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Department of Veteran's Affairs and
the Department of Defense (2010)
Clinical Practice Guideline:
Management of Opioid Therapy for
Chronic Pain



Clinical Practice Guideline

Management of Opioid Therapy for Chronic pain

May, 2010



VA/DoD Evidence Based Practice



FDA Warnings/Regulatory Alert Subsequent to CPG Completion

FDA has issued the following important revised regulatory and/or warning:

Drug Withdrawal

November 19, 2010 - Propoxyphene (Darvon, Darvocet):

Xanodyne Pharmaceuticals has agreed to withdraw propoxyphene, an opioid pain reliever used to treat mild to moderate pain, from the U.S. market at the request of the FDA, due to new data showing that the drug can cause serious toxicity to the heart, even when used at therapeutic doses. FDA concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses. FDA requested that the generic manufacturers of propoxyphene-containing products remove their products as well.

Healthcare professionals should stop prescribing and dispensing propoxyphene-containing products to patients, contact patients currently taking propoxyphene-containing products, inform patients of the risks associated with propoxyphene, and discuss alternative pain management strategies.

Drug Warning

May 25, 2010 – Ultram (tramadol hydrochloride):

Ortho-McNeil-Janssen and the U.S. Food and Drug Administration (FDA) changes to the Warnings section of the prescribing information for tramadol, a centrally acting synthetic opioid analgesic indicated for the management of moderate to moderately severe chronic pain. The strengthened Warnings information emphasizes the risk of suicide for patients who are addiction-prone, taking tranquilizers or antidepressant drugs and also warns of the risk of overdose.

X Propoxyphene and Tramadol are referred to in this guideline in:

- Table 1 (Page 16)
- Table 3 (Page 41)
- Table E1 (Page 108, 109)
- Table E2 (Page 113)
- Table E3 (Page 114)
- Table E4 (Page 124,125)
- Table E5 (Page 129,130)
- Table E6 (Page 132)

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

**Department of Veterans Affairs
Department of Defense**

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 Division, United States Army MEDCOM**

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based on the best information available at the time of publication. They are designed to provide information and assist in decision-making. They are not intended to define a standard of care and should not be construed as one. Also, they should not be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in any particular clinical situation.

Version 2.0 – 2010

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INTRODUCTION

The Clinical Practice Guideline (CPG) for the Management of Opioid Therapy (OT) for Chronic Pain was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

“Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:

- Determination of appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction; and
- Literature review to determine the strength of the evidence in relation to these criteria.”

The VA/DoD published the first Clinical Practice Guideline on management of opioid therapy for chronic pain in 2003. This original publication was intended to improve pain management, quality of life, and quality of care for veterans. The focus of the guideline has been to provide education and guidance to primary care clinicians, researchers and other health professionals as they encounter patients with persistent pain and its complications.

The current publication aims to update the evidence base of the 2003 Guideline. It is focused, as was the original CPG, on chronic opioid therapy (opioid therapy for more than one month). It is directed to the clinician who is interested in knowing more about this approach to the management of chronic pain.

The decision to widen the scope of the 2003 guideline to opioid therapy for chronic pain, as opposed to chronic non-cancer pain, was debated within the guideline Working Group (WG). The distinction between "non malignant" or "non cancer" pain is somewhat artificial. The success of opioid therapy in cancer treatment and the significant increase in the number of cancer survivors with pain required reconsideration of the narrow scope. There is no scientific evidence to suggest that the effects of cancer pain are any worse than non-cancer pain. However, long-standing societal aversion to opioid therapy for the population at large 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 opioid therapy for cancer pain, and in many areas of treatment and follow-up, it is possible to apply the same strategies to the patient with non-cancer pain. The working group evaluated several suggestions and accepted those that apply to this population. The target population of the current guideline is therefore inclusive of patients with cancer who have chronic pain due to the cancer or the treatment they are receiving. However, the recommendations may not be appropriate for patients treated in the palliative care setting.

