clear limit setting at the first instance, but repeated occurrence makes continuing therapy difficult. If a patient is cognitively impaired, assistance of a responsible caregiver may be required.

8. *Unwillingness or inability to comply with reasonable treatment plan*

Treatment of chronic pain often requires a multidisciplinary approach (such as physical therapy, relaxation training, or psychiatric treatment), which requires active participation of the patient. Similarly, patients must make lifestyle changes to accommodate chronic pain. Repeated failure of the patient to follow through raises questions about the motivation of the patient and the appropriateness of continued opioid therapy. Patients must be counseled about this, and barriers to participation should be addressed. When this fails to result in improved participation, consideration must be given to discontinuing opioid therapy.

9. *Social instability*

Patients living in chaotic or unsafe environments (e.g. homeless shelter, living with others who are using cocaine) should not receive opioids until social stability is achieved.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Absolute contraindications to opioid therapy: • Active diversion of controlled substances	Legal	-	-	-
2	Relative contraindications to opioid therapy: • Psychiatric instability • Adverse effect or lack of efficacy • Current SUD • Inability to manage therapy • Noncompliance with treatment • Social instability • Sleep apnea not on CPAP	Harden, 2002 Joranson et al., 1992 Becker et al., 2002 Large & Schug, 1995 Working Group Consensus	III III I III III	Fair	C
3	Consultation with an addiction specialist if legal or clinical problems indicate that more intensive management of opioids is indicated	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

E. Indication for Referral/Consultation?

OBJECTIVE

Assure appropriate care for complicated chronic pain patients.

BACKGROUND

Chronic pain patients often present with complicated medical and social histories. In many patients, a clear source for their ongoing reports of pain may not have been established or questions regarding their prior experience with substance abuse may arise during their evaluation. In this setting, referral to another provider to assist in diagnosis or evaluation of the chronic pain condition and implementation of treatment modalities beyond the expertise of the referring physician may be appropriate. In other patients with multiple issues beyond pain alone, referral to a multidisciplinary pain treatment program may be the most appropriate setting in which to initiate successful chronic opioid therapy as part of an overall pain treatment program.

RECOMMENDATIONS

1. The patient with complex pain conditions should be referred to a pain specialist for evaluation and treatment.

2. The patient with long standing pain problems or multiple issues beyond pain alone should be referred to a multidisciplinary pain clinic for evaluation and treatment.

3. In the patient with a history of addiction or substance use disorder, or if drug screens are indicative of a drug or alcohol use problem, consider consultation with an addiction specialist to evaluate the risk of recurrent substance abuse or to assist with ongoing management.

DISCUSSION

A multidisciplinary pain treatment center is staffed by physicians of different specialties and by other non-physician health care providers who specialize in the diagnosis and management of patients with chronic pain. These centers develop an integrated treatment plan that incorporates regular follow-up and communication between the team members (IASP, 1990). The outcome of multidisciplinary pain treatment has been demonstrated to be effective and economical in the treatment for chronic pain, with improvement sustained at two- and five-year follow up (Becker, 2000; Flor et al., 1992; Malone et al., 1988, Guzman et al., 2001).

Merely establishing a pain diagnosis and a pain management plan by a pain specialist, however, is unlikely to lead to comparable outcomes. Becker et al. (2000) reported that this approach was insufficient to enable the general practitioner to manage and improve the condition of severe chronic pain patients.

Patients with a history of prior substance abuse are more likely to abuse substances in the future. Patients with a history of drug abuse can be successfully treated with opioids over limited time periods (Dunbar & Katz, 1996). The success of long-term opioid therapy over extended periods has not been evaluated.

EVIDENCE

	Intervention	Sources of Evidence	QE	Overall Quality	R
1	Refer to pain specialist	Working Group Consensus	III	Poor	I
2	Refer to multidisciplinary pain clinic	Becker et al., 2000 Flor et al., 1992 Malone et al., 1988 Guzman et al., 2001	I	Fair	B
3	Refer to substance abuse specialist	Dunbar & Katz, 1996 Working Group Consensus	II III	Fair	C

QE = Quality of Evidence; R = Recommendation (See Appendix A)

F. Is Opioid Therapy Indicated at This Time?

OBJECTIVE

Consider opioid therapy for suitable candidates.

BACKGROUND

At this point the clinician will have assessed the suitability of the patient for opioid therapy. This assessment will have included a history and physical. The patient should have been found to have no absolute contraindications to opioids. Once the clinician decides to prescribe opioids to the patient, the process of patient education should begin (see Annotation G).

RECOMMENDATIONS

1. The use of opioid therapy is indicated for moderate to severe pain that has failed to adequately respond to other non-opioid therapeutic interventions.

2. The ethical imperative to relieve pain should be considered when evaluating therapeutic options.

DISCUSSION

The use of opioid therapy is indicated for moderate to severe pain that has failed to respond to other therapeutic interventions (Breivik, 2001). Its use is complementary to other therapies and only rarely should be the sole therapeutic intervention. The evidence for its use is based on the ethical imperative to relieve pain, as limited by the admonition to do no harm. Statements from various professional societies and state medical boards support this concept (Laval et al., 2002; Joranson et al., 2002). In some patients, opioid therapy may be the only safe alternative given the medical problems of the patient. For example, a patient with moderate pain, severe liver failure and history of bleeding complications may be best served with non-pharmacologic modalities and opioid therapy.

EVIDENCE

	Recommendations	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Opioid therapy is indicated for moderate to severe pain that has failed other therapeutic interventions	Breivik, 2001	III	Poor	I
2	Consider the ethical imperative to relieve pain	Joranson et al., 2002 Laval et al., 2002	III III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

Note: For more information on identifying patients who should be referred to a pain specialist or pain clinic see the Web-based educational program "Opioids in the Management of Acute and Chronic Pain", available at http://vaww.sites.lrn.va.gov/pain/opioids.

G. Educate Patient and Family about Treatment Options; Share Decision about Goal and Expected Outcome of Therapy

OBJECTIVE

Reduce barriers and address concerns regarding opioids so that the patient and care giver/family can make informed decisions about pain management, patient outcomes, and adherence to therapy.

BACKGROUND

Patient education about their therapy is of paramount importance for all patients with chronic pain. Helping patients to gain a clear understanding of the nature of the treatment, expected outcome and possible adverse effects is an important element of management. Some patients may harbor fears that use of opioids may cause more harm than benefit, while others may think of opioid therapy as a panacea. Unwarranted concerns of this kind may lead to undesirable attitudes and behaviors that may increase dysfunction and retard the alleviation of pain.

RECOMMENDATIONS

1. The patient and family/caregiver should be involved in the educational process.

2. Written educational material should be provided in addition to discussion with patient/family.

3. The opioid agreement should be discussed in detail (See Annotation H).

4. Patient education should be documented in the medical record.

5. The following topics should be included (See also Appendix B: Patient Education):
   - General Information: goals and expectations, addiction, tolerance, physical dependency, withdrawal symptoms
   - Patient responsibilities: prescriptions, adherence to treatment plan, obtaining medications from a single source, pain diary, feedback to the provider
   - Legal Issues
   - Instruction on how to take medication: importance of dosing and timing, interaction with other drugs
   - Prophylactic treatment of adverse effects and management of constipation.

DISCUSSION

There are no systematic reviews or randomized controlled trials concerning the role of patient education in opioid therapy. Valuable information, however, is available from *ad hoc* reviews of the medical and popular literature, and from clinicians' day-to-day interactions with patients who take opioids or who are contemplating taking opioids. These sources indicate that there is a great deal of anxiety on some patients' part when faced with opioid therapy. They fear the outcomes of addiction, tolerance, escalating doses, and physical dependence. It is important for the clinician to accompany any prescription for opioids with at least one informational session in which the patient can express anxieties and be reassured about the means by which misuse and addiction may be forestalled. It is also important for clinicians to be aware of portrayals of opioids in the media, and to attempt to correct misconceptions whenever possible (Brown et al., 1996; Cohen et al., 2001; Hancock & Burrow, 2002).

Although there is a lack of evidence to support the effectiveness of education to improve outcome in patients on opioids, the literature review on this issue supports education of patient and family before starting opioid therapy (Brown et al., 1996; Cohen et al., 2001; Hancock & Burrow, 2002). The intention is to improve the collaboration of the patient and family with the provider, to achieve realistic goals and expectations, to improve drug efficacy, and to decrease risks of adverse outcomes, such as addiction (McCaffery & Pasero, 1998),

diversion, drug interactions, and adverse drug effects. It is expected that a patient may have anxiety and fears related to the social stigma of chronic opioid use. It is very important to address and allay these issues, and especially important for some occupations such as pilots and commercial drivers, whose jobs, income, and social status could be jeopardized.

The knowledge about this topic comes from two sources: published letters and *ad hoc* literature reviews, some of which incorporate the author's own experience with prescribing opioids. On a general level, Knight and Avorn (2001) is an example of a review of patient education for all older patients. The authors report the outcomes of a small number of studies that support the value of education for improving compliance and awareness of potential medication adverse effects and benefits in older patients.

More specific to opioid therapy are two items, one letter (Jacobson et al., 1996) and one literature review (Cohen et al., 2001), that address patient education for patients with chronic pain. Cohen and his colleagues point out that education can go beyond informing the patient about medications, and can point the way to non-pharmacologic means of pain control such as exercise and effective body mechanics. The results of these non-pharmacologic methods can lead to pain control and can contribute to the patient's overall pain reduction. Jacobson et al. (1996) discuss another potential value of patient education: patient empowerment. The authors believe that patients should not place blind faith in opioids to eliminate their pain. Patients should be given information with which to develop realistic expectations and to make informed choices about opioids.

McCaffery and Pasero (1998) and Brown et al. (1996) address a critical component of education for patients contemplating taking opioids: the fear of dependence or abuse. Both literature reviews incorporate the authors' clinical interactions with patients. They point out that some patients will not accept opioid therapy until their concerns have been addressed. McCaffery and Pasero's review is a good source of common sense, specific advice on how to address patients' fears and allay them. For instance, they note "many people think that around-the-clock dosing is like addiction since the pain medicine is taken before it is needed" … patients may need to hear that "pain, like any disease, needs to be controlled with regularly scheduled medication."

On the most specific level, two authors (Hancock & Burrow, 2002; Heidrich, 2001) address concerns about controlled-release oxycodone hydrochloride as an opioid particularly susceptible to abuse. Both items address the need for a balanced portrayal of this drug in the media. Hancock and Burrow (2002) call for an effort "to publicize the need for cautious handling and management of oxycodone controlled-release, which helps to decrease the incidence of diversion and abuse without restricting its use as a legitimate analgesic for people experiencing pain."

Educational material is available at http://www.partnersagainstpain.com. Education is an ongoing and dynamic process that should be adjusted based on patient needs. Appropriate documentation is of paramount importance to ensure continuity of care.

EVIDENCE

	Intervention	Sources of Evidence	QE	Overall Quality	R
1	Education of patient and family/caregiver in an interactive and written format	Brown et al., 1996 Cohen et al., 2001 Hancock & Burrow, 2002 Jacobson et al., 1996 Knight & Avorn, 2001 McCaffery & Pasero, 1998	III III III III III III	Poor	I
2	Discussion of the opioid agreement	Working Group Consensus	III	Poor	I
3	Documentation of patient and family education in the medical record	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

H. Obtain a Treatment Agreement

OBJECTIVE

Define the responsibilities of the patient and the provider for the management of the chronic opioid therapy.

BACKGROUND

When a trial of opioid analgesic is selected, the physician should obtain informed consent from the patient or the patient's guardian. Informed consent should include discussion of the risks and benefits of therapy as well as the conditions under which opioids will be prescribed.

RECOMMENDATIONS

1. A patient consent in the form of a *written treatment agreement* should be obtained before initiating opioid therapy. The patient's responsibilities during therapy should be discussed with patient and family, addressing the following issues (for a sample agreement see Appendix C):

    - Goals of therapy -- Partial relief and improvement in physical, emotional and/or social functioning
    - The requirement for a single provider or treatment team
    - The limitation on dose and number of prescribed medications and the proscription against changing dosage without permission; discuss the use of "pill counts"
    - A prohibition on use with alcohol, other sedating medications, or illegal medications without discussing with provider
    - Agreement not to drive or operate heavy machinery until medication-related drowsiness is cleared
    - Responsibility to keep medication safe and secure
    - Prohibition of selling, lending, sharing or giving any medication to others
    - Limitation on refills: only by appointment, in person, and no extra refills for running out early
    - Compliance with all components of overall treatment plan (including consultations and referrals)
    - The role of urine drug screening, alcohol testing
    - Acknowledgement of adverse-effects and safety issues such as the risk of dependence and addictive behaviors
    - The option of sharing information with family members and other providers, as necessary
    - Need for periodic re-evaluation of treatment
    - Consequences of non adherence

DISCUSSION

Agreement between the patient and the provider is required. In particular, misunderstandings about the agreement can lead to later frustration and anger. With the exception of "Goals of therapy," the agreement is the same for all patients. "Goals of therapy" is very patient-specific. The improvements in pain and function that are expected, and that are critical to the decision to continue to opioid therapy, should be made clear at the beginning of therapy. It should be noted that a review of the literature found only a few references of improved function (Turk et al., 2002). There is very little evidence regarding the efficacy of treatment agreements as part of chronic opioid therapy for patients with chronic non-cancer pain. No controlled trials or systematic reviews of controlled trials were identified. Three case series were identified, two of which were retrospective chart reviews (Dunbar & Katz, 1996; Kirkpatrick at al., 1994). Two of these studies showed that all or nearly all patients who signed a written treatment agreement as part of a chronic opioid management plan had positive outcomes and that there was a low rate of drug tolerance and noncompliance with the treatment protocol (Burchman & Pagel, 1995; Kirkpatrick et al., 1994). The other study (Dunbar & Katz, 1996), which included only patients with a prior history of substance abuse, showed that nearly half of the patients who signed a written treatment agreement did not comply with it and that there was no obvious relationship between a signed agreement and positive outcomes. It is the consensus of most experts that such agreements are obtained to

assist with proper documentation (Fishman et al., 1999). Furthermore, it is also expected that medico-legal benefits from such documentation may also be obtained.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Discuss opioid use issues with patient and obtain patient's consent in writing	Burchman & Pagel, 1996 Dunbar & Katz, 1996 Fishman et al., 2000 Fishman et al., 1999 Kirkpatrick et al., 1994	II II III III II	Fair	C
2	Use of written patient opioid agreement	Burchman & Pagel, 1996 Dunbar & Katz, 1996 Fishman et al., 1999 Kirkpatrick et al., 1994	II II III II	Fair	C

QE = Quality of Evidence; R = Recommendation (See Appendix A)

I. Determine and Document Treatment Plan

OBJECTIVE

Identify and describe key elements of the opioid treatment plan.

BACKGROUND

The treatment plan for opioid therapy must acknowledge that the patient is likely to benefit from a range of therapies, both pharmacologic and non-pharmacologic. The long-term opioid therapy should be integrated into the overall treatment objectives and plan for the individual patient.

RECOMMENDATIONS

1. The treatment plan should be individually tailored to the patient's circumstances and to the characteristics of the patient's pain.

2. Consider the use of other treatment approaches (supervised therapeutic exercise, biofeedback, and cognitive behavior approaches), which should be coordinated with the opioid therapy.

3. Consider establishing a referral and interdisciplinary team approach, if indicated.

4. Establish a follow-up schedule to monitor the treatment and patient progress.

5. The treatment plan and patient preferences should be documented in the medical record.

DISCUSSION

Simply decreasing the severity of the patient's pain may be all that is required to improve quality of life. Other patients may require a more intensive and comprehensive treatment plan that addresses the psychological, social and behavioral contributors to their suffering. The Canadian Pain Society (1998) guideline for the establishment of a treatment plan provides a valuable basis for the development of individualized treatment plans for suitable candidates.

EVIDENCE TABLE

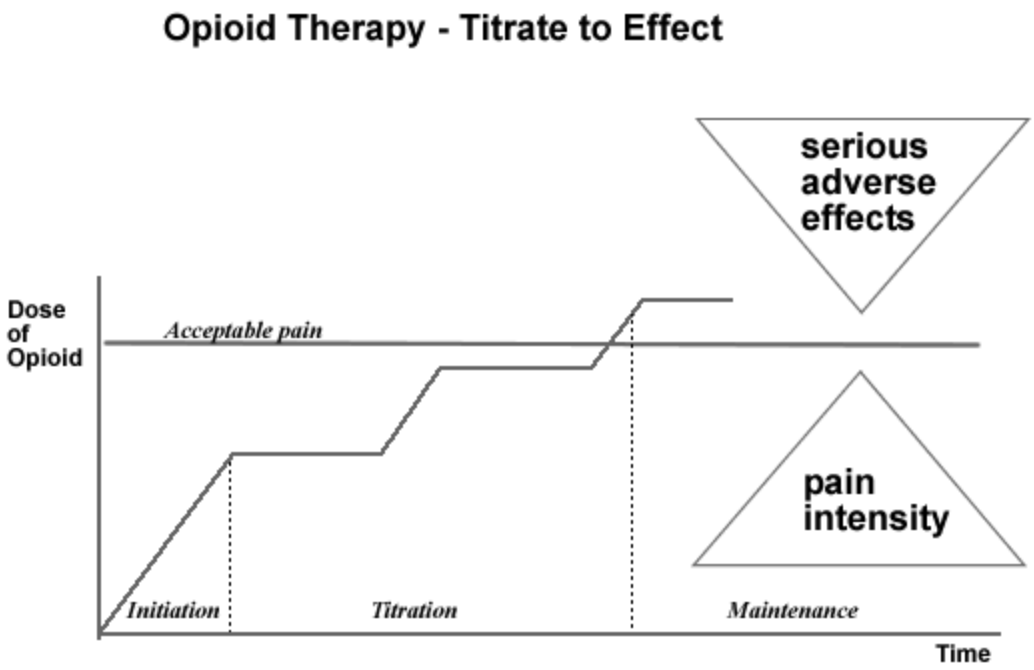
	Recommendations	Sources of Evidence	QE	Overall	R

				Quality	
1	A treatment plan that has been individually tailored to the patient's circumstances and the characteristics of the patient's pain	Canadian Pain Society, 1998	III	Poor	I
2	The use of other treatment approaches, which should be coordinated with the opioid therapy	Frost et al, 1998 Kuukkanen & Malkia, 1998 Moffett et al., 1999 Crider & Glaros, 1999 Stetter & Kupper, 2002	I	Good	A
3	A referral and multidisciplinary team approach	Working Group Consensus	III	Poor	I
4	Regular monitoring of the treatment process and patient progress	Working Group Consensus	III	Poor	I
5	Documentation of the treatment plan and patient preferences in the medical record	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

J. Candidate for Opioid Therapy, with Consent

Opioid therapy can be initiated in the form of a therapeutic trial. Prior to such a trial, the patient should be fully informed and should consent to the therapy. As treatment is administered, close monitoring of outcomes (pain relief, adverse effects, physical and psychosocial functioning, or any aberrant drug-related behaviors) along with careful titration, can establish successful long-term therapy.



A trial of opioid therapy consists of several phases: initiation, titration, and maintenance. The *initiation* phase involves selecting an appropriate opioid agent and dose for the individual patient, after considering the information obtained in the comprehensive assessment of the patient. The *titration* phase involves adjustment of the dosage to achieve the desired clinical outcomes (pain relief and improved function with minimal or tolerable adverse effects). During this phase, a lack of response despite dose escalation may indicate that the

patient has opioid non-responsive pain and opioid therapy should be discontinued (see Annotation W). The patient has entered the *maintenance* phase when the required daily dose remains relatively stable. This may be the longest phase of opioid therapy. Worsening pain after a period of stable evaluation maintenance may indicate disease progression, increased activity level, environmental factors (exposure to cold or reduced barometric pressure), development of psychosocial stressors, tolerance, or development of hyperalgesia. Additional evaluation may be indicated to determine the cause. Supplemental doses of non-opioids, short-acting opioids, or both should be considered during treatment (see Appendix E, Table E5).

With repeated administration of opioids, the patient will develop certain expected responses, including opioid *tolerance* and *physical dependence*.

During the opioid trial, a patient with *opioid responsive* pain (e.g., osteoarthritis) will obtain pain relief with initiation and titration of treatment. Over time, the patient may require a larger dose of medication to achieve the same degree of pain relief possibly because of *tolerance,* or because of increase in activity level as a result of initial pain relief. *Physical dependence* may be manifested as symptoms of withdrawal upon rapid taper or abrupt discontinuation of medication, which may arise when the patient forgets to pack medication when traveling away from home. Tolerance and withdrawal are two of the criteria for a potential diagnosis of substance dependency, but should not (per the DSM-IV) apply in the context of a patient receiving prescribed opioids on a chronic basis.

Addiction and *pseudo-addiction* are behaviors a patient may or may not develop. Repeated exposure to opioids in the context of pain treatment only rarely causes *addiction* (College of Physicians and Surgeons of Ontario, 2000; Mullican & Lacy, 2001; Peloso et al., 2000). There are a variety of biological, psychological, social, and spiritual factors that may increase the risk of *addiction* in susceptible patients who are prescribed opioid therapy. *Tolerance* to the analgesic effects of opioids may occur with regular therapeutic use in some patients. Most people taking opioids regularly will have characteristic withdrawal symptoms in the event of abrupt cessation or rapid taper.

The distinction between *addiction* and *physical dependence* (i.e. tolerance and/or withdrawal) means that clinicians should never label patients who are presumed to be at risk for a withdrawal syndrome (that is, physically dependent) as *addicted*. Such a description misrepresents the situation and stigmatizes the patient. For the same reason, use of the imprecise general term *dependent* should be avoided.

DEFINITIONS

Physical dependence
Physical dependence on an opioid is a physiologic state in which abrupt cessation of the opioid, rapid tapering (e.g. when a patient forgets to take the medication), or administration of an opioid antagonist, results in a withdrawal syndrome. Physical dependency on opioids is an expected occurrence in all individuals in the presence of continuous use of opioids for therapeutic or for non-therapeutic purposes. It does not, in and of itself, imply addiction (ASAM, 1997).

Tolerance
Tolerance is a form of neuroadaptation to the effects of chronically administered opioids (or other medications), which is manifested by the need for increasing or more frequent doses of the medication to achieve the initial effects of the drug. Tolerance may occur both to the analgesic effects of opioids and to some of the unwanted adverse effects, such as respiratory depression, sedation, or nausea. The appearance of tolerance is variable in occurrence, but it does not, in and of itself, imply addiction (ASAM, 1997).

Addiction
Addiction in the context of pain treatment with opioids is characterized by a persistent pattern of dysfunctional opioid use that may involve any or all of the following:

- Loss of control over the use of opioids
- Preoccupation with obtaining opioids, despite the presence of adequate analgesia
- Continued use despite physical, psychological, or social *adverse consequences* (ASAM, 1997).

Pseudoaddiction
Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may "clock watch," and may otherwise seem inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain relief. In contrast to true addiction, in pseudoaddiction the behaviors resolve when the pain is effectively treated (Definitions, 2001). Misunderstanding of this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label 'addict.' In the setting of unrelieved pain, the request for increases in drug dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels

K. Initiate Trial of Opioid Therapy

BACKGROUND

A trial of opioid therapy may be indicated for patients who have failed to respond to a reasonable documented trial of non-pharmacological and non-opioid pharmacological modalities. The trial involves a step-wise approach to the identification of the best agent or agents and the best dosage for the individual patient. The clinician is aided in this effort by feedback from the patient—a record of the time and dose of the medication, the degree of pain relief, and the occurrence of adverse effects.

The treatment of pain is guided by the premise that each patient is unique in his perception of pain and in his response to medications. Accordingly, the patient's response is the ultimate guide to treatment. To learn from patient response, medication trials must be conducted in a systematic and disciplined way. The goal of optimal opioid titration for a stable chronic pain condition is to decrease the need for breakthrough doses to a minimum.

RECOMMENDATIONS

Initiation Phase

Objective: To find the medication(s) that provides the best pain relief with the fewest adverse effects at the lowest effective dose.

Effective therapy is achieved when the patient reports improvement in pain relief and/or function along with minimal or acceptable adverse effects.

The general strategy for the initiation phase:

1. For intermittent pain begin with short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time.
2. For continuous pain an agent with a long duration of action, such as controlled-release morphine or methadone is recommended.
3. A trial should be considered for either nonciceptive or neuropathic pain. Neuropathic pain often requires higher doses of medication than nociceptive pain.
4. Begin with a low test-dose to make sure that the medication has no serious or intolerable adverse effects. Administration by the least invasive route is recommended; oral administration is preferred.
5. For patients with specific medical conditions, choice of agent will depend on route and special cautions. Preferred choices are suggested in Table 2, Use of Opioids for Chronic Pain in Special Populations.
6. In opioid-naïve patients, one medication should be tried at a time, with frequent evaluations to titrate the dose. Patients with prior experience with opioid medications for pain relief should use the medication that worked well in the past, at the dose to which the patient was accustomed.
7. Education that addresses anticipated adverse effects, the use of medication, and symptoms of opioid withdrawal should be provided to the patient and family.
8. Constipation, which is anticipated with all opioids, should be treated prophylactically.

9. Failure to show partial analgesia with incremental dose titration may be evidence for pain that is not opioid responsive, and suggests that the opioid therapy should be discontinued.

There is no evidence of the superiority of long- over short-acting opioids with respect to pain relief, adverse effects, or the rate at which tolerance develops. Generally, long-acting medications, with the exception of methadone, are more expensive than their short-acting versions. Patient preference, in terms of prescription regimen, number of pills per day, etc. are factors that affect that decision.

Titration Phase

Objective: To adjust the dose of opioid to achieve satisfactory pain relief and tolerable adverse effect profile.

Once a medication has been found that provides pain relief, it is likely to continue to provide pain relief, as long as the dose is increased to compensate for analgesic tolerance if it develops.

Opioids almost always need to be titrated upwards, and effective doses are commonly higher than the starting dose. The eventual dose must be one at which the clinician can comfortably maintain the patient. Personal discomfort by the clinician at the apparent level of opioid requirement is a valid reason not to proceed, and may warrant the referral of the patient to a physician who has more expertise in chronic pain management.

The general strategy for the titration phase:

10. Once a pain relief response has been achieved at a particular dose, repeat that dose as the level of pain begins to rise; this approach helps establish the dosing interval.
11. If necessary, the initial daily dose may be increased by 25%-100%. If the new dose is well tolerated but ineffective, additional increases in dose can be considered. See R3 for dosage titration recommendations.
12. As the patient develops tolerance, adverse effects noted during the initial period of exposure to a medication are likely to disappear.
13. If a medication provides less than satisfactory pain relief or uncontrollable adverse effects, consider rotating to an alternate opioid medication.
14. In general, there is no pharmacological rationale for using a predetermined maximal dose for pure agonist opioids. Long-term opioid therapy should be started at a low dose and carefully titrated until an adequate level of analgesia is obtained, or until unmanageable and persistent adverse effects warrant a decreased dose or a change in therapy. For some patients, however, opioids do not exert an appreciable analgesic effect until a threshold dose has been achieved.
15. If short acting medications are effective and well tolerated, it may be possible to achieve equivalent pain relief with fewer daily doses of medication by substituting an equivalent dose of long-acting opioid medication (such as methadone, morphine CR, or oxycodone CR). These long-acting medications may provide steadier serum levels and smoother pain control and can be supplemented with doses of short-acting medication to control pain exacerbation.
16. During the titration phase, reasonable doses of rescue opioid may be provided and can be used to assess the adequacy of the overall opioid dose (see Appendix E, Table E-5).
17. The conversion to a long-acting opioid should be based on an equianalgesic conversion (see Appendix E, Table E3 for conversion factors) and consideration of the incomplete cross-tolerance between opioids. To allow for incomplete cross-tolerance, in most cases the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose.
18. Precise record keeping of the time and dose of medication, the degree of pain relief, and the occurrence of adverse effects is essential for successful titration. Maintaining close communication with patients and families and explicitly laying out the criteria for evaluating the effects of analgesic medications can help in defusing the anxiety that often accompanies visits to the physician.

The daily consumption of the rescue drug can be an indicator of the adequacy of the sustained-release drug. By titrating the sustained-release drug accordingly, the minimum dose needed to ameliorate the pain can usually be quickly established. Patients sometimes do well at the beginning of opioid therapy and then seem to lose

ground within a few weeks. In those who have been severely limited in their activities, the recurrence of pain is not necessarily a sign of growing tolerance to the medication--the patient may be experiencing more pain because of increased activity. In this case, the patient can be reassured that more medication is required to alleviate the pain of someone with a busy schedule than of someone lying in bed all day.

Maintenance Phase

Objective: To maintain reliable pain control and improvement in function by repeating the effective dose in a routine schedule, varying the timing or dose only to accommodate changes in activity level or exacerbations of pain.

The general strategy for the maintenance phase:

19. The dose should not be lowered once a plateau has been achieved that provides adequate pain relief, satisfactory functional status, and is tolerated.
20. To ensure patient safety, continue routine patient reporting and monitoring. Patients should be asked to report not only on their medical conditions and medication requirements, but also any changes in their activity, employment, or social situation.
21. When prescribing an opioid analgesic for around-the-clock pain, it should also be dosed around-the-clock using a pharmacologically appropriate, time-contingent, dosing schedule.
22. In addition to the maintenance opioid analgesic, supplemental doses of short-acting medications may be considered to control break-through occasional episodes of pain exacerbation, such as those listed below (also see Appendix E, Table E5).
    a. Incidental pain: pain related to an increase in activity
    b. End-of-dose pain
    c. Natural conditions: pain related to predictable phenomena, such as changes in the weather.
    d. Specific medical conditions.

    Higher doses of the long-acting maintenance medication may also be useful in certain situations, but the potential for drug accumulation and adverse effects should be considered. If episodes of pain exacerbation occur frequently, re-evaluation of the adequacy of the maintenance dosage regimen is warranted.
23. Patients need to be assessed every 1- 6 months, keeping the following in mind:
    a. No specific visit frequency applies to all patients
    b. The visit frequency should be adjusted based on patient characteristics, comorbidities, type of pain, and type and dose of opioids. The provider should select a frequency that allows close follow-up of the patient's adverse effects, pain status, and appropriate use of medication.
    c. The patient should be able to request an early evaluation.
    d. In general, any change of dose or drug should be done during a clinic visit.

Individuals who develop a tolerance to the analgesic effects of opioids vary in the extent to which they become tolerant. Some maintain adequate pain relief at modest doses for very long periods of time. Others require frequent dosage increases to maintain effect. Most patients treated with opioids for chronic pain do not seem to develop a problem due to analgesic tolerance. Most patients reach a plateau within the first few months of treatment, after which only small adjustments in dose are necessary.

Although the choice of medication and dose are relatively routine during this phase, circumstances arise which require adjustments in the regimen or more aggressive clinical support. First, new adverse effects may emerge or become more clinically significant with prolonged opioid administration, and their treatment may require dosage adjustment or the addition of adjunctive medications. Second, the underlying condition causing pain may worsen, requiring new evaluation and therapeutic intervention. And third, a patient may experience new medical or psychological symptoms, the evaluation and treatment of which is complicated by the medications to treat pain.

Table 2: Use of Opioids for Chronic Pain in Special Populations

Medication	Swallowing difficulty	GI mal-absorption	Elderly or debilitated	Hepatic dysfunction	Renal dysfunction	Seizures	Decreased CYP-2D6 activity (c)
Codeine	✚ (OS)		◆ and ↓	✖	◆ and ↓		Less effective
Fentanyl TDS (a)	✚	✚		◆ and ↓			
Hydrocodone	✚ (OS)						? less effective
Hydromorphone	✚ (OS, RS)	✚ (RS)					
Levorphanol							
Methadone (b)	✚ (OS)						
Morphine	✚ (OS, RS)	✚ (RS)			↓ or ✖		
Morphine CR/SR					↓ or ✖		
Oxycodone	✚ (OS)				◆ and ↓		? less effective
Oxycodone CR					◆ and ↓		? less effective
Propoxyphene			✖	✖	✖	◆	
Tramadol			◆ and ↓	◆ and ↓	◆ and ↓	✖	? less effective

See Appendix E, Tables E1 and E2 and Appendix F Methadone Dosing Recommendations for Treatment of Chronic Pain for further details and references.

CR = Controlled release
OS = Oral solution
RS = Rectal suppository
SR = Sustained release
TDS = Transdermal system

✚ = Recommended
◆ = Use with caution
↓ = Reduce dose
✖ = Not recommended
? less effective = conversion to the active metabolite may be decreased. Impact on analgesic efficacy is unknown.

(a) Transdermal System, consider if oral intake or bowel absorption is impaired.
(b) The only long-acting opioid available as an oral solution.
(c) **CYP-2D6 Inhibiting Drugs**: *Antiarrhythmics* (amiodarone, propafenone, quinidine [strong inhibitor]); *analgesics* (methadone [weak inhibitor], propoxyphene); *antihistamines* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine$_2$ receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir), *quinine compounds* (hydroxychloroquine, quinacrine, quinine); *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).

DISCUSSION

A trial of opioid therapy has been endorsed as a standard therapeutic approach to chronic pain by several professional organizations (AAPM & APS, 1996; Canadian Pain Society, 1998). The initial treatment with an opioid agent is a trial. During the trial, the clinician attempts to establish effective pain relief and function improvement by trying opioid agents, and by making specific and well-documented dosage adjustments in response to feedback from the patient.

Choice of agent:

There are very few well-designed studies that compare the efficacy, safety and tolerability of different opioids in the treatment of patients with chronic pain. In general, no single agent is superior to the others. However, an individual may obtain a better response, have a greater degree of safety, or have better tolerability with certain agents or delivery methods. If a decision is made to begin opioid therapy in the opioid-naïve patient, this may be accomplished with a short-acting opioid or an equivalent dose of a long-acting opioid (see Appendix E, Tables E1 and E2).

Quang-Cantagrel and his colleagues (2000) performed a chart review of 86 outpatients receiving long-acting opioids. They found that although 85% of the patients eventually received adequate short-term pain relief from opioids, some patients tried as many as five opioids before settling on a successful treatment. The authors concluded "If it is necessary to change the opioid prescription because of intolerable adverse effects or ineffectiveness, with each new opioid tested, the number of patients to whom this new prescription will be effective increases…Failure of one opioid cannot predict the patient's response to another opioid."

Short-acting v. long-acting:

Of the randomized controlled trials that directly compared the efficacy of long-acting opioids to short-acting opioids in patients with chronic non-cancer pain, 5 trials found no significant difference in outcome (Hale et al., 1999; Salzman et al., 1999; Caldwell et al., 1999; Caldwell et al., 2002; Peat et al., 1999).

For oxycodone, three articles address this issue directly, and all compare controlled-release (CR) vs. immediate-release (IR) oxycodone (Caldwell et al., 1999; Hale et al., 1999; Salzman et al., 1999). The papers were all published the same year and have several authors in common. Patients had chronic pain associated with osteoarthritis (first paper), low-back pain (second paper), and cancer or low-back pain (third paper, which presents two separate trials). The first two papers had a double-blind phase (n = 107 and 47, respectively), but both trials in the third paper were open-label (n = 48 and 57). Despite these issues, all three studies reached essentially the same conclusion: Oxycodone CR dosed every 12 hours is comparable to the equivalent dosage of oxycodone IR given 4 times daily. Comparable efficacy was noted with regard to percentage of patients achieving pain relief, intensity of pain relief, time to achieve stable pain control, and enhanced quality of sleep. One study noted a slightly lower incidence of some adverse effects with oxycodone CR, but adverse events were also fairly comparable.

The abundance of other studies making use of long-acting formulations also report similar efficacy of long- and short-acting opioids. Of 13 additional trials that address the issue of predetermined maximal dose vs. to-effect dosing, 12 specifically state that long-acting formulations (codeine, fentanyl, morphine, oxycodone, or tramadol) were used. One of these studies addresses the use of twice daily vs. once-daily extended-release morphine and finds comparable analgesic efficacy and adverse effects, but improved sleep for the latter formulation (Caldwell et al., 2002).

Long-acting preparations may be preferred over short-acting agents in patients who require around-the-clock analgesic therapy because they allow less frequent dosing and, potentially, may decrease pain fluctuations and improve compliance.

Patient considerations:

Type of pain: A perception exists that neuropathic pain does not respond to opioids. Some new studies, however, suggest that opioids may be useful in treating at least some forms of neuropathic pain (Huse et al., 2001; Leung et al., 2001; Sindrup et al., 1999a & 1999b; Watson, 2000).

In his literature review of the treatment of neuropathic pain with antidepressants and opioids, Watson (2000) reports that for postherpetic neuralgia (PHN), "uncontrolled data related to a long-acting oral opioid and single-dose intravenous controlled trials have supported an effect of opioids in PHN." Huse et al. (2001) tested the effect of oral morphine in 12 patients with phantom limb pain. The authors found that not

only did the patients experience a clinically relevant lessening of pain, but also that "neuromagnetic source imaging of 3 patients showed initial evidence for reduced cortical reorganization under [morphine] concurrent with the reduction in pain intensity, which was larger in patients with higher pain reduction." Leung and his colleagues compared the effects of alfentanil and ketamine infusions in 12 patients with post-nerve injury allodynia and hyperalgesia, and concluded "clinical utilization of opioids with careful titration may be beneficial in post-nerve injury patients with partial deafferentation" (2001). Sindrup et al. (1999a, 1999b) also found opioids to be useful in neuropathic pain. In a small study of tramadol for painful polyneuropathy the authors found "tramadol appears to relieve both ongoing pain symptoms and the key neuropathic pain feature allodynia in polyneuropathy."

Dosing issues:
In general, begin with a low dose to gauge initial response, minimize adverse effects, ensure the patient does not have a hypersensitivity to the drug, and allow the patient to develop tolerance before making further dosage increases.

Time-contingent vs. p.r.n. dosing: Hale et al. (1999) address this issue in concluding that controlled-release oxycodone is appropriate for selected patients whose pain is inadequately controlled by use of as-needed therapy. The need for constant pain relief seems to be an implicit assumption with chronic pain patients, and 16 of the 18 studies that address dosing issues make use of time-contingent pain control, although many supplement this baseline with additional medication for as-needed pain relief. In contrast, the two Palangio et al. studies (2000; 2002) use a set dosage every 6-8 or 4-6 hours, respectively, as needed for pain relief, not to exceed a maximum daily dosage. The second study also allowed supplemental analgesic. These studies did show significant improvement in pain relief over baseline, but since comparisons were between different drug combinations and not different dosing methods, no conclusions can be drawn regarding time-contingent therapy.

Predetermined maximal dose vs. to-effect dosing: Sixteen trials directly and/or indirectly address this issue. Fifteen of these make use of titration to effect at some point in the trial, and the one that does not states that the lack of sufficiently high dosages (of morphine) disallows interpretation of their results. Dosing decisions represent a balance (see figure 1) and are therefore set by the patient's needs. Nearly all studies do, however, establish a specific predetermined maximal dose for dosage titration, but in most cases the mean final dosage was well below the maximum allowed limit. Also, this (relatively high) ceiling was able to meet the analgesic needs of a large majority of the patients. Some example of maximal titration dosages include: codeine = 400 mg/day; fentanyl = 100μg/hr; morphine = 70-300 mg/day; oxycodone = 60-400 mg/day; tramadol = 400 mg/day. Several authors explicitly stress the need for individual dose titration to optimize analgesic effect while maintaining adverse effects at a tolerable level.

Six of the 16 trials commenced with more than 100 patients; four of these included osteoarthritis patients exclusively, one trial included diabetic neuropathy patients exclusively, and the remaining trials included 256 patients with various chronic, non-malignant pain etiologies. All six of these trials made use of to-effect dosage (Allan et al., 2001; Caldwell et al., 1999; Caldwell et al., 2002; Harati et al., 2000).