The intent of this updated guideline is:

- To promote evidence-based management of individuals with chronic pain
- To identify the critical decision points in management of patients with chronic pain who are candidates for opioid therapy
- To improve patient outcomes, i.e., reduce pain, increase functional status and enhance the quality of life
- To decrease the incidence of complications
- To allow flexibility so that local policies or procedures, such as those regarding referrals to, or consultation with, substance abuse specialty, can be accommodated

Chronic Pain:

Chronic pain, which can be caused by many medical conditions and syndromes with different pathophysiologies, is an important and common medical concern worldwide. In the United States, pain is the most common complaint that leads patients to seek medical care. Although opioid use for acute/postsurgical pain and for palliative care is accepted in the United States, controversy continues among pain practitioners concerning the use of opioids for the treatment of chronic pain. More recently, this controversy has resurfaced, in part through press and media reports of opioid medication abuse and alleged practitioner misconduct.

Much of this controversy stems from the limited evidence regarding the long-term benefits and hazards associated with daily use of opioids. Despite a substantial increase in prescription opioids, there remains a paucity of data regarding long-term opioid efficacy. In the absence of these data, providers must rely on whatever information is available to inform their clinical judgment, balancing the benefit and harm, in order to make decisions regarding their individual patient. Clinicians need to recognize that opioid analgesics can be helpful to some individuals with chronic pain, but are ineffective or potentially harmful to others.

Opioid treatment of pain has been, and remains, severely hampered because of actual and legal constraints related to substance abuse and diversion. The guideline algorithm and recommendations suggest a structured goal-directed approach to chronic opioid treatment, which aims to select and monitor patients carefully, and wean therapy if treatment goals are not reached.

OT in VA population:

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

More than 50% of male VA patients in primary care report chronic pain. The prevalence may be even higher in female veterans. Pain is the most frequent presenting complaint of returning Operation Enduring Freedom / Operation Iraqi Freedom (OEF/OIF) soldiers (> 50% of OEF/OIF veterans signing into the VHA), and is particularly prevalent (>90%) in those with polytrauma. In some studies, the prevalence of comorbid post traumatic stress disorder (PTSD), traumatic brain injury (TBI) and pain exceeds 40%.

OT in DoD population:

Pain is the most frequent symptom reported in the community and primary care setting, and accounts for nearly 20% of all ambulatory visits. Chronic pain is the most common cause of work disability. Chronic pain is frequently accompanied by psychiatric disorders that add to patient suffering and complicate treatment. Chronic pain is a serious and highly prevalent condition among OIF/OEF service members (active duty personnel and veterans). The absence of studies of the prevalence or treatment in this population is concerning because chronic pain may prove to be even more prevalent and disabling in these veterans than for previous combat veterans. A soldier or marine routinely carries heavy body armor and equipment, often over 80 pounds, which over multiple deployments increases the likelihood of musculoskeletal injury. Better body armor and helmets combined with advanced medical care and transport in the field improve the survival rate (>90%) from serious injuries caused by blasts or projectiles, increasing the frequency of limb amputations and severe nerve and musculoskeletal damage in survivors. The multiplicity and severity of wounds in OEF/OIF soldiers, coupled with cognitive impairments associated with TBI and mental health morbidity such as PTSD complicate pain assessment and intervention efforts and consequences, and impacts on readiness.

Target Population:

- Adults (18 or older) with chronic pain conditions who are treated in any VA or DoD clinical setting
- Special populations: polytrauma, TBI, mTBI, PTSD, substance misuse, and psychiatric comorbidity.

Audiences:

- Healthcare professionals who are providing, or directing, opioid therapy treatment services to patients with chronic pain in any VA/DoD healthcare setting.

Scope of the Guideline:

- Offers best practice advice on the care of adults who may benefit from OT
- Addresses assessment and evaluation of chronic pain and appropriateness of OT
- Discusses primary intervention, referral, consultation and shared care in OT
- Addresses initiation, titration and maintenance of OT
- Presents and discusses formal treatment plans and treatment agreements for OT
- Presents updated pharmacotherapy advice on opioid medications that are FDA approved
- Provides guidance on assessing response to treatment, and determinations of adherence or abuse (aberrant drug-related behaviors)
- Addresses discontinuation of opioid therapy and follow-up
- Discusses potential outcomes
- Does *not* address the use of opioids for patients receiving end of life treatment

Development Process:

The development process of this guideline follows a systematic approach described in "Guideline-for-Guidelines," an internal working document of the VA/DoD Evidence-Based Practice Working Group that requires an ongoing review of the work in progress. Appendix A clearly describes the guideline development process followed for this guideline.