Titration:

Long-term opioid therapy should be started at a low dose and carefully titrated until an adequate level of analgesia and function is obtained, or until unmanageable and persistent adverse effects warrant a decreased dose or a change in therapy (Jamison et al., 1998; Petrone et al., 1999; Ruoff, 1999). For some patients, however, opioids do not exert an appreciable analgesic effect until a threshold dose has been achieved. *Methadone dosing:* Because methadone is excreted slowly, it must be started at a low dose, (e.g., 2.5 mg every 8 hours in opioid-naïve patients). The dose may be increased after 5 to 74 days if there is no problem with daytime sedation (also see Appendix F).

Equianalgesic conversion: In the patient receiving chronic pain therapy with a short-acting opioid, the patient may benefit from conversion to a long-acting opioid preparation to enhance dosing convenience and maintain more stable analgesia. The conversion to a long-acting opioid should be based on an equianalgesic conversion (see Appendix E, Table E-3 for conversion factors) and consideration of the

incomplete cross tolerance between opioids. To allow for incomplete cross-tolerance, in most cases the starting conversion dose should be 50% to 67% of the calculated equianalgesic dose. The conversion calculation to methadone varies with the total daily dose of the previous opioid. Brief recommendations for this conversion may be found in Appendix E, Table E-3. If additional detailed information is desired, it may be found in Appendix F, Methadone Dosing Recommendations.

EVIDENCE

	Recommendations	Source of Evidence	QE	Overall Quality	R
1	A trial of opioids for chronic pain when other analgesic approaches are insufficient	Consensus Statement, AAPM & APS, 1996	III	Poor	I
2	No single agent is superior; in most patients, trials with several medications may be required; rotation among opioids may improve long-term efficacy	Quang-Cantagrel et al., 2000 (SR)	II	Fair	B
3	Long-acting agents are effective for continuous, chronic pain	Caldwell et al., 1999 Caldwell et al., 2002 Hale et al., 1999 Lloyd et al., 1992 Peat et al., 1999 Salzman et al., 1999	I I I I I I	Good	A
4	Try one medication at a time for opioid-naïve patient. Discontinue opioid trials if opioid naïve patient does not experience at least partial analgesia with incremental dose titrations	Joranson et al., 1992	III	Poor	I
5	Start with agent and dose that have been effective in the past for patient who has used opioid therapy	Canadian Pain Society, 1998	III	Poor	I
6	An opioid trial for either nociceptive or neuropathic pain	Huse et al., 2001 Leung et al., 2001 Sindrup et al., 1999a & 1999b Watson, 2000	I I I I	Good	A
7	Time-contingent dosing schedule	Hale et al., 1999 Canadian Pain Society, 1998 College of Physicians and Surgeons of Ontario, 2000	I III III	Good	A
8	Set dose levels based on patient need, not predetermined maximal dose	Allan et al., 2001 Caldwell et al., 1999 Caldwell et al., 2002 Harati et al., 2000	I I I I	Good	A
9	Titrate until an adequate level of analgesia is obtained	Jamison et al., 1998 Petrone et al., 1999 Ruoff, 1999	I I I	Good	A
10	During the titration phase, reasonable doses of rescue opioid may be provided	Canadian Pain Society, 1998 College of Physicians and Surgeons of Ontario, 2000	III III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

L. Document Therapy

OBJECTIVE

Guide proper use and documentation of opioid therapy.

BACKGROUND

Opioid analgesics are controlled substances under federal and state law because of their potential to produce psychological and physical dependence (see Appendix D) as well as other medical complications. The federal Controlled Substances Act (CSA) has established a framework for the use of opioids for the treatment of pain. In order to demonstrate compliance with all aspects of the various requirements as well as to comply with good medical practice, documentation must be timely, accurate, and thorough.

RECOMMENDATIONS

1. When writing a prescription for opioid therapy, be certain to record the name of the drug, the strength, the number of dosage units (written numerically and in text) and how the drug is to be taken. Record any changes to therapy and the reason for the changes. For methadone, indicate on the prescription that it is for chronic pain.

2. The VA regulations for the use of controlled substances (Controlled Substances [Pharmacy Stock], VHA Handbook 1108.1) must be followed by clinicians within the VA system, and provide a useful guide for other clinicians.
   - All prescriptions for controlled substances will be dated as of and signed on the day when issued and bear the full name and address of the patient, and the name, address, and DEA registration number of the practitioner. Prescriptions should not be filled if they are more than 7 days old when presented.
   - An intern, resident, mid-level practitioner, foreign-trained physician, physician, or dentist on the staff of a VA facility exempted from registration (21 CFR 1301.24) will include on all prescriptions issued the registration number of the VA facility and the special internal code number assigned by the VA facility in lieu of the registration number of the practitioner required by law (21 CFR 1306.05b). Each written prescription will have the name of the physician or authorized practitioner stamped, typed, or hand printed on it, as well as the signature of the physician or authorized practitioner.
   - The label of any drug listed as a "Controlled Substance" in Schedule II, III, IV, or V of the Controlled Substances Act will, when dispensed to or for a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."

M. Assess Therapy

M1. Assess Adverse Effects

OBJECTIVE

Identify adverse effects that may potentially change the treatment plan.

BACKGROUND

Opioid-induced adverse effects may occur acutely or with long-term therapy. The long-term adverse effects of opioids are not well defined because studies are generally of short duration. It is well known that the use of opioid analgesics can produce adverse effects such as constipation, drowsiness, nausea, pruritus, and confusion. Patients generally develop tolerance to these adverse effects except constipation. As a general rule, nausea and constipation can be minimized by the use of antiemetics and bowel stimulants. When opioids are dosed and monitored appropriately, respiratory depression is relatively uncommon.

RECOMMENDATIONS

1. Evaluate patient for opioid adverse effects: constipation, nausea, vomiting, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, hyperalgesia, sexual dysfunction, and sedation.

2. Many adverse effects spontaneously resolve with continued administration and development of tolerance. Consider individual levels of tolerability to different opioid agents.

3. If not already done, anticipate and consider preventive treatment for common adverse effects, particularly constipation and nausea.

4. Modifying the dose and rotating the opioid agents should successfully treat most adverse effects.

DISCUSSION

Typical opioid adverse effects are common (Caldwell et al., 2002; Mullican & Lacy, 2001; Roth et al., 2000). They include constipation, nausea, vomiting, somnolence, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, and sedation. Patient discontinuation due to adverse events is often reported. Titration of dosage needs to be in balance with a tolerable level of adverse effects. Development of tolerance to adverse effects (with the exception of constipation) is commonly observed over time.

Most studies evaluating adverse effects of opioid therapy in patients with chronic non-cancer pain have been short-term (range: 2 weeks to 12 months) (Caldwell et al., 1999; Caldwell et al., 2002; Mullican & Lacy, 2001; Roth et al., 2000; Peloso et al., 2000). In one study, the most common adverse effects after 26 weeks of extended-release morphine were constipation and nausea (Caldwell et al., 2002). Of 295 patients with osteoarthritis, 67% experienced at least one adverse effect and 20% discontinued the study early because of an adverse effect. Roth's study (2000) of 133 patients with osteoarthritis reported similar rates of adverse effects (65.4%), however, no clinically significant safety observations were made and there was reduction in pain intensity. In addition, adverse effects decreased in frequency as therapy was continued. There is evidence that slow titration of tramadol (50-mg increments every 3 days up to 200 mg per day) can improve tolerability with significantly fewer discontinuations due to nausea, vomiting, dizziness, vertigo, or any adverse event. Most adverse events were mild or moderate in intensity and resolved with continued therapy (Ruoff, 1999).

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Evaluate patient for adverse effects	Working Group Consensus	III	Poor	I
2	Many adverse effects resolve	Roth et al., 2000	II	Fair	C
3	Anticipate and treat adverse effects	Working Group Consensus	III	Poor	I
4	Treat adverse effects by modifying dose or by drug rotation	Ruoff, 1999	I	Fair	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

M2. Assess Adherence

OBJECTIVE

Determine whether patient is adhering to the essential components of the treatment plan.

BACKGROUND

Though research confirmation is lacking, adherence to the treatment plan is likely to be associated with positive outcomes. Non-adherence may take the form of serious or minor variations. Serious variations are those that jeopardize the safety of the patient or society, or which are illegal. Minor variations are behaviors that do not immediately jeopardize health or safety but may negatively impact treatment effectiveness and the provider-patient relationship, and may signal the potential for more serious non-adherence.

RECOMMENDATIONS

1. At every visit, assess and document adherence with appropriate use of opioid analgesics, including evidence of misuse, abuse or addiction. (Consider random pill counts or urine drug screens to assess adherence.)

2. Assess and document adherence to other components of the treatment plan, such as follow up with referrals, tests, and therapies.

3. Assess and document patient motivation and barriers to adherence.

4. Assess patients for behaviors that are predictive of addiction.

5. If the meaning of the behavior is not clear, some time may be required to assess the patient correctly and observe the reaction to additional requirements, such as frequent clinic visits or periodic drug screens.

DISCUSSION

Although the risk of developing true opioid addiction appears to be low in patients with no prior history of a substance use disorder (Friedman, 1990; Twycross, 1974; Twycross & Wald, 1976), less serious non-adherence to medication use is probably more common. For example, patients may escalate the dose beyond that prescribed, necessitating early refills. Clinicians may be under-dosing due to inexperience, fear of creating substance abuse/addiction, or fear of legal complications or stigma. Patients new to opioid therapy may misunderstand proper use, or may demonstrate other variations from the agreed upon treatment plan. It is important to evaluate how and when the patient is taking medication, use of other medications including nonprescription and herbal preparations, and use of alcohol and illicit drugs. Behaviors suggestive of opioid abuse or addiction include rapidly escalating demands for dose increases, or unusual increase in doses; observed or reported intoxication or unexplained withdrawal symptoms; repeatedly reporting that opioid medication was lost, stolen, or destroyed; injection of opioids; threatening or harassing staff; repeatedly seeking prescriptions from other providers or emergency rooms; and alteration of, borrowing, stealing or selling prescriptions. Adherence to other components of the treatment plan such as referrals, tests and therapies (such as physical therapy) is also important in order to minimize the need for opioid therapy and to optimize outcomes. Patient motivation to follow through with these recommendations should be assessed, especially when non-adherence is present. Other barriers to adherence that could be addressed may be present. For example, patients may lack the cognitive capacity to manage a complex regime, or may lack transportation. Interviewing family members or other collateral sources is frequently helpful in determining adherence and barriers.

The clinician should determine whether the variation from the treatment plan is relatively minor, and therefore amenable to educational intervention or adjustment of the treatment plan, or whether it is serious and requires termination of opioid therapy. The occurrence of minor variations should prompt the clinician to review the terms of the opioid plan/agreement and to incorporate strategies for responding to the variations as part of the treatment plan.

If non-adherence to the treatment plan has occurred, the clinician must explore its nature and implications. Non-adherence may take many forms, and the clinician must be alert to those behaviors.

Not every episode of variation from the agreed management plan warrants a diagnosis of addiction. If the clinician is not sure of the meaning of the action, more frequent clinic visits, addiction specialist consultations, or periodic drug screens might be employed. The behaviors that should prompt clinician's concern are summarized in Table 3 Predictors of Opioid Misuse.

Table 3: Predictors of Opioid Misuse

I	Illegal or Criminal behavior
	• Diversion (sale or provision of opioids to others) • Prescription forgery • Stealing or "borrowing" drugs from others
II	Dangerous behavior
	• Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects • Intentional overdose or suicide attempt • Aggressive/threatening/belligerent behavior in the clinic
III	Behavior that suggests addiction
	• Use of prescription medications in an unapproved or inappropriate manner (such as cutting time-release preparations, injecting oral formulations, and applying fentanyl topical patches to oral or rectal mucosa) • Obtaining opioids outside of medical settings • Concurrent abuse of alcohol or illicit drugs • Repeated requests for dose increases or early refills, despite the presence of adequate analgesia • Multiple episodes of prescription "loss" • Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber, or after warnings to desist • Evidence of deterioration in the ability to function at work, in the family, or socially, which appears to be related to drug use • Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug • Positive urine drug screen—other substance use
IV	Aberrant behavior that requires attention
•	• Aggressive complaining about needing more of the drug • Drug hoarding during periods of reduced symptoms • Requesting specific drugs • Openly acquiring similar drugs from other medical sources • Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions • Unapproved use of the drug to treat another symptom • Reporting psychic effects not intended by the clinician • Resistance to a change in therapy associated with "tolerable" adverse effects, with expressions of anxiety related to the return of severe symptoms • Missing appointment(s) • Not following other components of the treatment plan (physical therapy, exercise, etc.)

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Assess adherence to opioid therapy and other components of the treatment plan	Working Group Consensus	III	Poor	I
2	Assess motivation and barriers to adherence	Working Group Consensus	III	Poor	I
3	Assess patients for behaviors that are predictive of addiction	Portenoy, 1996a	III	Poor	I
4	Address safety risks immediately and apply legal mandate as appropriate	Working Group Consensus	III	Poor	I
5	If the meaning of the behavior is not clear, assess patient over time and frequent clinic visits or periodic drug screens	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

M3. Assess Efficacy (Pain, Function, and Satisfaction)

OBJECTIVE

Evaluate the pain treatment plan in a timely manner to ensure appropriate opioid titration, evaluation of adverse effects, and progress towards goal attainment.

BACKGROUND

Although there is no evidence to support a specific follow-up period, there is clinical experience that supports follow up appointments every 1-4 weeks during titration. Patients who are on a stable dose of medication without evidence of adverse effects or adherence problems may be followed every 1-6 months. Patient assessment via phone or physician extender should be completed each time a prescription is written.

Upon the initiation of opioid therapy, ongoing in-person or telephone contacts with the patient must be scheduled. While the goal is reduction of pain intensity and improvement of functional status, the provider also must assess for potential functional decline induced by treatment.

RECOMMENDATIONS

1. The provider should evaluate pain intensity at each visit.

    - Intensity of pain should be measured in the following manner using an NRS (0-10) scale:
        - Current pain
        - Least pain in last week
        - "Usual" or "Average" pain in the last week

    - The patient's response to current pain medications should be assessed each visit using the following question:
        - "What is your intensity of pain after taking your current treatment/medication?"
        - "How long does your pain relief last after taking your medication?"

2. Providers should evaluate pain-related function using validated instruments or NRS rating scales on a monthly basis during titration and every six months after the patient is on stable opioids. Assessment of function should include:

    - Employment
    - Enjoyment of life
    - Emotional distress (depression and anxiety)
    - Housework, chores, hobbies, etc.
    - Sleep
    - Mobility
    - Self-care behaviors
    - Sexual function

3. The patients' satisfaction with pain control should be assessed at each visit.

DISCUSSION

There are advantages to using numeric rating scales for assessing pain and function. The NRS has been found to be valid and reliable, and to be sensitive to changes in acute, cancer, and chronic pain (Breivik & Skoglund, 1998; De Conno et al, 1994; Paice & Cohen, 1997). Research indicates that "least" and "usual" pain ratings provide the best estimate of actual pain intensity (Jensen et al., 1996). Measurement of other aspects of pain-related functioning may be accomplished using one or more validated measures of pain interference or functional status. Although there are no data establishing the validity of individual numeric rating scales of function, numeric scales facilitate the assessment of goal attainment and treatment related changes, and assist with clinical decision-making (Serlin et al., 1995).

In a 30-day study of 167 patients with moderate to severe osteoarthritis, Caldwell et al. (1999) compared opioid treatment to placebo (all patients were allowed to maintain baseline NSAID therapy). The study demonstrated that global quality of sleep improved in the active treatment group compared to the placebo cohort. Peloso et al. (2000) compared controlled release codeine to placebo in a 4-week study of 103 patients with osteoarthritis of the hip or knee, and reported an improvement in physical function in the codeine group.

Roth et al. (2000) reported that patient self-evaluations of general activity, sleep, enjoyment of life, and mood improved during treatment with controlled release oxycodone therapy versus placebo in a group of elderly patients with moderate osteoarthritis.

NOTE: The VA Pain Outcomes Toolkit recommends several optional instruments for functional status assessment. [Link to Web site http://www.va.gov]

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Evaluate pain intensity using 0-10 scales	Breivik & Skoglund, 1998 De Conno et al., 1994 Jensen et al., 1996 Ogon et al., 1996 Serlin et al., 1995	II-1 III III II-2 II-2	Fair	B
2	Evaluate function related to chronic pain after initiation of therapy	Caldwell et al., 1999 Jensen et al., 1992 Peloso et al., 2000 Roth et al., 2000	I II-1 I I	Good	A
3	Frequent reassessment	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

N. Indication to Stop Opioid Therapy

N1. Are There Severe and Uncontrollable Adverse Effects?

OBJECTIVE

Determine whether adverse effects warrant adjustment of opioid therapy or discontinuation of opioid therapy.

BACKGROUND

Adverse effects associated with opioid therapy cannot always be resolved despite maximal attempts to mitigate them. The determination of tolerability rests primarily with the patient and the care provider attempts to find solutions. When the options have been exhausted and the therapy is a greater detriment than benefit, as determined in consultation with the patient and family, opioid therapy should be discontinued.

RECOMMENDATIONS

1. When therapy is a greater detriment than benefit as determined in consultation with the patient and family, opioid therapy should be discontinued.

DISCUSSION

Constipation, nausea and sedation are common adverse effects. Nausea and sedation are generally short-term, and often resolve with continued therapy. Nausea is not a contraindication to opioid therapy, although antiemetics may be necessary to control nausea during initial dose titration. Sedation can often be controlled by careful titration; tolerance to this adverse effect will often develop. One adverse effect that is not likely to be self-limiting is constipation. Every patient should, therefore, receive prophylactic measures to ensure regular bowel movements. Patients usually develop rapid tolerance to the respiratory depressant effects of opioid therapy, so discontinuation for this reason is rarely indicated (Joranson, et al., 1992).

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Terminate opioids when harm outweighs benefit of therapy	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

N2. Serious Non-Adherence: Illegal, Criminal or Dangerous Behaviors?

OBJECTIVE

Identify serious non-adherence to opioid use that may warrant discontinuation of opioid therapy.

BACKGROUND

These behaviors are those that jeopardize the safety of the patient or society, or are illegal. Active diversion (selling drugs), prescription forgery, medication theft, and assault behaviors are illegal and mandate prompt documentation and consideration of notifying police authorities. Their occurrence may require the immediate cessation of the opioid with appropriate treatment of potential withdrawal symptoms.

Table 3a: Predictors of Opioid Misuse

Illegal or Criminal behavior
• Diversion (sale or provision of opioids to others) • Prescription forgery • Stealing or "borrowing" drugs from others
Dangerous behavior
• Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects • Intentional overdose or suicide attempt • Aggressive/threatening/belligerent behavior in the clinic

RECOMMENDATIONS

1. Address safety issues immediately. Apply legal mandates as appropriate.

2. Dangerous or illegal behaviors may require immediate cessation of the opioid therapy with appropriate treatment of potential withdrawal symptoms.

3. Consider notifying police about criminal behaviors. Consult with counsel prior to doing so to clarify current confidentiality laws and regulations.

DISCUSSION

The opioid management plan or agreement instituted between the patient and the provider creates a structure to guide and evaluate adherence. There may be harmless errors if the patient misunderstands directions for proper use of the agents. Clinicians may erroneously undermedicate pain disorders. Issues of opioid therapy misuse that may be reflective of an opioid addiction problem evolving during opioid pharmacotherapy should be addressed before discontinuation of opioids.

Clinicians who are prescribing opioids must ensure that documentation of the overall management plan for opioid therapy adheres to the standards of the organization in which they practice. State and Federal regulations must also be followed. As always, the relationship that exists between the provider and patient must remain one of trust, and variations from this agreed upon plan must prompt appropriate actions. The clinician should be ready to institute necessary actions and to document these actions in the medical record.

Dangerous or criminal behaviors have impact beyond the patient and clinician, and must be addressed at the time the action becomes apparent to the treatment team.

EVIDENCE

	Recommendations	**Sources of Evidence**	**QE**	**Overall Quality**	**R**
1	Address safety issues immediately. Apply legal mandate as appropriate	Working Group Consensus	III	Poor	I
2	Document and refer to police/legal actions those patients demonstrating criminal behaviors	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

N3. Non-effective Therapy or Other Indications to Stop Therapy?

OBJECTIVE

Determine when to discontinue chronic opioid therapy due to lack of efficacy or change in need.

BACKGROUND

A well-designed opioid trial should help to determine whether opioid therapy is appropriate for the patient. If there has not been an overall improvement in function or satisfaction, opioids should usually be discontinued.

If the patient has returned to work or has demonstrated substantial improvement both in function and reported pain levels, reasonable doses of opioids could continue. Re-evaluation of the need for opioids every two months can be accomplished using techniques such as weaning and/or substitution of alternative treatments.

RECOMMENDATIONS

1. Consider tapering off opioid medication if the patient claims or exhibits:

- Lack of efficacy:
  - Continuing pain despite titration of dose to intolerable adverse effects
  - Lack of response despite trials of several different kinds of opioids
  - Decrease in overall function

- Resolution of the pain problem:
  - Pain problem may be resolved due to surgical intervention
  - Pain problem may be resolved due to physical therapy or other modalities
  - Pain may now be responding to non-opioid medications

- Desire to discontinue therapy:
  - Patient desires to stop opioid due to personal goals or interference with lifestyle, work or quality of life.
  - Patient desires to change to non-opioid therapy
  - Patient had been using opioids to enable other therapy which is now completed

DISCUSSION

The efficacy of opioids is measured not just by impact on pain but also by impact on function (including sleep, eating, physical and social activities), interpersonal relationships and mood. Discussions with patients regarding the impact of opioids on all these aspects determine whether to continue or discontinue therapy (Galer et al., 1992; Portenoy, 1996b). Input from caregivers or significant others may be helpful in making this decision.

Pain may sometimes be resolved or decreased by surgery or physical therapy, therefore enabling a decrease or discontinuation of opioid therapy.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Taper off opioid if the patient exhibits evidence of a lack of efficacy	Galer et al., 1992 Portenoy, 1996b Working Group Consensus	III	Poor	I

2	Taper off opioid if the pain problem is resolved	Working Group Consensus	III	Poor	I
3	Taper off opioid if the patient no longer desires opioid therapy	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

O. Is There Evidence of Non-Adherence or Medication Misuse Suggestive of Addiction to Prescribed Opioid?

OBJECTIVE

Identify patients who may need referral to addiction therapy or to a substance use disorder specialist.

BACKGROUND

Addiction in the context of pain treatment with opioids is characterized by a persistent pattern of opioid misuse that may involve any or all of the following:

Table 3b: Predictors of Opioid Misuse

Behavior that suggests addiction
• Use of prescription opioids in an unapproved or inappropriate manner (such as cutting time-release preparations, injecting oral formulations, and applying fentanyl topical patches to oral or rectal mucosa) • Obtaining opioids outside of medical settings • Concurrent abuse of alcohol or illicit drugs • Repeated requests for dose increases or early refills, despite the presence of adequate analgesia • Multiple episodes of prescription "loss" • Repeatedly seeking prescriptions from other clinicians or from emergency rooms without informing prescriber, or after warnings to desist • Evidence of deterioration in the ability to function at work, in the family, or socially, which appears to be related to drug use • Repeated resistance to changes in therapy despite clear evidence of adverse physical or psychological effects from the drug • Positive urine drug screen—other substance use (cocaine, opioids, amphetamines or alcohol) • Meets DSM IV criteria for dependence on opioids

Ongoing serious dependence on alcohol or illegal drugs is incompatible with the prescription of opioids for chronic pain.

RECOMMENDATIONS

1. Screen for substance use disorders in patients who are unable or unwilling to adhere to the treatment plan.

2. Document and refer to addiction specialists those patients demonstrating behaviors suggesting addiction to prescribed opioids or substance use disorders.

3. Consider referring patients with significant, chronic, substantiated pain who develop addiction behaviors in the context of chronic opioid therapy. An addiction specialist may be better able to evaluate the risks and benefits of continuing opioid therapy in such a situation.

DISCUSSION

Addiction, unlike tolerance and physical dependence, is not a predictable drug effect, but represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals. Addiction is a primary chronic disease, and exposure to drugs is only one of the etiologic factors in its development. Addiction is recognized by the observation of one or more of its characteristic features: impaired control over drug use, craving and compulsive use, and continued use despite negative physical, mental and/or social consequences. An individual's behaviors that suggest addiction may, on occasion, be a reflection of other problems unrelated to pain therapy. Therefore, good clinical judgment must be used in determining whether the pattern of behavior signals the presence of addiction or reflects a different issue.

It should be emphasized that no single event is diagnostic of addictive disorder. Rather, the diagnosis is made in response to a pattern of behavior that usually becomes obvious over time.

Some healthcare providers misinterpret the seeking of additional pain relief in a patient with pain. The iatrogenic syndrome known as "pseudoaddiction" is a direct consequence of inadequate pain relief. The patient's demand for analgesics increases, and the patient becomes intensely focused on finding relief when pain is unrelieved. These behavioral changes are driven by the severity of the pain and are resolved with provision of adequate pain relief.

The patient may acknowledge the addictive behavior or deny it. Tapering the opioid and controlling withdrawal symptoms are best achieved in a coordinated addiction therapy program, provided by a substance use specialist. The VA/DoD Guideline for the Management of Substance Use Disorders includes modules that describe and discuss such programs.

The prevalence of addiction among patients with chronic, non-cancer pain is unknown. There are no systematic longitudinal surveys of heterogeneous populations with this type of pain. The exposure of patients to an opioid does not necessarily elicit behavior consistent with addiction (Portenoy, 1996). The rate of drug abuse and addiction in patients with chronic pain has been estimated between 3.2% and 18.9% (Kouyanou, et al., 1997); Turk (2002) reviewed 13 studies and reported a rate of 18% for abuse, addiction, and noncompliance.

Referral To Addiction/Substance Specialty For Redirecting Addictive Behaviors And/Or Tapering Off Opioids

Continued chronic opioid prescribing for significant chronic pain despite addiction/abuse behaviors arising out of the prescribing relationship should rely upon input from an addiction specialist. As with other chronic medical disorders (such as diabetes, asthma, and hypertension), substance use disorders are treatable medical disorders with biological as well as psychosocial determinants. Opioid abuse and addiction are known complications of appropriate chronic opioid prescribing. Thus, for select cases where the pain condition is significant and the addiction behaviors are redirectable, continuation of chronic opioid therapy may be considered within a more well-described and rigid prescribing setting.

In general, positive predictors and negative predictors of this approach are outlined below:

Positive predictors:

- Previously good patient compliance and motivation within the primary care provider-patient relationship
- Patient willingness to comply with heightened compliance supervision measures (i.e. pill counts, more frequent visits, random drug and alcohol screens, smaller prescriptions, zero tolerance for lost medications/refills, etc.)
- Opportunities for improvement exist in the management of the chronic pain; including the use of: (1) non-opioid pharmacotherapy; (2) non-medication physical therapies (TENS, ultrasound/deep heat, massage,

physical therapy, etc.); and (3) the provision of psychosocial therapies (biofeedback, formal relaxation techniques, supportive and cognitive psychotherapy, etc.)
- The addiction/abuse behaviors are limited in both severity and number
- Patient education by the addiction specialist regarding addiction/abuse behaviors results in significantly improved insight regarding addiction/abuse behaviors and their harm
- Patient motivation for changing addiction/abuse behaviors relative to ongoing opioid prescribing is responsive to addiction specialist consultation and is internally located (i.e. motivated by an internal desire to adhere to prescribing boundaries in the interest of preserving the therapeutic relationship and maximizing pain control)
- Absence of other pre-existing or concurrent substance abuse/addiction
- A supportive recovery environment (spouse, partner, family, supervisor), where someone is willing to assist (with patient's consent) in monitoring compliance issues.

Negative predictors:

- Previously poor or questionable patient compliance and motivation within the primary care provider-patient relationship
- Patient unwilling to comply with heightened compliance supervision measures
- Chronic pain management is already biopsychosocially maximized
- The addiction/abuse behaviors are significant in severity or number
- Patient education by the addiction specialist regarding addiction/abuse behaviors results in only mildly improved insight regarding addiction/abuse behaviors and their harm
- Patient motivation for changing addiction/abuse behaviors is externally located (i.e. motivated by the desire to re-acquire a source for drug abuse, pressures from the court or family) and unresponsive to the addiction specialist's consultation
- Pre-existing or concurrent other substance abuse/addiction
- An unsupportive recovery environment, including active substance abuse by others in the home

The patient should be referred to psychosocial treatments specific to prescription medication addiction/abuse. This may include addiction counselors comfortable with such topics and also self-help organizations (Pills Anonymous/PA, the National Chronic Pain Outreach association, etc.).

The primary care provider must not continue to prescribe in the context of prescription opioid abuse/addiction if he or she is uncomfortable regarding the patient's situation. The local support of a knowledgeable addiction specialty provider who is willing to collaborate is also essential.

Note that urine drug screening often must include specific requests to the lab for a full opioid panel (sometimes referred to as a "health care provider" panel), and perhaps even dextromethorphan screening, when suspected. Most urine drug screens do not screen for synthetic and semisynthetic opioids. Thus, such screens may fail to detect a variety of prescribed opioids (examples below), as well as commonly abused over-the-counter opioidergic antitussives (dextromethorphan-containing products):

- oxycodone
- fentanyl
- hydromorphone
- hydrocodone
- propoxyphene
- meperidine
- methadone

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R

1	Screen for substance use disorders in patients who are unable or unwilling to adhere to the treatment plan	Working Group Consensus	III	Poor	I
1	Document and refer to addiction specialists those patients demonstrating behaviors suggestive of addiction	Working Group Consensus	III	Poor	I
2	Consultation/referral to SUD specialty for redirecting addiction behaviors and continue opioid therapy	Dunbar & Katz, 1996 Pappagallo et al., 1997	I III	Fair	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

P. Is Treatment Effective and Tolerable?

OBJECTIVE

Determine whether the treatment trial should be continued.

BACKGROUND

Failure to achieve at least partial analgesia, or improved function, at relatively low initial doses in the non-tolerant patient raises questions about the potential efficacy of opioid therapy for the patient's pain syndrome.

RECOMMENDATIONS

1. Assess the safety and efficacy of the opioid trial, using the following criteria:

    - Patient's report of pain intensity and/or functional status
    - Persistence of analgesia between doses (i.e., pain relief is of adequate duration)
    - Patient satisfaction with the level of pain relief
    - Patient's improvement in functional status, quality of life
    - Patient's ability to participate in other modalities such as physical therapy
    - Patient's tolerance and management of adverse effects

2. Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function; opioid therapy should be considered complementary to other analgesic and rehabilitative approaches.

DISCUSSION

The findings of several studies of different cultures have found that, on a 0-10 pain rating scale, pain ratings of 5 or more interfere significantly with daily functions in patients with cancer pain (Cleeland et al., 1984; Cleeland et al., 1994; Serlin et al., 1995). Further research suggests that 4, rather than 5, is the point at which pain significantly interferes with function. The results of using the Brief Pain Inventory to assess 111 patients with pain and advanced cancer showed that, on a 0-10 scale, pain ratings of 4 or greater interfered markedly with activity, and interference with enjoyment increased markedly between scores of 6 and 7 (Twycross et al., 1996). This study and others, combined with clinical experience, has led many clinicians to the conclusion that a pain rating greater than 3 signals the need to revise the pain treatment plan with higher doses of analgesics or different medications and other interventions (Cleeland & Syrjala, 1992; Syrjala, 1993). A study of 255 patients attempted to replicate the non-linear association between pain and pain interference with a non-cancer sample and determine whether the cutoffs that have been identified as optimal for cancer patients are optimal for persons with pain associated with amputation and determine whether the optimal cutoffs replicate across pain types (phantom limb, back and general pain). Findings were similar in patients with low back pain. However, in the other groups, the degree of pain interference appeared to vary as a function of pain type. The

same level of back pain interfered more significantly with daily function then phantom limb pain did after pain levels reached five or more (on a 0-10 scale) (Jensen et al., 2001).

Although improving patient comfort is a valid and important goal, effective chronic opioid therapy should ideally foster improved function. Pain rating goals should be individualized with each patient. Pain ratings of less than 4 may not be attainable. However, patients who set ongoing goals greater than 3 need to be reminded that quality of life requires that they easily perform certain activities. Emphasize to the patient that satisfactory pain relief is a level of pain that is noticeable but not bothersome. Also, explain that a pain rating equal to or less than the goal should be maintained as much of the time as possible. Once again, be specific about the activities that accompany the pain rating goal. Ask the patient what pain rating would make it easy to sleep, eat, or perform other physical activities.

Not only does setting a comfort/function goal help the entire team -- including the patient and significant others -- to know what the pain treatment plan should achieve, but it also helps the patient see how pain relief contributes to improved quality of life. The patient's comfort/function goal should be visible on all records where pain ratings are recorded (McCaffery & Pasero, 1999).

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Assess effectiveness of treatment; revise treatment plan when pain rating is greater than 3	Cleeland & Syrjala, 1992 Twycross et al., 1996 Jensen et al., 2001	II II	Fair	B
2	Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function	McCaffery & Pasero, 1999	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

Q. Are There Complications, Comorbidities or Other Indications for Referral?

OBJECTIVE

Identify patient who may benefit from referral to pain specialty care.

RECOMMENDATIONS

1. Referral to a specialist in pain medicine may be warranted depending on the expertise of the provider and the complexity of the problem.

2. Referral to a psychiatrist or psychologist may be indicated in cases of significant psychiatric comorbidity

3. Patients with other psychosocial problems or comorbidities may benefit from disease or case management.

R. Adjust Therapy:

R1. Address Minor Non-adherence or Medication Misuse

OBJECTIVE

Redirect the treatment to address emergent issues or relatively minor behavioral problems, so that appropriate opioid therapy can be continued.

BACKGROUND

Once a problem in adherence to the treatment plan has been identified, a highly structured response to the aberrant behaviors is required, in order to maintain an appropriate therapeutic environment. The response may incorporate new explicit instructions for dosing (enforcing the written contract), more frequent visits, smaller prescriptions, periodic urine drug screens and alcohol screens, ongoing psychotherapy, or other interventions. Consultation with a specialist in addiction medicine or addiction psychiatry may again be helpful.

The decision to continue therapy should rest on the resolution of the immediate issue and the reestablishment of an agreement for the future. Any questions or uncertainties should be explicitly addressed and appropriate consultation or referral should be considered.

Table 3c: Predictors of Opioid Misuse

Non-adherence behaviors that requires attention
1. Aggressive complaining about needing more of the drug
2. Drug hoarding during periods of reduced symptoms
3. Requesting specific drugs
4. Openly acquiring similar drugs from other medical sources
5. Unsanctioned dose escalation or other noncompliance with therapy on one or two occasions
6. Unapproved use of the drug to treat another symptom
7. Reporting psychic effects not intended by the clinician
8. Resistance to a change in therapy associated with "tolerable" adverse effects, with expressions of anxiety related to the return of severe symptoms
9. Missing appointment(s)
10. Not following other components of the treatment plan (physical therapy, exercise, etc.)

RECOMMENDATIONS

1. Consider adjustment of the initial treatment agreement, with emphasis upon specific adherence issues that have been identified; a more rigid approach may be required.
   Possible responses to medication misuse might include:

   - Education and discussion along with restatement of the opioid management plan or agreement
   - Reviewing the written opioid prescribing agreement
   - Recommending or insisting on consultation with a pain and/or addiction specialist
   - Discussion, including discussion with others involved in the patient's care
   - Administration of medications under supervision or with the assistance of others
   - Change of medication or amount dispensed
   - More frequent clinic contacts (telephonic, physician extenders, or clinic visits)
   - Instituting regular or random urine toxicology screens as a condition for prescription renewal

2. Consider consultation with or referral to mental health if exacerbation of an underlying psychotic disorder is an issue.

3. Consider setting up a grievance procedure with the patient

4. Consider whether the patient requires a living situation with greater structure (e.g. nursing home, assisted living facility)

5. Strongly consider involving the patient's family or significant others in finding solutions to non-adherence, as well as monitoring future adherence.

DISCUSSION

The provider should be aware that there may be patients with psychiatric disorders, especially personality disorders, whose conditions may become manifest during therapy. These patients should be referred to the appropriate mental health clinic if simple strategies ordinarily used by the primary care doctor do not prove successful. In particular, if a patient develops suicidal ideation, immediate referral should occur. Suicidal ideation is most frequent in mood disorders, psychotic disorders, personality disorders, substance use/gambling disorders, and in panic disorder.

The provider might consider setting up a grievance procedure with the patient in the event that a further disagreement may occur between the patient and the provider about the patient's treatment plan. The provider can present the plan either before or during ongoing therapy. JCAHO has specific recommendations (in Behavioral Health Standards—Appendix B: Standards for Substance Abuse Programs) that may be helpful in this regard. Also, a provider may alert the patient representative of the hospital in advance about possible treatment disagreements. The primary care provider should also alert other treatment providers about any controversy so that a coordinated approach is used among different providers.

Some unsafe behaviors are unintentional but still may be quite dangerous. For example, a cognitive deficit may result in repeated overuse of medications. Minor non-adherence or misuse should result in the prompt review of the agreement, modification of the management plan as indicated, and documentation of these actions. The clinician should be aware that physical dependence and tolerance may mimic some of the minor variations and these variables should be evaluated appropriately. Be aware that, for the patient receiving chronic prescribed opioid therapy, a diagnosis of "substance dependence" (i.e. prescription opioid dependence) should not based on the two DSM criteria for physical dependence (tolerance, withdrawal). These criteria normally apply to assessing a general population of patients for diagnoses of substance dependence (addiction); however, in patients receiving chronic, prescribed opioid therapy, they are expected, iatrogenic phenomena.

Therefore, in patients suffering significant, chronic, substantiated pain and who are suspected of addiction/abuse of opioid prescriptions, consultation with an addiction specialist knowledgeable about the treatment of pain may be helpful prior to considering withdrawal of prescribed opioids. The goal is not only to more carefully identify opioid abuse or addiction behaviors arising out of the context of chronic opioid therapy, but also to consider whether the patient's addiction/abuse behaviors can be successfully redirected so as to allow for continued chronic opioid prescribing concurrent with addiction specialty follow-up and coordination. Lastly, it is important to consider whether dose adjustment or opioid rotation is indicated prior to considering opioid discontinuation. Involvement of the patient's family may be an important strategy to address non-adherence.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Adjustment of the initial treatment consent or agreement, with emphasis upon specific adherence issues that have been identified; a more rigid approach may be required	Working Group Consensus	III	Poor	I
2	Consultation/referral to mental health if exacerbation of an underlying psychotic disorder is an issue	Working Group Consensus	III	Poor	I
3	Set up a grievance procedure with the patient	JCAHO, Behavioral Health Standards—Appendix B: Standards for Substance Abuse Programs	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

R2. Address Adverse Effects

OBJECTIVE

Modify treatment to achieve effective pain control with minimal harm and adverse effects.

BACKGROUND

Adverse effects are a common and predictable consequence of opioid therapy. The most common are constipation, drowsiness, nausea, pruritus, and confusion. Development of tolerance to adverse effects (with the exception of constipation) is commonly observed over time.

RECOMMENDATIONS

Adverse effects can be minimized through the use of preventive therapy, or by switching to a different opioid:

1. A general strategy to minimize adverse effects is modifying the dose of medication during titration or rotating the opioid agent.

2. The following adverse effects are the most common. A prophylactic treatment and specific patient education should be provided together with initiation of therapy. Symptomatic treatment should be augmented with dose modification and/or opioid rotation.

    a. **Constipation -** Provide prophylactic treatment for the predictably constipating effects of opioid therapy. Constipation can be managed with a stepwise approach that includes an increase in fiber and fluids, osmotic agents (e.g., sorbitol or lactulose), or with a combination stool softener and a mild peristaltic stimulant laxative such as senna or bisacodyl as needed. (Sykes, 1996; Passik & Weinreb, 2000)

    b. **Nausea and vomiting** - Consider prophylactic antiemetic therapy.

    c. **Itching** - Rule out an allergic reaction; consider treatment with antihistamines.

3. Opioids may cause adverse behavioral or cognitive effects. Evaluation and treatment may be indicated and consultation or referral to a mental health specialist may be considered. Specific attention should be given to other non-opioid medications that the patient is using.

    a. **Cognitive adverse effects** - Sedation, confusion, deterioration of cognitive function can be managed effectively using such measures as: dosage reduction (with or without coanalgesia); change of opioid agent; addition of psychostimulant; elimination of other drugs or conditions that may contribute to adverse effects (Passik & Weinreb, 2000).
    Concurrent sedative use may cause cognitive deficits in patients on chronic opioid therapy (Canadian Pain Society, 1998). Cognitive deficits may worsen on opioid therapy; therefore caution is advised.

    b. **Perceptual or affective adverse effects** (hallucinations, depression)
    Evaluation of hallucinations is often performed by "trial and error" techniques. All nonessential CNS-acting medications (e.g. steroids) should be eliminated.

4. **Sexual dysfunction** – Hypogonadism may occur with chronic opioid therapy (Daniell, 2002). Further evaluation and treatment should be considered.
    .

5. The following adverse effects are best treated by dose reduction during titration or opioid rotation:

- Sweating
- Peripheral edema
- Urinary retention
- Myoclonus
- Hyperalgesia
- Dyspepsia

DISCUSSION

All of the RCTs (27) that were reviewed report that typical opioid adverse effects are common and include constipation, nausea/vomiting, and somnolence. Adverse events contributed to patient discontinuation. Individual titration and tailoring to patient needs, including anticipating and treating adverse effects, is generally advised.

Older Patients

Adverse effects are of special concern in older patients. In a literature review, Herr (2002) cautions caregivers to be particularly aware of adverse effects that may be more severe in older patients. She notes "selecting the appropriate medication for use with older patients is often complicated by multiple illnesses and multiple medications. The potential is high for drug-drug and drug-disease interactions … many drugs may also be subject to altered pharmacokinetics because of decreased renal and hepatic function in older patients." She lists the following adverse effects to which older patients are prone: constipation, nausea, vomiting, sedation, respiratory depression, urinary retention, intestinal obstruction, delirium, and cognitive impairment. Herr specifically cautions against the use of morphine in older patients because "substantial variability in half-life among patients, ranging from 4 to 48 hours, necessitates constant monitoring before steady-state levels are achieved … accumulation can lead to profound sedation." In a tutorial, Pappagallo (1999) recommends "with the elderly, low doses of short-acting agents may be used, as drug blood levels tend to accumulate."

All Patients

Constipation

- Because opioids slow gastric motility, begin all patients on a stool softener and mild peristaltic stimulant (Sykes, 1996; Passik & Weinreb, 2000)
- Increase the dose if no bowel movement (BM) in 48 hours
- If no BM in 72 hours, perform a rectal exam
- If not impacted provide additional therapy (i.e. suppository, enema, magnesium citrate, etc.)
- Tolerance does not develop to constipation

When gastrointestinal function is a concern, the results of two studies of Wilder-Smith et al. (1999, 2001) may be useful. The authors compared the effects of tramadol to morphine and to dihydrocodeine, and found that tramadol is equally effective and interferes significantly less with gastrointestinal function.

Nausea and Vomiting

- Because of the high incidence of nausea, prophylactic antiemetic therapy is often given (Canadian Pain Society, 1998; Cohen et al., 1992; Gan et al., 1997; Pitkanen et al, 1997; Wang et al., 1996)
- Rule out other causes of nausea
- Add or increase non-opioid adjuvants
- If analgesia is satisfactory, decrease opioid dose by 25%
- Treat based on cause
    - Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist
    - Slowed GI motility: metoclopramide
    - Nausea associated with motion: dimenhydrinate or scopolamine

Itching/Pruritus

- Rule out an allergic reaction
- If analgesia is satisfactory, reduce opioid dose by 25%
- Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid dose can be reduced
- Consider treatment with antihistamines (Cherny et al., 2001)
- Change opioid

Sedation

- Usually decreases over time on stable doses (Canadian Pain Society, 1998; Jacox et al., 1994)
- Determine whether sedation is due to the opioid; eliminate nonessential CNS depressant medications (Passik & Weinreb, 2000).
- If analgesia is satisfactory, reduce opioid dose by 10-15%
- Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced
- Addition of caffeine during the day
- Change opioid (Cherny et al., 2001).

Hallucination/Dysphoria

- Evaluate underlying cause; consider role of primary therapy. Hallucinations in the chronic pain patient can be due to a variety of causes, including change in surroundings and sleep deprivation
- Evaluation of hallucinations is often performed by "trial and error" techniques. Eliminate nonessential CNS-acting medications (e.g. steroids)
- If analgesia is satisfactory, reduce opioid by 25%
- Reevaluate and treat underlying process if appropriate
- If hallucinations/dysphoria persist:
    - Trial antipsychotic
    - Switch to another opioid
    - Switch route
    - Dysphoria is more common with mixed opioid agonists/antagonists and antidopaminergic medications
    - Consult psychiatry.

Sexual dysfunction

- Sexual dysfunction is a common adverse effect of chronic opioid administration. In men taking chronic opioids, erectile dysfunction and loss of libido and decrease in gonadal function are commonly encountered (Daniell, 2002). This side effect occurs even in patients with previously normal function. As with any patient experiencing erectile dysfunction, a complete evaluation may be necessary to rule out other causes.

Hyperalgesia

- Hyperalgesia has been seen in patients receiving chronic methadone therapy (Doverty et al., 2001)
- Change opioid
- May need to taper and discontinue opioid.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Recommend modifying the dose or rotating the opioid agent to minimize adverse effects	Cherny et al., 2001	I	Good	A
2	**For constipation:** • Prophylactic mild peristaltic stimulant for all patients	Passik & Weinreb, 2000	I	Good	A

	• Increase the dose if no bowel movement (BM) in 48 hours • If no BM in 72 hours, perform a rectal exam • If not impacted provide additional therapy (i.e. suppository, enema, magnesium citrate, etc.)	Sykes, 1996			
3	**For N&V:** • Consider prophylactic antiemetic therapy • Add or increase non-opioid adjuvants • If analgesia is satisfactory, decrease opioid dose by 25% • Treat based on cause — Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist — Slowed GI motility: metoclopramide — Nausea associated with motion: dimenhydrinate or scopolamine	Canadian Pain Society, 1998 Cohen et al., 1992 Gan et al., 1997 Pitkanen et al, 1997 Wang et al., 1996	I	Good	A
4	**For sedation:** • Determine whether sedation is due to the opioid; eliminate nonessential CNS depressants • If analgesia is satisfactory, reduce opioid dose by 10-15% • Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced • Add stimulant drug during the day such as caffeine • Change opioid	Passik & Weinreb, 2000 Canadian Pain Society, 1998 Jacox et al., 1994 Cherny et al., 2001	I I	Fair	B
5	**For itching**: • Consider treatment with antihistamines • Change opioid	Cherny et al., 2001	I	Fair	B
6	**For hallucination/dysphoria**: • Evaluate underlying cause • Eliminate nonessential CNS-acting medications (e.g. steroids)	Cherny et al., 2001	I	Fair	B
7	**For sexual dysfunction** • Dose reduction • Testosterone injections may be helpful for men	Daniell, 2002	I	Fair	B

QE = Quality of Evidence; R = Recommendation (See Appendix A)

R3. Titrate Dosage or Agent to Achieve Stable Pain Relief

OBJECTIVE

Adjust dosage or agent in an attempt to achieve therapeutic goals.

BACKGROUND

Drug therapy should be individualized to the patient's specific pain condition and chosen on the basis of each drug's pharmacologic activity.

RECOMMENDATIONS

1. Documentation is essential, and should demonstrate the evaluation process—including consultation, prescriptions, and periodic review of patient status.

2. Consider one or more of the following adjustments in therapy:
   - Increase dose titration. Increase dose by 25-100%. An increase of less than 25% is not appropriate
   - To ensure that the full effect from a dosage change has been manifest and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every 5 half lives
   - If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate medications should be tapered while initiating an appropriate pharmacologic regimen
   - Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy
   - Rotate to another agent based on equianalgesic table and titrate as in 1-4 above
   - Provide a drug holiday
   - In some patients receiving long-term opioid therapy, rotation between opioids may help to improve efficacy and reduce dose escalation.

3. For a patient with continuous pain an agent with a long duration of action, such as controlled-release morphine or methadone, is recommended.

4. Maintain patients on as few medications as possible. Drug interactions and adverse events increase as the number of medications in a regimen increases. Discontinue medications, especially adjuvant medications, which do not add substantially to patient function or comfort.

DISCUSSION

Use of an opioid with a long duration of action has many advantages for treating chronic pain (see Annotation K for further discussion). It can facilitate patient compliance with around-the-clock dosing; can provide a more consistent blood level--thereby allowing better tolerability to adverse effects, such as cognitive impairment--and may reduce the reinforcement of pain behavior that can occur with an a prn dosing regimen. A goal of optimal opioid titration for a stable chronic pain condition is to decrease the frequency of rescue doses to a minimum (Canadian Pain Society, 1998).

In some patients receiving long-term opioid therapy, rotation between opioids may help to improve efficacy and reduce dose escalation (Thomsen et al., 1999).

Stable pain relief can often be achieved with titration. Roth et al. (2000) report that osteoarthritis patients treated with oxycodone for 6 months (n=58), 12 months (n=41) or 18 months (n=15) maintained stable pain intensities after being titrated to constant dosages. In a second study of osteoarthritis patients, 86 patients were able to maintain a constant morphine dosage for 26 weeks (Caldwell et al., 2002). This study explicitly allowed an increase in dosage if necessary to optimize pain control. The authors state that the stability of dosage suggests tolerance is not a problem. Huse et al. (2001) found that stable pain reduction was achieved for patients treated with morphine for phantom limb pain (n=9 for long-term phase of 6-12 months). Normal pain thresholds were also tested and were not affected over the course of the study. The authors therefore do not believe that chronic morphine use influences peripheral pain sensitivity.

In contrast, another osteoarthritis study found a pain increase in active-treatment groups after titration with oxycodone. However, given that this increase occurred over a relatively short period of time (30 days), the authors suggest that insufficient titration time, not the development of tolerance, is the likely reason for pain instability (Caldwell et al., 1999).

Consultation with a specialist in pain medicine or with a pain psychiatrist or psychologist may be warranted, depending on the expertise of the practitioner and the complexity of the presenting problem.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Documentation of evaluation process and any consultations	Working Group Consensus	III	Poor	I
2	Consultation to demonstrate compliance with controlled substance legislation	Canadian Pain Society, 1998	III	Poor	I
3	In cases of non-efficacy • Individual dose titration. Increase dose by 25-100%. • Do not increase dose more frequently than every 5 half lives • Titrate only one drug at a time, while observing the patient for additive effects • Increase medication until limited by adverse effects or clear evidence of lack of efficacy • Rotate to another opioid based on equianalgesic table and titrate • Provide a drug holiday	 Roth et al., 2000 Caldwell et al., 2002 Thomsen et al., 1999	 I I II	 Good Fair	 A B
4	Long-acting agents are effective for continuous, chronic pain	Caldwell et al., 1999 Caldwell et al., 2002 Hale et al., 1999 Peat et al., 1999 Salzman et al., 1999	I I I I I	Good	A

QE = Quality of Evidence; R = Recommendation (See Appendix A)

S. Follow-up at Appropriate Intervals

OBJECTIVE

Evaluate pain as a guide to further intervention.

BACKGROUND

The goal of stable relief of pain and effective management of adverse effects depends on a regular evaluation of the patient's status.

RECOMMENDATIONS

1. At each visit, assessment should address:
   - Comfort (degree of analgesia)
   - Opioid-related side-effects
   - Functional status (physical and psychosocial)
   - Adherence to opioid therapy contract and other aspects of treatment plan

2. Use of self-report instruments (diary, opioid log) may be helpful but should not be required.

3. Documentation is essential and the medical record for each encounter should specifically address comfort, function, adverse-effects, and treatment plan adherence.

4. Visits should be scheduled at least every 2-4 weeks for the first 1-2 months of the trial (titration phase), and then at least once every 1-6 months for the duration of the therapy (maintenance).

5. A consultation should be requested if:

   - The patient requires doses of opioids beyond what is usually required for his condition, or beyond what the provider is comfortable prescribing
   - Pain and functional status have not substantially improved after 3 months of opioid treatment
   - A patient has a new or recurrent substance use disorder, or is at high risk for relapse to a substance use disorder (substance use disorder specialist consultation)
   - A patient appears to have significant problems with depression, anxiety or irritability (a psychiatric consultation may be indicated in such cases).

6. Laboratory studies (especially liver or kidney function screens), and/or drug screens should be ordered as indicated.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Evaluate and document comfort, adverse effects, functional status, and aberrant behaviors at each visit	College of Physicians and Surgeons of Ontario, 2000	III	Poor	I
4	See the patient every 2-4 weeks for first 1-2 months, then every 6-8 weeks	College of Physicians and Surgeons of Ontario, 2000	III	Poor	I
5	Request a consultation, as indicated	Working group consensus	III	Poor	I
6	Laboratory studies and/or drug screens, as indicated	College of Physicians and Surgeons of Ontario, 2000	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

T. Indication to Discontinue Opioid Therapy

At this point the clinician will have reached the decision to discontinue opioid therapy for one of the following reasons: (1) uncontrolled adverse effects; (2) serious non-adherence to the treatment plan or unsafe behaviors; (3) lack of effectiveness of therapy or a desire on the part of the patient to discontinue therapy.

The patient may not understand or agree with the decision to withdraw the opioid therapy. This may lead to a variety of unwanted behaviors. The patient may seek to take advantage of the provider's desire to help, and may therefore engage in a prolonged debate about continuing the therapy. The provider should keep in mind the reasons that led to the decision; another provider's support can be very helpful in this situation. In other cases, the patient may resort to threats and intimidation in an effort to obtain a prescription. All providers have a right to work in a safe and secure place. If a provider anticipates a threatening response, a system that summons security should be in place, the provider should avoid situations where it might be difficult to escape an unsafe situation, and should consider asking additional staff members to be present while seeing the patient. In fact, acts of violence are rare, but do occur, and the provider should never act based on intimidation.

U. Is There Evidence of Illegal or Unsafe Behavior; Stop Opioid Therapy; Apply Legal Mandates; Document in Medical Record

OBJECTIVE

Discontinue opioid therapy in situations in which patients engage in illegal activities.

If the clinician has a reason to believe the patient engaged in prescription fraud or diversion, it will be necessary to discontinue opioid therapy. Opioid prescription is regulated by the Controlled Substances Act (see Appendix D). Serious variations are those that jeopardize the safety of the patient or society, or are illegal. Active diversion, forgery, theft, or assaultive behaviors are illegal and mandate prompt documentation and notification of authorities.

RECOMMENDATIONS

1. Opioid therapy should be discontinued immediately in the following cases:

Table 3a: Predictors of Opioid Misuse

Illegal or Criminal behavior
• Diversion (sale or provision of opioids to others) • Prescription forgery • Stealing or "borrowing" drugs from others
Dangerous behavior
• Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects • Intentional overdose or suicide attempt • Aggressive/threatening/belligerent behavior in the clinic

2. Consider notifying law enforcement authorities about patients who are suspected of prescription fraud or diversion (e.g., VA police, risk manager, and/or regional counsel).

3. Carefully document the details of the situation.

4. Document and refer to mental health specialists those patients demonstrating behaviors suggestive of suicide.

DISCUSSION

DEA regulations require reporting of suspicion of prescription fraud (forgery) or diversion of controlled substances (provision of the substance to someone other than the prescribed user). It is illegal to continue to prescribe controlled substances that are being diverted. Rarely, a patient on opioid therapy will become severely agitated and assaultive at being denied a prescription. Discontinue opioids immediately. Offer inpatient rapid withdrawal or clonidine with or without hydroxyzine to treat withdrawal symptoms. Discuss withdrawal symptoms, which will be unpleasant but not life threatening. Offer to continue treatment with non-controlled medications and to continue follow up. Notification of law enforcement authorities is required for evidence of prescription fraud or diversion of controlled substances. It is important to fully document all the facts of the case as well as the process that led to the decision to stop opioids and contact law enforcement authorities.

The provider should be aware that there may be patients with psychiatric disorders whose conditions may become manifest during medical withdrawal. These patients should be referred to the appropriate mental health clinic if simple strategies ordinarily used by the primary care doctor do not prove successful. In particular, if a patient becomes suicidal, there should be immediate referral to mental health. Suicidal ideation is most frequent in depressive disorders, psychotic disorders and in panic disorder.

Table 4a: Case Examples

Aberrant Behavior (forged script)	**Action**	**Discontinuation of Drugs**
Patient with low back pain is using oxycodone 10mg QID. He is	Call security services. Document the incident	Clonidine may be provided for the patient to ease withdrawal symptoms,

discovered by the pharmacy with a forged prescription for additional oxycodone.	in the record. No further opioid is provided for this patient.	although this patient is likely to be sent to jail.

Aberrant Behavior (selling medication)

Patient with chronic pancreatitic pain is prescribed morphine controlled-release 120mg q8h, but the urine drug screen is negative for morphine in the absence of withdrawal symptoms. The patient denies selling the medication.	Discontinue prescription of medication.	No taper would be needed, as the patient is not actually using the medication.

V. Addiction Behavior: Refer to Substance Use Disorder Specialist

OBJECTIVE

Safe termination of opioid therapy.

RECOMMENDATIONS

Patients manifesting behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to a substance use disorder specialist. If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal addressed.

In other circumstances, a decision might be made to either taper and discontinue opioid prescribing, or wait until after consultation has been obtained.

If opioid agonist therapy for opioid addiction (e.g., methadone maintenance) is being considered, it may be helpful to wait to taper the prescribed opioids until the diagnosis is clarified and opioid agonist therapy induction begun.

Patients with complex conditions with multiple co-morbidities including other psychiatric disorders, should be referred to an addiction medicine or addiction psychiatry specialist for the management of opioid discontinuation.

Table 4b. Case Examples

Patient #1	Action	Taper
40 year-old male with history of chronic testicular and back pain with normal examination and no indication for surgical intervention. Taking 6 tablets of oxycodone/acetaminophen per day. No functional deficits except heavy lifting. Shortly after transferring to my care the patient begins displaying drug-seeking behavior with repeated requests to increase the daily dose, refusal to follow through with adjunctive therapy, non-opioid medications and referrals. Finally, the patient loses his prescriptions twice in a short period of time.	Refer to substance use disorder treatment clinic, rapid taper treatment over one week	Current: oxycodone /acetaminophen 2 tab TID PO Taper by 25% per week Day 1: 2 tab every 8 hrs Day 2: 2 tab every 12 hrs Day 3: 11/2 tab every 12 hrs Day 5: 1 tab every 12 hrs Day 6: 1/2 tab every 12 hrs Day 7: DC oxycodone/acetaminophen

Patient #2	Action	Taper
40 year-old female with history of heroin dependence, treated for LBP with oxycodone/ acetaminophen and morphine controlled-release – and exhibiting behavior consistent with addiction (seeing multiple providers for scripts, multiple visits to ER, not using drugs as prescribed, evidence of use to intoxication per family, etc.) Patient is requesting help with her addiction.	Refer to Substance Use Disorder Treatment Program, and options include abstinence-oriented rehabilitation or transition to methadone with plans for long-term taper.	Plan to taper off of opioids while patient is attending substance abuse program. Inpatient withdrawal of opioid (usually 4-7 days) – utilizing methadone or clonidine, etc. for symptoms of withdrawal Transition to equivalent methadone dose, and enrollment in opioid agonist therapy program. *Methadon*e 5-10 mg PO q4-6h PRN withdrawal signs. Stabilize 1 to 3 days, then taper by 5 mg per day until the dose is reduced to 10 mg/day, then taper by 2.5-5 mg per day. OR Estimate the methadone equivalent, then give two-thirds the total in divided doses, then taper by 10-15% per day. OR Induction into opioid agonist therapy in a licensed opiate treatment program, or with buprenorphine by a certified physician.

W. Address Safety and Misuse; Begin Process to Discontinue Opioid Use

OBJECTIVE

Safe termination of opioid therapy.

BACKGROUND

The provider may refer to a grievance procedure or treatment agreement if one has previously been negotiated with the patient. JCAHO has specific recommendations (in Behavioral Health Standards—Appendix B: Standards for Substance Abuse Programs) that may be helpful in this regard. Also, a provider may alert the patient representative of the hospital in advance about possible treatment disagreements. The primary care provider should also alert other treatment providers about any controversy, to ensure prescription from a single provider.

RECOMMENDATIONS

1. Maintain contact with any patient who withdraws from treatment due to a disagreement.

2. Refer patients with comorbid psychiatric disorders to appropriate mental health providers.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Do not abandon a patient under any circumstances	Working Group Consensus	III	Poor	I
2	Maintain contact with any patient who withdraws from treatment due to a disagreement	Working Group Consensus	III	Poor	I
3	Refer patients with comorbid psychiatric disorders to appropriate mental health providers	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

X. Discontinue Opioid Therapy; Taper Medication

OBJECTIVE

Provide medication to help maintain patient safety and comfort during the initial phase of opioid abstinence.

RECOMMENDATIONS

1. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate for selected opioid-dependent patients.

2. Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.

Y. Educate on Withdrawal Symptoms; Taper Medications

OBJECTIVE

Prepare the patient to discontinue opioids with a minimum of withdrawal symptoms.

BACKGROUND

Discontinuing opioids for patients who elect to stop therapy due to adverse effects or lack of efficacy can easily be done on an outpatient basis with minimal withdrawal symptoms. Pain may temporarily increase during the tapering if withdrawal symptoms occur. Patients who are having opioid therapy discontinued due to non-adherence may need additional support and counseling to understand the reasons regarding the decision to discontinue their opioid therapy.

RECOMMENDATIONS

1. Complete evaluation of treatment, comorbidity, psychological condition, and other relevant factors should be completed prior to the initiation of the taper.

2. Clear, written instructions should be given to patients/family to educate them about the slow taper protocol that will minimize abstinence (withdrawal) syndromes.

3. Patients who are unable to tolerate the taper as described should be considered for referral to or consultation with a pain specialist, substance use specialist or other expert.

4. Detoxification for addicted patients is not part of this guideline. Refer to the VA/DoD Guideline for the Management of Substance Use Disorders.

Protocol for Tapering:

- Taper by 20%-50% per week [of original dose] for patients who are not addicted. The goal is to minimize adverse/withdrawal effects.
- The rapid detoxification literature indicates that a patient needs 20% of the previous day's dose to prevent withdrawal symptoms.
- Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.
- Some experts suggest that the longer the person has been on opioids, the slower the taper should be.
- Remain engaged with the patient through the tapering process, and provide psychosocial support as needed.

DISCUSSION

Opiate withdrawal can develop within hours of cessation of the drug. While it is not life threatening, it can be quite uncomfortable. Signs and symptoms include gastrointestinal symptoms (such as abdominal cramping, nausea, vomiting and diarrhea), musculoskeletal symptoms (such as myalgias, arthralgias, or muscle spasms), anorexia, yawning, lacrimation, salivation, rhinorrhea, piloerection, insomnia, anxiety, irritability, dysphoria, and manifestations of sympathetic hyperactivity such as diaphoresis, tachycardia, fever, mydriasis, or mildly elevated blood pressures.

According to Mattick & Hall (1996), detoxification is successful to the degree the patient:

- Is physiologically stable
- Avoids hazardous medical consequences of withdrawal
- Experiences minimal discomfort
- Reports being treated with respect for his or her dignity
- Completes the detoxification protocol (e.g., no longer requires medication for withdrawal symptom management)
- Engages in continuing care for SUD

The suggestions below represent a relatively rapid taper. The duration of the taper can always be longer.

- Methadone:
  - Decrease dose by 20-50%per day until you reach 30 mg/day.
  - Then decrease by 5 mg/day every 3-5 days to 10 mg/day
  - Then decrease by 2.5 mg/day every 3-5 days.

- Morphine SR/CR:
  - Decrease dose by 20-50%per day until you reach 45 mg/day.
  - Then decrease by 15 mg/day every 2-5 days

- Oxycodone CR:
  - Decrease dose by 20-50%per day until you reach 30 mg/day.
  - Then decrease by 10 mg/day every 2-5 days

- IR Opioids similar schedule

- Clonidine 0.1 mg BID or TID may be used if there are no contraindications to control any withdrawal symptoms.

- The patient on fentanyl should be rotated to a different opioid, either long-acting morphine or to methadone. Once the patient is converted the same guidelines will apply.

Table 4c. Case Examples

1. Serious Uncontrollable and Intolerable Adverse Effects	**Action**	**Rapid Taper**	**Slow Taper**
Hyperalgesia – complains of gradually increasing pain until everything hurts. Morphine had previously been effective, now no longer effective. Patient has pain all over.	Slow taper over 2-4 weeks. Decrease dose by 25% every 3-7 days	Current: Morphine SR 90 mg bid PO Day 1-3 – 90 mg PO bid. Day 4-6 – 60 mg PO bid; Day 7-9 – 30 mg PO bid; Day 10-13 –15 mg PO bid; Day 14 - DC morphine.	Day 1 – Morphine SR 90 mg PO bid. Day 8- 60 mg PO bid; Day 15 -30 mg PO bid; Day 22 - 15 mg PO bid; Day 29 - DC

2. Serious Adverse effect	**Action**

50 year old male obese patient on morphine controlled-release 30 mg tid for LBP. Patient noted to stop breathing at night and snore heavily.	Opioid discontinued for suspected sleep apnea. Rapid taper over 7 days. Decrease dose by 30% - 50% every 2-3 days	Current: 30 mg morphine controlled-release tid Day 1 - 15 mg tid Day 2 - 15 mg bid Day 3 - 15 mg qd Day 4 - 15 mg qd Day 5 – 15 mg qd Day 6 – 15 mg qd Educate on withdrawal symptoms Referral for sleep evaluation and possible CPAP. Consider restarting opiate after evaluation and CPAP.	N/A

3. Adverse Effects	**Action**
Patient on high-dose oxycodone CR and experiencing hallucinations with poor pain relief despite reduction to current dose of 320 mg q12h of oxycodone CR.	A trial of opioid rotation to methadone will be attempted. The total 24-hour dose of current opioid is oxycodone 640 mg/d. The oral morphine equianalgesic dose is about 960 to 1280 mg/d. Because the oral morphine equivalent dose is greater than 500 mg/d, a pain specialist is consulted and inpatient hospitalization considered. A rapid "stop and go" conversion will be undertaken to avoid confusion in case the patient develops adverse effects. The conversion dose of methadone for an oral morphine equivalent dose of about 1000 mg is 48 to 64 mg/d (5% of oral morphine equivalent dose) given in divided doses q8h. Methadone 20 mg q8h (60 mg/d) is started and oxycodone CR is discontinued. The dose of methadone is subsequently titrated to patient's response.

4. Opioid Unresponsive	**Action**	**Rapid Taper**	**Slow Taper**
49 year old male with chronic bilateral foot pain secondary to chemotherapy induced neuropathy, who has failed a trial of 3 opioids, including methadone, morphine CR and oxycodone CR.	Patient is currently taking 120 mg of oxycodone CR BID and would like to taper off the medication.	Current: 120 mg of oxycodone CR BID Week 1: 90 mg bid Week 2: 70 mg bid Week 3: 50 mg bid Week 4: 40 mg bid Week 5: 30 mg bid Week 6: 20 mg bid Week 7: 10 mg bid Week 8: DC oxycodone CR	N/A

5. Elective Decision	**Action**		
78 year old female tolerating taking two tab of oxycodone/acetaminophen every 6 hours for past two years due to arthritis. She wants to stop her medication due to financial constraints.	Discuss withdrawal symptoms Taper by 25% per week	Wk 1: 2 every 8 hrs Wk 2: 2 every 12 hrs Wk 3: 1 every 12 hrs Wk 4: 1/2 every 12 hrs Day 28 DC oxycodone/acetaminophen	Discuss withdrawal symptoms Taper by 50% per 3 days Day 1-3 2 every 8 hours Day 4-7 2 every 12 hrs Day 8-11 1 every 12 hours Day 12-14 1/2 every 12 hours Day 14 DC oxycodone/acetaminophen

Z. Follow-up as Indicated

OBJECTIVE

Provide appropriate long-term surveillance.

RECOMMENDATIONS

1. Do not abandon a patient under any circumstances.
2. Maintain contact with any patient who withdraws from treatment due to a disagreement.
3. Refer patients with comorbid psychiatric disorders to appropriate mental health providers.
4. Discontinue opioid therapy using a safe tapering protocol

DISCUSSION

A provider should never abandon a patient. This has both legal and ethical ramifications. Providers should seek both legal and ethical consultations if they fear their actions may be interpreted as patient abandonment. Providers should make every effort to find another treatment option for the patient. Providers should be aware, however, that prescribing opioid medications other than for legitimate medical purposes is against the law.

Often, after a patient disagrees with the treatment decision to medically withdraw from opioid therapy, the patient will drop out of treatment. If this occurs the provider should send a registered letter to the patient. The letter should inform the patient that he has two weeks to return to treatment or his case will be closed and he would have to go through intake again before care is resumed.

EVIDENCE

	Recommendations	Sources of Evidence	QE	Overall Quality	R
1	Do not abandon a patient under any circumstances	Working Group Consensus	III	Poor	I
2	Maintain contact with any patient who withdraws from treatment due to a disagreement	Working Group Consensus	III	Poor	I
3	Refer patients with comorbid psychiatric disorders to appropriate mental health providers	Working Group Consensus	III	Poor	I

QE = Quality of Evidence; R = Recommendation (See Appendix A)

VA/DoD CLINICAL PRACTICE GUIDELINE FOR
THE MANAGEMENT OF **OPIOID THERAPY CHRONIC PAIN**

APPENDICES

Version 1.0

APPENDIX A: Guideline Development Process

The Guideline for the Management of Opioid Therapy for Chronic Pain is the product of many months of diligent effort and consensus building among knowledgeable individuals from the Veterans Administration (VA), Department of Defense (DoD), academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group that included primary care physicians, pain specialists, rehabilitation specialists, anesthesiologists, psychiatrists, psychologists, pharmacists, nurses, and social workers, as well as consultants in the field of guideline and algorithm development.

Development Process

"Only well-focused questions and search terms will lead to a successful search for evidence" (AHCPR, 1996). The process of developing this guideline was evidence-based whenever possible. Evidence-based practice integrates clinical expertise with the best available clinical evidence derived from systematic research. Where evidence is ambiguous or conflicting, or where scientific data are lacking, the clinical experience of the multidisciplinary Working Group was used to guide the development of consensus-based recommendations. The developers incorporated the evidence and recommendations into a format that would maximally facilitate clinical decision-making (Woolf, 1992). The review of the literature, evaluation of evidence, and development of the guideline proceeded in sequential steps.

The following six documents were identified by the Working Group as appropriate seed guidelines. They served as the starting point for the development of questions and key terms.

- American Academy of Pain Medicine and American Pain Society. The Use of Opioids for the Treatment of Chronic Pain. (1996)
- Canadian Pain Society. Use of opioid analgesics for the treatment of chronic noncancer pain – A consensus statement and guidelines from the Canadian Pain Society. (1998)
- College of Physicians and Surgeons of Ontario. Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain. (2000)
- Harden, R. Norman MD. Chronic Opioid Therapy: Another Reappraisal. (2002)
- Portenoy, R.K. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. (1996)
- Washington State Department of Labor and Industries. Guideline for Outpatient Prescription of Oral Opioids for Injured Workers with Chronic, Noncancer Pain. (2000)

Five researchable questions and associated key terms were developed by the Working Group after orientation to the seed guidelines and to goals that had been identified by the Working Group. The questions specified:

- Population – characteristics of the target population
- Intervention – diagnostic, screening, therapy, and assessment
- Control – the type of control used for comparison
- Outcome – the outcome measure for this intervention (morbidity, mortality, patient satisfaction, and cost)

A systematic search of the literature was conducted for each key question, starting with studies at the top of the hierarchy of study types—evidence-based reviews and clinical trials. In addition to PubMed, the following databases were searched: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness (DARE), and Cochrane Central Register of Controlled Trials (CCTR). For PubMed, limits were set for language (English), data of publication (1998 through July 2002) and type of research (randomized controlled trial [RCT] and meta-analysis). For the CCTR, limits were set for date of publication (1998 through 2002).

The results of the search were organized and reported using reference manager software. At this point, additional exclusion criteria were applied. Typical exclusions were studies with physiological endpoints, or studies of populations that were not comparable to the population of interest. Once definitive clinical studies that addressed the question were identified, the search stopped. It was extended to studies/reports of lower quality only if there were no high quality studies.

Evidence Appraisal Reports for each of the five questions were prepared by the Center for Evidence-Based Practice at the State University of New York, Upstate Medical University, Department of Family Medicine and by ACS staff. (These reports are available by request.) Each report covered:

- Summary of findings
- Methodology
- Search terms
- Resources searched
- Articles critically appraised
- Findings

The Working Group suggested some additional references. Copies of specific articles were provided to participants on an as-needed basis.
The clinical experts and the research team evaluated the evidence for each question according to criteria proposed by the U.S. Preventive Services Task Force (USPSTF) (2001). See "Rating the Evidence," below.

The Working Group participated in two face-to-face sessions to reach a consensus about the guideline recommendations and to prepare a draft document. The draft was revised by the experts through numerous conference calls and individual contributions to the document. The guideline presents evidence-based recommendations that have been thoroughly evaluated by practicing clinicians. This document is a work in progress. It will be updated every two years, or when significant new evidence is published.

Rating the Evidence
Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group reviewed the evidence and graded it using the rating scheme developed by the USPSTF (2001). The experts themselves, after an orientation and tutorial on the evidence grading process, formulated Quality of Evidence ratings (see Table 1), a rating of Overall Quality (see Table 2), a rating of the Net Effect of the Intervention (see Table 3), and an overall Recommendation (see Table 4).

TABLE 1: Quality of Evidence (QE)

I	At least one properly done RCT
II-1	Well designed controlled trial without randomization
II-2	Well designed cohort or case-control analytic study
II-3	Multiple time series, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, case reports, and expert committees

TABLE 2: Overall Quality

Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

TABLE 3: Net Effect of the Intervention

Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering; *or* An infrequent condition with a significant impact on the individual patient level.

TABLE 4: Grade the Recommendation

A	A strong recommendation that the intervention is always indicated and acceptable
B	A recommendation that the intervention may be useful/effective
C	A recommendation that the intervention may be considered
D	A recommendation that a procedure may be considered not useful/effective, or may be harmful.
I	Insufficient evidence to recommend for or against – the clinician will use clinical judgment

Abstract of the USPSTF:

- Once assembled, admissible evidence is reviewed at three strata: (1) the individual study, (2) the body of evidence concerning a single linkage in the analytic framework, and (3) the body of evidence concerning the entire preventive service. For each stratum, the Task Force uses explicit criteria as general guidelines to assign one of three grades of evidence: good, fair, or poor.

- Good or fair quality evidence for the entire preventive service must include studies of sufficient design and quality to provide an unbroken chain of evidence-supported linkages that generalize to the general primary care population and connect the preventive service with health outcomes. Poor evidence contains a formidable break in the evidence chain, such that the connection between the preventive service and health outcomes is uncertain.

- For services supported by overall good or fair evidence, the Task Force uses outcomes tables to help categorize the magnitude of benefits, harms, and net benefit from implementation of the preventive service into one of four categories: substantial, moderate, small, or zero/negative.

- The Task Force uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). It gives an "I" recommendation in situations in which the evidence is insufficient to determine net benefit (Harris et al., 2001).

Algorithms

The overall view of the Opioid Therapy for Chronic Pain guideline is presented in an algorithmic format. There are indications that this format improves data collection and clinical decision-making and helps to change patterns of resource use. It allows the clinician to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken.

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (SMDMC, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.

Rounded rectangles represent a clinical state or condition.

Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.

Rectangles represent an action in the process of care.

Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. A complete bibliography, which includes all the sources used—directly or indirectly—in the development of the text, is provided at the end of the document.

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APPENDIX B: Patient Education

Patient/family/caregiver education:

- Involve the family, guardian, or other caregivers in the educational process.
- Provide appropriate written educational materials to patients and caregivers.
- Discuss the opioid agreement.
- Document all patient education activities in patients' medical records.

Topics to be included in patient education:

General information:

- Explain that the purpose of long-term opioid therapy is to improve functional status and alleviate, rather than eliminate, pain.
- Establish realistic and specific functional goals and expectations that can be assessed to evaluate the success of therapy.
- Review the process of the opioid trial, titration and maintenance stages, and discuss expected responses such as opioid responsiveness, tolerance, and physical dependency.
- Explain the monitoring process and discuss the criteria to stop therapy if COT is no longer indicated as the preferred treatment for pain. These criteria include: the treatment is not effective; patients experience serious adverse effects; there is a decrease in function; or patients are unable to adhere to the treatment plan.
- Explain the importance of patient self-reporting and feedback in monitoring the effectiveness of treatment and the management of adverse effects.
- Review the procedure for patients to follow if a problem related to opioid therapy (emergency situation) occurs outside your regular office hours.
- If therapy is to be discontinued, explain the process of tapering the medications in a controlled fashion and discuss withdrawal symptoms and how to manage them.
- If patients are pregnant, advise that opioid therapy use may adversely affect the fetus.
- If patients are breastfeeding, advise that COT use may adversely affect the breastfeeding child.

Medication:

- Emphasize the importance of keeping the medication in a safe and secure place.
- Provide instruction on the use of the medication, including dosage, route, and timing.
- Explain the importance of adherence to dosing instructions.
- Provide advice on potential drug interactions with opioids.
- Advise that drowsiness is a common adverse effect during titration, and patients should not try to drive or operate heavy machinery until drowsiness is cleared.
- Review common adverse effects of opioid medications and how to manage them (prophylactic treatment).

Patient responsibilities:

Adherence to treatment plan:

- Inform patients that opioids are part of a total treatment plan. Inform patients that they are expected to participate fully in the treatment and to follow advice regarding physical therapy, psychotherapy, vocational rehabilitation, counseling, other medication and other prescribed or recommended treatment.
- Inform patients that adherence to the treatment plan and dosage regimen, consultations, assessments, and adjunctive treatments is required. Patients should communicate any questions or concerns such as adverse effects or dosing questions to provider or nurse.
- Discuss patient and caregiver responsibilities for reporting pain and adherence, and explain patients' responsibilities for providing feedback, possibly in the form of a pain diary.

Obtaining prescriptions and refill policy:

- Advise patients to obtain medications from the same provider or designee and the same pharmacy and inform them that they are expected to fill medication prescriptions on time during a scheduled clinic appointment. They should not get their medications filled in an emergency room. Prescriptions cannot be filled early.
- Patients should inform any hospital or emergency room doctors that they receive pain medications from your office. Tell patients to ask their dentist to contact your office before giving any medications.
- Notify patients to contact their physician before taking other medications such as sedatives, muscle relaxants, other pain medications, or allergy and cold medications. Advise patients to avoid the use of alcohol, cocaine, marijuana or other illegal drugs.

Safety:

- Advise patients not to drive or operate heavy machinery if they feel tired, mentally foggy or are experiencing other adverse effects from the medications. It is patients' responsibility to keep themselves and others from harm.

The opioid agreement:

- Notify patients that random urine drug screens may be required.
- Explain the consequences of non-adherence to the agreement.

Legal issues:

- Review regulatory issues with patients and make it clear that it is illegal to give away, trade, share or sell opioids to anyone other than the person being prescribed therapy.
- Review the potential impact of regulatory issues on occupation, lifestyle, and use (e.g., pilots, commercial drivers).
- Remind patients that they should keep COT medications in a secure place. Patients must immediately report stolen medications both to the police and to your office.

Patient concerns:

- Address concerns and misconceptions such as the risk of addiction and possible stigma associated with opioid therapy.
- Review the differences between tolerance, physical dependence and addiction.
- Explain and describe withdrawal symptoms and how to manage them.
- Answer any other questions patients or family may have regarding the therapy.

APPENDIX C:
Agreement Sample

1. I understand that my provider and I will work together to find the most appropriate treatment for my chronic pain. I understand the goals of treatment are not to completely eliminate pain but to partially relieve my pain in order to improve my ability to function. Chronic opioid therapy is only ONE part of my overall pain management plan.

2. I understand that my provider and I will continually evaluate the effect of opioids on achieving the treatment goals and make changes as needed. I agree to take the medication at the **dose** and **frequency prescribed** by my provider. I agree not to increase the dose of opioids on my own and understand that doing so may lead to the treatment with opioids being stopped.

3. I understand that the common adverse effects of opioid therapy include constipation, nausea, sweating and itchiness of the skin. Drowsiness may occur when starting opioid therapy or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears.

4. I will not seek opioid medications from another physician. Regular follow-up care is required and only my provider will prescribe these medications for me at scheduled appointments.

5. I will attend all appointments, treatments and consultations as requested by my providers. I will attend all pain appointments and follow pain management recommendations.

6. I will not give or sell my medication to anyone else, including family members; nor will I accept any opioid medication from anyone else. I agree to be responsible for the secure storage of my medication at all times. If these medications are stolen, I will report this to police and my provider and will produce a police report of this event.

7. I understand that if my prescription runs out early for any reason (for example, if I lose the medication or take more than prescribed), my provider will not prescribe extra medication for me. I will have to wait until the next prescription is due.

8. I understand that the use of other medications can cause adverse effects or interfere with opioid therapy. Therefore, I agree to notify my provider of the use of all substances, including marijuana, alcohol, tranquilizers and all illicit drugs.

9. I agree to periodic unscheduled drug screens.

10. I understand that I may become dependent on opioid medications, which in a small number of patients may lead to addiction. I agree that if necessary, I will permit referral to addiction specialists as a condition of my treatment plan.

11. I understand that my failure to meet these requirements may result in my provider choosing to stop writing opioid prescriptions for me. Withdrawal from the medications will be coordinated by the provider and may require specialist referrals.

12. I hereby agree that my provider has the authority to discuss my pain management with other health care professionals and my family members when it is deemed medically necessary in the provider's judgment.

Patient Signature: _____

APPENDIX D:
Prescribing Controlled Substances

Any physician or authorized practitioner in the VA system who prescribes controlled substances is bound by a set of regulations established by the VHA as well as by applicable Federal Laws. The Drug Enforcement Agency (DEA) is the Federal agency responsible for enforcing both the provisions of the Controlled Substances Act (CSA) and applicable regulations from the Code of Federal Regulations (CFR).

Note: Physicians and practitioners who are not employed in the federal sector should consult with their individual State authority to determine whether there are State-level laws that cover the prescribing of controlled substances.

Federal Regulations

The DEA, in a Drug Policy Briefs and Background paper (http://www.usdoj.gov/dea/pubs/csa.html), provides a useful introduction to the CSA:

> "The Controlled Substances Act (CSA), Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, is the legal foundation of the government's fight against the abuse of drugs and other substances. This law is a consolidation of numerous laws regulating the manufacture and distribution of narcotics, stimulants, depressants, hallucinogens, anabolic steroids, and chemicals used in the illicit production of controlled substances.
>
> The CSA places all substances that are regulated under existing federal law into one of five schedules. This placement is based upon the substance's medicinal value, harmfulness, and potential for abuse or addiction. Schedule I is reserved for the most dangerous drugs that have no recognized medical use, while Schedule V is the classification used for the least dangerous drugs. The act also provides a mechanism for substances to be controlled, added to a schedule, decontrolled, removed from control, rescheduled, or transferred from one schedule to another."
>
> "The CSA also creates a closed system of distribution for those authorized to handle controlled substances. The cornerstone of this system is the registration of all those authorized by the DEA to handle controlled substances. All individuals and firms that are registered are required to maintain complete and accurate inventories and records of all transactions involving controlled substances, as well as security for the storage of controlled substances."

The DEA Website maintains a current list of scheduled substances at http://www.usdoj.gov/dea/pubs/scheduling.html. An additional resource for the clinician is the U.S. Department of Justice's Drug Enforcement Administration Diversion Control Program Website at http://www.deadiversion.usdoj.gov/. Clinicians can obtain online versions of the CSA and CFR at this site, as well as registration forms and additional information for physicians.

Veteran's Health Administration Regulations

The Department of Veterans Affairs has published a Handbook covering controlled substance regulations (1997). This Handbook is available at http://www.va.gov/publ/direc/health/handbook/1108-1.htm. The Handbook "defines procedures for the Department of Veterans Affairs (VA) accountability of all controlled substances and compliance with Drug Enforcement Administration (DEA) Regulations."

As noted in the Handbook (1997), "VA maintains perpetual inventory of all controlled substances. These items will consist of the drugs and other substances by whatever official name, common or usual name, chemical name, or brand name designated, listed in Title 21 Code of Federal Regulations (CFR) Part 1300:

(1) Schedule II drugs are found in 21 CFR 1308.12,
(2) Schedule III drugs are found in 21 CFR 1308.13,
(3) Schedule IV drugs are found in 21 CFR 1308.14, and
(4) Schedule V drugs are found in 21 CFR 1308.15."

Regulations concerning prescribing and labeling controlled substances are as follows:

- All prescriptions for controlled substances will be dated as of and signed on the day when issued and bear the full name and address of the patient, and the name, address, and DEA registration number of the practitioner. Prescriptions should not be filled if they are more than 7 days old when presented.
- An intern, resident, mid-level practitioner, foreign-trained physician, physician, or dentist on the staff of a VA facility exempted from registration (21 CFR 1301.24) will include on all prescriptions issued the registration number of the VA facility and the special internal code number assigned by the VA facility in lieu of the registration number of the practitioner required by law (21 CFR 1306.05b). Each written prescription will have the name of the physician or authorized practitioner stamped, typed, or hand printed on it, as well as the signature of the physician or authorized practitioner.
- The label of any drug listed as a "Controlled Substance" in Schedule II, III, IV, or V of the Controlled Substances Act will, when dispensed to or for a patient, contain the following warning: "CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed."

The clinician may wish to consult the Handbook for further details on controlled substance regulations in the VA system.

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APPENDIX E: Drug Tables

Table E1. Use of Short-acting, Orally Administered Opioids in OPIOID-NAIVE Adults (70 kg)

SHORT-ACTING OPIOID [†]	INITIAL ORAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Codeine (alone or in combination with APAP or ASA)	30 mg q 4 to 6 h	Increase dose as needed and tolerated to a maximum of 360 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) Ceiling effect occurs at doses > 60 mg/dose	15 to 30 30 to 60 4 to 6	Elderly or debilitated– Use with caution Hepatic dysfunction – conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease Renal dysfunction – use lower dosage or an alternative analgesic	May be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[‡]) because of decreased conversion to the active metabolite, morphine CODEINE ALONE IS A WEAK ANALGESIC AND MORE EFFECTIVE ALTERNATIVES ARE AVAILABLE (INCLUDING CODEINE IN COMBINATION WITH APAP OR ASA)
Hydrocodone (in combination with APAP, ASA, or IBU)	5 to 10 mg q 4 to 6 h	Increase dose as needed and tolerated Maximum dose: 60 mg/d (4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) for hydrocodone + APAP combination, or 37.5 mg/d (1000 mg/d IBU) for hydrocodone + IBU combination	15 to 30 30 to 60 4 to 8	Elderly or debilitated – Use with caution; start at low end of dosing range Hepatic / Renal dysfunction – Use with caution	Conversion to the active metabolite, hydromorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[‡]). Impact of decreased formation of hydromorphone on analgesic efficacy of hydrocodone is unknown
Hydromorphone	2 mg q 4 to 6 h	Individually titrate as needed and tolerated; doses ≥ 4 mg q 4 to 6 h may be necessary	15 to 30 30 to 60 4 to 6	Elderly or debilitated – Use with caution, starting at low end of dosing range. Hepatic / Renal dysfunction – Use with caution.	

SHORT-ACTING OPIOID †	INITIAL ORAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Morphine	10 to 30 mg q 4 h	Individually titrate as needed and tolerated	15 to 60 60 to 90 2 to 6	Elderly or debilitated – give with extreme caution; use lower dose Hepatic dysfunction – use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 h) and bioavailability is increased Renal dysfunction – reduce dose or, if severe renal impairment exists, avoid use	M6G, an active metabolite, may accumulate in renal impairment and contribute to toxic effects M3G, a metabolite without analgesic activity, may accumulate in renal impairment. This metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia.
Oxycodone (alone or in combination with APAP or ASA)	5 mg q 6 h	Increase dose as needed and tolerated For combination products, maximum dose is limited by APAP or ASA content (4000 mg/d for both; 2000 mg/d APAP in chronic alcoholics)	10 to 15 30 to 60 3 to 6	Elderly or debilitated– reduce dosage Hepatic / Renal – Use with caution	Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs‡). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown
Propoxyphene (alone or in combination with APAP)	HCl: 65 mg q 6 to 8 h Napsylate: 100 mg q 6 to 8 h	Increase dose as needed and tolerated Maximum daily dose is 390 mg/d for HCl salt and 600 mg/d for napsylate salt (Maximum daily dose of APAP: 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics)	15 to 60 120 to 180 4 to 6	Co-ingestion of alcohol or other CNS depressants with moderate (6 to 20 capsules or tablets) overdoses of propoxyphene has been associated with serious toxicity including death Elderly or debilitated – Use is not recommended in elderly[1]; half-life of propoxyphene and norpropoxyphene may be markedly prolonged (36 and 53 h, respectively) in elderly patients.[2] Use with caution in debilitated patients. Hepatic disease – Increased bioavailability of propoxyphene; reports of hepatotoxicity; avoid use in patients with liver disease Renal dysfunction – Propoxyphene and norpropoxyphene accumulate in renal insufficiency; may result in respiratory or CNS depression, neurotoxicity, or cardiotoxicity; avoid use	Seizures and cardiac arrhythmias may occur with the use of high doses or with renal failure Equianalgesic doses for propoxyphene salts: 65 mg HCl ≡ 100 mg napsylate

SHORT-ACTING OPIOID [†]	INITIAL ORAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Tramadol (alone or in combination with APAP)	25 mg q.a.m.	Increase by 25 mg as separate doses every 3 d to 100 mg/d (25 mg q 6 h) Subsequent increments of 50 mg/d may be made every 3 d to 200 mg/d (50 mg q 6 h) After titration, may give 50 to 100 mg q 4 to 6 h Maximum daily dose: 400 mg/d (Maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics)	< 60 ~120 to 240 3 to 6	Elderly or debilitated: In elderly patients >75 y: give < 300 mg/d in divided doses. Use with caution in debilitated patients. Hepatic dysfunction – Decrease dosage to 50 mg q 12 h in patients with cirrhosis Renal dysfunction (CrCl < 30 ml/min) – Increase dosing interval to 12 h and decrease maximum daily dose to 200 mg. Dialysis patients can receive their regular dose on the day of dialysis (< 7% of a dose is removed by hemodialysis).	Slower initiation and titration improves tolerability When converting to tramadol in patients who have physical opioid dependence and who are receiving substantial amounts of prior opioids, consider tapering the previous opioid to avoid inducing withdrawal symptoms May be less effective in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs[‡]) because of decreased conversion to the active metabolite, M1 Risk of seizures may be increased in the following patients: those taking MAOIs, SSRIs, tricyclic antidepressants, neuroleptics, or other drugs that reduce seizure threshold; patients with epilepsy; patients with risk factors for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections); or patients who take overdoses of tramadol (≥ 500 mg p.o.)

Sources: Ortho-McNeil, Tylenol with codeine package insert (2000)[3]; Ortho-McNeil, Ultram package insert (2001)[4]; Drug Facts and Comparisons (2002)[5]; Endo, Percocet, Percodan and Zydone package inserts (2001) [6,7,8]; Purdue, MSIR package insert (2001)[9] and OxyIR package insert (2000)[9,10]; Michalets (1998)[11]; Davis and Homsi (2001)[12]

APAP = Acetaminophen; ASA = Aspirin (acetylsalicylic acid); IBU = Ibuprofen; MAOI = Monoamine oxidase inhibitor

[†] Check local formulary for available formulations.

[‡] **CYP-2D6 Inhibiting Drugs**: *Antiarrhythmics* (amiodarone, propafenone, quinidine [strong inhibitor]); *analgesics* (methadone [weak inhibitor], propoxyphene); *antihistamines* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine$_2$ receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir), *quinine compounds* (hydroxychloroquine, quinacrine, quinine); *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).

Table E2. Use of Long-acting Opioids in OPIOID-NAIVE Adults (70 kg)

LONG-ACTING OPIOID [†]	INITIAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Fentanyl Transdermal System	25 mcg/h t.d. q 72 h	Increments should be based on supplemental opioid doses, using a ratio of 25 mcg/h t.d. fentanyl for every 90 mg/24 h of supplemental oral morphine equivalent Make increments at least 3 d after initial dose then not more often than q 6 d thereafter as necessary	12 to 18 (h) 24 to 72 (h) 48 to 72	Elderly or debilitated – Avoid initiation at doses > 25 mcg/h unless patient is already taking > 135 mg oral morphine or equivalent. In elderly patients, clearance of i.v. fentanyl may be greatly decreased; relevance to t.d. fentanyl is unknown; use reduced dose Hepatic / Renal dysfunction – Insufficient information; use with caution Patients with fever– increased body temperature may increase release of fentanyl from the t.d. system; monitor patients for opioid adverse effects and modify dosage as necessary	Consider t.d. fentanyl in patients who cannot take oral long-acting morphine and methadone After application of t.d. fentanyl, continued absorption of fentanyl may occur from intradermal depots of drug. Steady-state is reached after several 72-h sequential applications Application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, or heated water beds) to the application site while the patch is worn may increase release of fentanyl from the t.d. system; monitor for opioid adverse effects and adjust dosage as necessary
Levorphanol	2 mg p.o. q 6 to 8 h Longer initial dosing intervals (e.g., q 12 h) may be possible	Maximum initial individual dose: 3 mg Maximum initial total daily dose: 6 to 16 mg/d Individually titrated as needed and tolerated Allow at least 36 to 72 h before making dosage increments	30-60 60 to 120 4 to 14 (dose-dependent)	Elderly or debilitated – Reduce dose; in elderly, consider reducing dose by 50% or more Hepatic / Renal dysfunction – No pharmacokinetic data; use with caution Respiratory disease / respiratory depressants – Reduce initial dose by ≥ 50% Patients taking MAOIs – Use with MAOIs is not recommended (even though no interaction between levorphanol and MAOIs has been reported)	Limited published information available on this agent Like methadone, levorphanol has a plasma half-life that is longer than the duration of analgesia. Therefore, delayed analgesia or toxicity is possible due to accumulation of levorphanol (e.g., on about days 2 to 3)

LONG-ACTING OPIOID †	INITIAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Methadone	2.5 mg p.o. q 6 to 8 h	Increments of 2.5 mg q 8 h may be made every 5 to 7 d	30 to 60 — 4 to 12 Analgesic duration increases with continued use and cumulative effects	Elderly or debilitated–reduce dosage; in elderly, clearance may be decreased Hepatic dysfunction – in patients with stable chronic liver disease or mild to moderate hepatic dysfunction, no dosage adjustments required Renal dysfunction – methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50% is recommended in end-stage renal failure or dialysis patients	Recommended first- or second-line long-acting agent Some evidence suggests methadone may be beneficial in neuropathic pain The only long-acting opioid available as an oral solution Once a stable analgesic dose is reached (in about 4 to 5 d), the dosing interval may be extended to q 8 to 12 h or longer Plasma half-life (22 to 128 h short-term; 24 to 48 h at steady-state) may be longer than the analgesic duration Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses (e.g., on days 2 to 5) NOT USUALLY RECOMMENDED FOR AS-NEEDED (P.R.N.) SUPPLEMENTAL OPIOID THERAPY (there may be delayed responses to changes in dose) For dosing recommendations in patients previously exposed to opioids, see *Methadone Dosing Recommendations for Treatment of Chronic Pain* Urinary excretion decreases and elimination half-life increases when urinary pH exceeds 6
Morphine Control Release [CR] Sustained Release [SR]	15mg q 24 h 15 mg q 12h 20 mg q 24h	Total daily increments of < 30 to 40 mg/d may be made q 2 d	30 to 60 30 to 60 8 to 12 (Controlled-release); 8 to 24 (Sustained-release)	Elderly or debilitated – use with caution and at lower dose Hepatic dysfunction – use carefully in patients with cirrhosis and consider reducing dose or extending dosing interval by 1.5 to 2 times; half-life may be doubled (3 to 4 h) and bioavailability is increased Renal dysfunction – reduce dose or, if severe renal impairment exists, avoid use	Preferred first-line long-acting agent because of similar efficacy to other long-acting opioids, comparable safety profile, provider familiarity with its use, and lower cost M6G, an active metabolite, may accumulate in renal impairment and contribute to toxic effects M3G, a metabolite without analgesic activity, may accumulate in renal impairment. This metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia. Controlled-release tablets should be swallowed whole, not broken, chewed, or crushed. For patients who have difficulty swallowing, SR and ER capsules may be opened and the pellets may be sprinkled onto a small

LONG-ACTING OPIOID †	INITIAL DOSAGE	DOSAGE TITRATION	ANALGESIC ONSET (MIN) PEAK (MIN) DURATION (H)	DOSING IN SPECIAL POPULATIONS	OTHER CONSIDERATIONS
Extended Release [ER]	30 mg q 24 h				amount of soft food (such as apple sauce). The mixture should be taken within 30 minutes of sprinkling. The pellets must not be chewed or crushed, and the mouth should be rinsed to ensure that all pellets have been swallowed.
Oxycodone Controlled Release	10 mg p.o. q 12 h	May increase to 20 mg q 12 h after 1 or 2 d Thereafter, the total daily dose may be increased by 25% to 50% of the current dose every 1 or 2 d	30 to 60 90 to 180 8 to 12	Elderly or debilitated patients – reduce initial dosage to 1/3 to 1/2 of the usual dose Hepatic dysfunction – Reduce initial dose to 1/3 to 1/2 of the usual dose and use with caution Renal dysfunction – Plasma concentrations of oxycodone are increased about 50% in patients with CrCl < 60 ml/min; dose conservatively, adjusting dosage according to clinical situation	Recommended for patients who experience intolerable, unmanageable adverse effects to long-acting morphine and to methadone Controlled-release tablets should be swallowed whole, not broken, chewed, or crushed Conversion to the active metabolite, oxymorphone, may be decreased in patients with decreased CYP-2D6 activity (due to poor CYP-2D6 metabolism or CYP-2D6 inhibiting drugs‡). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown

Sources: ICN, Levo-Dromoran package insert (1995)[13]; Roxane Laboratories Inc., Levorphanol tartrate package insert (2000)[14]; Janssen Pharmaceutica, Duragesic package insert (2001)[15] CPSO, *Evidence-based recommendations for medical management of chronic non-malignant pain* (2000);[16] Drug Facts and Comparisons (2002)[5];Purdue Pharma, OxyContin package insert (2001)[17]; Purdue Pharma, MS Contin package insert (2000)[18]; American Pain Society, *Principles of analgesic use in the treatment of acute pain and cancer pain* (1999)[19]

P.o. = Per os (orally); t.d. = Transdermally

† Check local formulary for available formulations.

‡ **CYP-2D6 Inhibiting Drugs**: *Antiarrhythmics* (amiodarone, propafenone, quinidine [strong inhibitor]); *analgesics* (methadone [weak inhibitor], propoxyphene); *antihistamines* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine$_2$ receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir), *quinine compounds* (hydroxychloroquine, quinacrine, quinine); *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).

THIS GUIDELINE DOES NOT RECOMMEND THE USE OF LONG-ACTING OPIOID AGONISTS FOR AS-NEEDED (P.R.N.) ADMINISTRATION.

Table E3. Equianalgesic opioid conversion ratios for patients previously receiving other opioids

OPIOID AGENT	ESTIMATED ORAL EQUIANALGESIC DOSE (MG)*	INITIAL CONVERSION DOSE (NOT EQUIANALGESIC)†
Codeine	180 to 200‡	30 mg q 4 to 6 h
Fentanyl	— (transdermal)	For converting ONLY to fentanyl from another opioid, use about 25 mcg/h fentanyl transdermally for every 90 mg of oral morphine or equivalent (see Table E4, *Initial Fentanyl Transdermal Dosage)*
Hydrocodone	30	50% to 67% of estimated oral equianalgesic dose
Hydromorphone	7.5	50% to 67% of estimated oral equianalgesic dose
Levorphanol	4 acute 1 chronic	50% to 67% of estimated oral equianalgesic dose
Methadone	20 acute 2 to 4 chronic	Methadone-to-morphine dosage proportion (%) is dependent on morphine-equivalent dose of previous opioid For gradual conversion to methadone: **Oral morphine** — **Methadone** < 200 mg/d — 5 mg q 8 h 200 to 500 mg/d — ~7% of oral morphine-equivalent dose, given in divided doses q 8 h > 500 mg/d — See *Methadone Dosing Recommendations for Treatment of Chronic Pain* Consider consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain
Morphine	30	50% to 67% of estimated oral equianalgesic dose
Oxycodone	15 to 20§	50% to 67% of estimated oral equianalgesic dose
Propoxyphene	100 to 130‡	HCl: 65 mg q 6 to 8 h Napsylate: 100 mg q 6 to 8 h
Tramadol	100 to 150‡	25 mg q.a.m.

Sources: American Pain Society, *Principles of analgesic use in the treatment of acute pain and cancer pain* (1999)[19]; CPSO, *Evidence-based recommendations for medical management of chronic non-malignant pain* (2000)[16]; Drug Facts and Comparisons (2002)[5]

* Many other equianalgesic dosing tables are available that may provide equivalent doses different from those shown here.

† The initial dose of the new drug applies to patients who are not tolerant to the new opioid and should be given at 50% to 67% of the calculated dose for all potent opioids except fentanyl and methadone to allow for incomplete cross-tolerance (the new drug may have more relative analgesic efficacy and more adverse effects). For methadone, use dosage proportions (%) based on the morphine-equivalent dose of previous opioid (also see *Methadone Dosing Recommendations for Treatment of Chronic Pain*). Initial doses should be individualized. The patient's medical condition, the potency, dose, and type of previous opioid, the patient's degree of opioid exposure and tolerance, the patient's past analgesic response and adverse experiences, and the accuracy and reliability of opioid conversion factors may all influence the choice of starting dose. For fentanyl, see Table E4.

‡ When converting from weak opioid analgesics to stronger opioids, use the recommended initial doses of the new opioid for opioid-naive patients (see **Table E**1 and **Table E**2). Dose of tramadol should NOT be considered equianalgesic to the doses of pure agonists.

§ Exceeds recommended initial dose (oxycodone 5 mg)

Opioid Conversion Instructions

1. Determine the total 24-hour dose of the current opioid.
2. Using the estimated equianalgesic dose, calculate the equivalent dose of new analgesic for the desired route of administration.
3. When converting to a different opioid, for most agents, the starting conversion dose of the new opioid should be 50% to 67% of the equianalgesic dose because of incomplete cross-tolerance. (For methadone and fentanyl, see conversion doses in Table E3).
4. Take the 24-hour starting dose of the new opioid and divide by the frequency of administration to give the new dose for the new route.
5. Consider rescue opioid therapy during the conversion process.

Examples

Conversion to methadone

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. From the equianalgesic table, we determine that the initial conversion dose of methadone is about 7% of the oral morphine-equivalent dose. The initial conversion dose would be about 25 mg per day.
2. The recommended frequency of administration for methadone is q 8 h (3 doses per day).
3. Consulting the local drug formulary, we find that methadone is available in 5 mg scored tablets. The starting dose of methadone would be 7.5 mg q 8 h (22.5 mg/d).
4. Titrate dose at appropriate intervals depending on response and adverse effects.

Conversion to oxycodone CR

Patient is receiving a total of 360 mg oral morphine in a 24-hour period.

1. From the equianalgesic table, we calculate that the estimated equianalgesic dose of oxycodone is 180 to 240 mg per day.
2. The initial conversion dose of oxycodone is 50% to 67% of 180 to 240 mg per day or about 90 to 160 mg per day.
3. The recommended frequency of administration for oxycodone is every 12 hours (2 doses per day).
4. Consulting the local drug formulary, we find that oxycodone is available in 10-, 20-, 40-, and 80-mg controlled-release tablets. The starting dose of oxycodone controlled-release would be 40 to 80 mg q 12 h. To be conservative, a dose of 40 mg q 12 h (80 mg/d) is selected.
5. Titrate dose at appropriate intervals depending on response and adverse effects.

Table E4. Initial Fentanyl Transdermal Dosage (only for converting another opioid to fentanyl)

Oral 24-hour morphine (mg/d)	Fentanyl transdermal (mcg/h)
45–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

Source: Drug Facts and Comparisons (2002)[5]

Note: **Do not use this table to convert from fentanyl transdermal system to other opioid analgesics because these conversion dosage recommendations are conservative.** Use of this table for conversion from fentanyl to other opioids can overestimate the dose of the new agent and may result in overdosage of the new agent.

Table E5. Recommendations for supplemental opioid therapy

TYPE OF THERAPY	DESCRIPTION OF PAIN EPISODE	RECOMMENDATION	GENERAL GUIDELINES FOR SUPPLEMENTAL OPIOID THERAPY
Rescue	Insufficient analgesia during dosage titration	In patients being started on a new opioid, consider giving rescue medication	Use supplemental short-acting opioid, non-opioid, or a combination of both agents on an as-needed basis
		Rescue therapy is often used when pain is severe or escalating	When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10% of the daily opioid dose as needed
Breakthrough pain	Unpredictable exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid	Controversial, not routinely recommended	When using combination products, do not exceed maximum recommended doses of acetaminophen (4000 mg), aspirin (4000 mg), or ibuprofen (1000 mg)
		If necessary, use breakthrough pain medications sparingly	
Incident pain	Predictable, activity-related exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid	Many patients taking long-acting opioid analgesics may need supplemental analgesia for incident pain (e.g., 8 to 12 doses per month of short-acting opioid preparation)	Encourage the use of nonpharmacologic modalities
			Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence

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APPENDIX F:
Methadone Dosing Recommendations for Treatment of Chronic Pain

Summary

- Although it has unique pharmacokinetic and pharmacodynamic properties, the general principles of dosing methadone are similar to those of other opioids.
- Methadone is most easily titrated by using small initial doses or adjusting the initial dose according to the previous opioid dose.
- A number of methods are available for titrating methadone using conversion ratios, as detailed below. However, titration should be based on patient response and not solely based on equianalgesic dosing tables.
- Consultation with a pain specialist, clinical pharmacist, or other practitioner who has experience with using methadone for chronic pain is recommended if questions arise about dosing or titrating methadone.

Background

While methadone has gained increasing acceptance as an alternative to morphine for treatment of moderate to severe pain, a number of authors have cautioned clinicians about the complexities of dosing methadone or have suggested the drug be prescribed by practitioners with relevant experience in an adequately monitored setting.[1-7] Significant toxicity has occurred particularly when dosage increments were made too frequently, conversion doses were too high, or dosing intervals were too close.[5,8-10] Accruing experience, however, suggests that methadone can be safely used when initial doses are small, conversion ratios are adjusted to the previous opioid dose, and dosage is slowly titrated to patient response.[2,3,5,6,9,11-15] The general principles of dosing methadone are similar to those of other opioids.

The pharmacokinetic and pharmacodynamic properties of methadone are complex and incompletely documented.[16,17] Although methadone may have a long elimination half-life (range of mean/medians among studies: 3 to 128 h in healthy volunteers, opiate addicts, patients with chronic pain, and patients with acute pain),[18-31] the elimination half-life does not necessarily reflect duration of analgesia.[28,32] Patients may require dosing intervals of 6 hours to achieve adequate pain relief, although repeated oral administration of methadone for cancer pain may lead to progressively longer dosing intervals.[33,34] As a result of the dissociation between half-life and analgesic duration, tissue accumulation of methadone can occur. Patients need to be reassessed more frequently (e.g., every few days) when methadone is initiated and when the dose is increased. However, once a stable dosing is established, follow-up can be as clinically indicated. With a 3-day phased conversion from morphine to methadone, the analgesic effects have taken a median of 5 days (range: 4 to 13 days) to stabilize.[3]
It is important to note that the equianalgesic conversion ratios between methadone and other opioids are imprecise

Summary

- Methadone is a synthetic opioid analgesic with similar adverse effects to other opioids
- Duration of action is usually 6 hours or longer
- Methadone is the only long-acting opioid available as an oral solution
- Long half-life and drug accumulation can lead to delayed toxicity (e.g., on days 2 to 5)
- The analgesic effects of methadone may take about 1 to 2 weeks to stabilize
- The equianalgesic dose of methadone in repetitive dosing is much smaller (1/5th to 1/10th) than that suggested by single-dose studies
- Initial doses of methadone should be small and adjusted to the previous opioid dose, using smaller methadone–to–morphine-equivalent conversion ratios (%) the larger the previous morphine-equivalent dose

- As with other opioids, methadone requires close patient monitoring for analgesic and adverse effects

Table F1. Points to consider about equianalgesic conversion ratios

A number of equianalgesic dosing tables underestimate the potency of methadone.†
Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids.
The morphine- or hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the previous dose of morphine or hydromorphone increases.‡
Conversion ratios may not be bi-directional (i.e., the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio).§
There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients.§
The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone.
The relative analgesic potency ratio of oral to parenteral methadone is 2:1; however, confidence intervals are wide.‖

† Management of Cancer Pain, Clinical Practice Guidelines, AHCPR (1994)[35]; Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984)[36]; Twycross (1990)[37]; Levy (1985)[38]

‡ The oral morphine to oral methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.[2-4,39]

§ Bruera (1999)[40]

‖ Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain.[1]

The present dosing recommendations are provided to offer guidance on dosing methadone in the treatment of patients with chronic noncancer pain (CNCP) or chronic cancer pain, particularly when converting from another opioid to methadone. If in doubt, a practitioner should consult a pain management specialist, clinical pharmacist, or another practitioner who has the relevant knowledge.

Dosing Strategies

Recommendations for the use of methadone in the management of chronic non-cancer pain are extrapolated from studies involving mostly patients with cancer pain.

Table F2. Dosing recommendations for patients receiving codeine preparations or no previous opioids

Dosing strategy	Initial MET dose	Increments	Comments
Gradual titration (For CNCP and situations necessitating less frequent monitoring)[44]	2.5 mg q 8 h	2.5 mg q 8 h every 5 to 7 d	As a general rule, *start low and go slow.*
Faster titration (For cancer pain and situations where frequent monitoring is possible)	2.5 mg q 6 or 8 h	2.5 mg q 6 or 8 h as often as every day over about 4 d	

The dosing recommendations for gradual titration were modified with permission from *Evidence-Based Recommendations for Medical Management of Chronic Non-Malignant Pain*, College of Physicians and Surgeons of Ontario, November 2000. **All doses refer to oral administration.** CNCP = Chronic noncancer pain; MET = Methadone

Table F3. Dosing recommendations for patients previously receiving other opioids

Gradual Conversion (For CNCP and patients monitored less frequently) [44]			
MOR-E [mg/d]	**Calculated MET dose [mg /d]**	**Initial MET dose**	**Increment**
< 200	15 mg	5 mg q 8 h	Increase by calculated MET dose every 5–7 d
200 – 500	~ 7% of MOR-E *	Calculated MET dose given in divided doses q 8 h	Increase by calculated MET dose every 5–7 d
>500	~ 7% of MOR-E *	1/3rd of calculated MET dose given in divided doses q 8 h	Add 1/3rd of calculated MET dose every 5 d Decrease previous opioid by 1/3rd every 5 d (Complete conversion period = 15 days)

* Calculation of MET dose based on oral morphine-equivalent [MOR-E] doses:

Methadone	[MET]	2 mg	*Examples*:
Morphine	[MOR]	30 mg	250 mg/d MOR = 250 x 2 /30 = 17 mg/d MET ~ 5 mg q 8 h
Hydromorphone	[HMO]	8 mg	60 mg/d HMO = 60 x 2 / 8 = 15 mg/d MET = 5 mg q 8 h
Oxycodone	[OXY]	15 mg	120 mg/d OXY = 120 x 2 /15 = 16 mg/d MET ~ 5 mg q 8 h

600 mg/d MOR = 600 x 2/30 = 40 mg/d MET
1/3rd of 40 mg/d = 13 mg/d or about 15 mg/d
Give:
MET 5 mg q 8 h + MOR 400 mg/d (in divided doses) x 5 d
MET 10 mg q 8 h + MOR 200 mg/d (in divided doses) x 5 d
MET 15 mg q 8 h + discontinue MOR

Rapid Conversion (For cancer pain and patients monitored frequently) [2,3,5,11,12,45,46]

MOR-E [mg/d]	MET-to-MOR-E Ratio [%]	Initial MET dose	Increment
< 200	10% - 30%	Calculated daily MET dose in divided doses q 8 h (up to a maximum 50 mg q 8 h)	**Phased Conversion:** Replace 1/3 of MOR-E dose with calculated dose of MET every day (complete conversion in 3 days) **Rapid (Stop-and-Go)**: Discontinue MOR-E and start calculated dose of MET on day 1
200 – 500	10% - 20%		
500 – 1000	5% - 10%		
> 1000	5% or less		

Example of Phased Conversion:
600 mg/d MOR = 30 to 60 mg/d MET (or about 45 mg/d)
1/3rd of MET dose = 10 to 20 mg/d (or about 15 mg/d)
Day 1: MET 5 mg q 8 h + MOR 400 mg/d (in divided doses)
Day 2: MET 10 mg q 8 h + MOR 200 mg/d (in divided doses)
Day 3: MET 15 mg q 8 h + discontinue MOR

1. *For the most conservative approach, use 5% MET/MOR-E (or less with very high MOR-E doses) to calculate the initial MET dose irrespective of the previous MOR-E dose*
2. *Titrate MET day by day according to patient's symptoms and the number of rescue doses administered*
3. *Smaller MET-to-MOR-E conversion ratios(%) should be used the larger the previous MOR-E dose*

CNCP = Chronic noncancer pain
HMO = Hydromorphone
MET = Methadone; MOR = Morphine
MOR-E = Morphine-equivalent
OXY = Oxycodone

It is important to note that various dosing methods have been used (including a patient-controlled regimen[6,47]) and are still evolving. Two dosing strategies[2,11] have been prospectively studied, but no clinical trials comparing systematic dosing methods have been performed. A literature search (PubMed 1966 to 2001) identified only a small case series that discussed methadone dosing during the treatment of CNCP.[48] The lack of prospective and comparative studies highlights the need to carefully individualize the dosing regimen of methadone, as is done with other opioids.

As a general rule, smaller methadone-to-morphine conversion proportions (%) should be used the larger the previous morphine-equivalent dose, remembering that precise conversions from another opioid to methadone

are impossible. Disproportionately smaller methadone doses may be required with the larger morphine doses. However, it is important to remember that the equianalgesic conversion ratio is only one part of the process of properly dosing methadone and other opioids.
For inadequately treated pain during titration, a short-acting opioid preparation (such as acetaminophen with codeine, oxycodone with or without acetaminophen, or immediate-release morphine) may be used as necessary. Keep in mind that the use of supplemental opioid medications in patients with CNCP is controversial. If opioid medications for breakthrough pain (BTP) are indicated following titration to a stable methadone dose in a patient with CNCP, they should be used sparingly.[44] Methadone has been used for inadequately treated pain during titration (in doses 10% to 30% of the calculated daily methadone dose up to 3 to 8 doses per day as needed)[6,11,46,47]; however, the short-acting opioids are generally preferred to avoid drug accumulation.

Special patient populations
Patients 65 years and older may have a decreased clearance of methadone.[30] In patients with stable chronic liver disease, no dosage adjustments appear to be necessary.[49] Methadone and its metabolites do not accumulate in patients with renal failure.[50] The two prospective studies on methadone dosing strategies excluded patients with liver or renal disease.[2,11] Use extra caution when dosing any opioid in all of these patient populations.[1]

COMMENTS

- Once a stable analgesic dose is reached, dosing intervals may be extended to 8 to 12 h or longer.
- Provide careful dose titration until adequate pain relief is achieved or adverse effects limit further dose escalation.
- Absence of a graded analgesic response (in CNCP) suggests that the patient's pain may not be "opioid responsive."
- Patients should be closely monitored, at least once weekly during titration and at least once a month during maintenance.
- Patients should be warned about potential adverse effects (drowsiness, respiratory depression) and the possibility that analgesic and adverse effects may continue to evolve during the week after each dose adjustment.
- If drowsiness develops, patients (family member) should contact the provider to obtain advice about further dosing.
- Use additional caution with elderly patients (65 years and older), patients with liver, renal, or pulmonary disease, debilitated patients, and patients previously receiving high doses of opioid. Patients who cannot be monitored at home may be considered for inpatient titration of methadone.

Patient education
- Explain to patients that the initial dose may not provide optimum pain relief but that the starting dose is chosen in order to reduce the chance of adverse effects. A pain and pain medicine diary should be kept.
- Reassure patients that the dose will be titrated to achieve adequate analgesia.
- When applicable explain the reason for and how to use the short-acting opioid during methadone dose titration.
- Advise patients that the effects of methadone will increase over at least one week following a dosage increment. Pain relief during the last few days of that week will be greater than at the first few days of the week.
- Remind patients about the need for and the frequency of monitoring during the titration and maintenance periods. Provide patients with instructions on what to do if they develop increasing or intolerable adverse effects.
- Advise patients to avoid abrupt discontinuation of their opioid medication without first consulting their physician. Educate patients about withdrawal symptoms.

[1] For patients with liver or renal disease, special consideration can be given locally to use an alternative opioid at the discretion of the care team or provider.

– Since patients may become concerned about the social stigma associated with the use of methadone for treatment of opioid dependence, reassure them that methadone is also an accepted pain medication and that they are not "addicts" because they are taking methadone for pain control. Explain the difference between addiction and dependence.[2]

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[2] For more information on the definitions of addiction and dependence, see the Web-based educational program for VA employees entitled *Opioids in the Management of Acute and Chronic Pain*; available at: http://vaww.sites.lrn.va.gov/pain/opioids/ or reference 51.

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APPENDIX G: Acronym List

BID	Bis In Die (Latin: twice a day)
BM	Bowel Movement
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPG	Clinical Practice Guideline
CR	Controlled-Release
CSA	Controlled Substances Act
DC	Discontinue
DEA	Drug Enforcement Administration
DoD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual – Version IV
EMG	Electromyography
ER	Emergency Room
GI	Gastrointestinal
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LBP	Low Back Pain
MAOI	Monoamine Oxidase Inhibitors
NRS	Numerical Rating Scale
NSAID	Non-Steroid Anti-Inflammatory Drug
PA	Pills Anonymous
PHN	Postherpetic Neuralgia
PO	Per Os (Latin: by mouth, orally)
PRN	Pro Re Nata (Latin: as needed)
RCT	Randomized Controlled Trial
SR	Sustained-Release
SUD	Substance Use Disorder
TENS	Transcutaneous Electrical Nerve Stimulation
TID	Ter In Die (Latin: three times a day)
UDS	Urine Drug Screen
VA	Veterans Administration

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