In completing this OT guideline update, the WG relied heavily on the following evidence-based guideline:

Chou R, Fanciullo GJ, Fine PG, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. (APS/AAPM) *The Journal of Pain* 2009(Feb); 10(2):113-230.

The WG reviewed the APS/AAPM 2009 guideline and made the decision to adopt several of their recommendations. The Working Group developed a revised comprehensive clinical algorithm that incorporates the assessment and determination of the appropriateness of OT as well as the management of therapy. Additional recommendations were added addressing treatment of specific adverse effects and for the diagnosis and management of aberrant behaviors that the Working Group considered to be of importance to patients in the healthcare systems of the VA and DoD.

Literature Searches:

The review of the American Pain Society (APS) /American Academy of Pain Medicine (AAPM) also revealed the lack of solid evidence based research on the efficacy of long-term opioid therapy. Almost all of the randomized trials of opioids for chronic noncancer pain were short-term efficacy studies. Critical research gaps on the use of opioids for chronic noncancer pain include: lack of effectiveness studies on long term benefits and harms of opioids (including drug abuse, addiction, and diversion); insufficient evidence to draw strong conclusions about optimal approaches to risk stratification, monitoring, or initiation and titration of opioid therapy; and lack of evidence on the utility of informed consent and opioid management plans, the utility of opioid rotation, the benefits and harms specific to methadone or higher doses of opioids, and treatment of patients with chronic noncancer pain at higher risk for drug abuse or misuse. The best available long-term evidence of efficacy is from open-label, uncontrolled, time-series studies. The WG decided to focus the search on specific topics related to management of therapy that addressed 13 Key Questions that the

multidisciplinary expert group believed to be critical to answer in order to develop evidence-based recommendations. (See Appendix A – List of Questions [page 101]).

These literature Searches were conducted covering the period from January 2003 through March 2009 that combined terms for opioids and chronic pain on Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials. Electronic searches were supplemented by reference lists and additional citations suggested by experts. The identified and selected studies on those issues were critically analyzed and evidence was graded using a standardized format. The evidence rating system for this document is based on the system used by the U.S. Preventive Services Task Force (USPSTF).

Evidence Rating System

SR	
A	A strong recommendation that clinicians provide the intervention to eligible patients. <i>Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</i>
B	A recommendation that clinicians provide (the service) to eligible patients. <i>At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</i>
C	No recommendation for or against the routine provision of the intervention is made. <i>At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. <i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. <i>Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</i>

SR = Strength of recommendation

Grading of Recommendations:

If evidence exists, the discussion following the recommendations for each annotation includes an evidence table that identifies the studies that have been considered, the quality of the evidence, and the rating of the strength of the recommendation [SR]. The Strength of Recommendation, based on the level of the evidence and graded using the USPSTF rating system (see Table: Evidence Rating System), is presented in brackets following each guideline recommendation.

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations are based on the clinical experience of the Working Group. Although several of the recommendations in this guideline are based on weak evidence, some of these recommendations are strongly recommended based on the experience and consensus of the clinical experts and researchers of the Working Group. Group Consensus statements were provided to minimize harm and increase patient safety. Recommendations that are based on consensus of the Working Group include a discussion of the expert opinion on the given topic. No [SR] is presented for these recommendations. A complete bibliography of the references in this guideline can be found in Appendix I.

This Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, and DoD, and a guideline facilitator from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The draft document was discussed in two face-to-

face group meetings. The content and validity of each section was thoroughly reviewed in a series of conference calls. The final document is the product of those discussions and has been approved by all members of the Working Group. The list of participants is included in Appendix H to the guideline.

Implementation:

The guideline and algorithms are designed to be adapted by individual facilities in considering needs and resources. The algorithms serve as a guide that providers can use to determine best interventions and timing of care for their patients to optimize quality of care and clinical outcomes. *This should not prevent providers from using their own clinical expertise in the care of an individual patient.* Guideline recommendations are intended to support clinical decision-making and should never replace sound clinical judgment.

Although this guideline represents the state of the art practice on the date of its publication, medical practice is evolving and this evolution requires continuous updating of published information. New technology and more research will improve patient care in the future. The clinical practice guideline can assist in identifying priority areas for research and optimal allocation of resources. Future studies examining the results of clinical practice guidelines such as these may lead to the development of new practice-based evidence.

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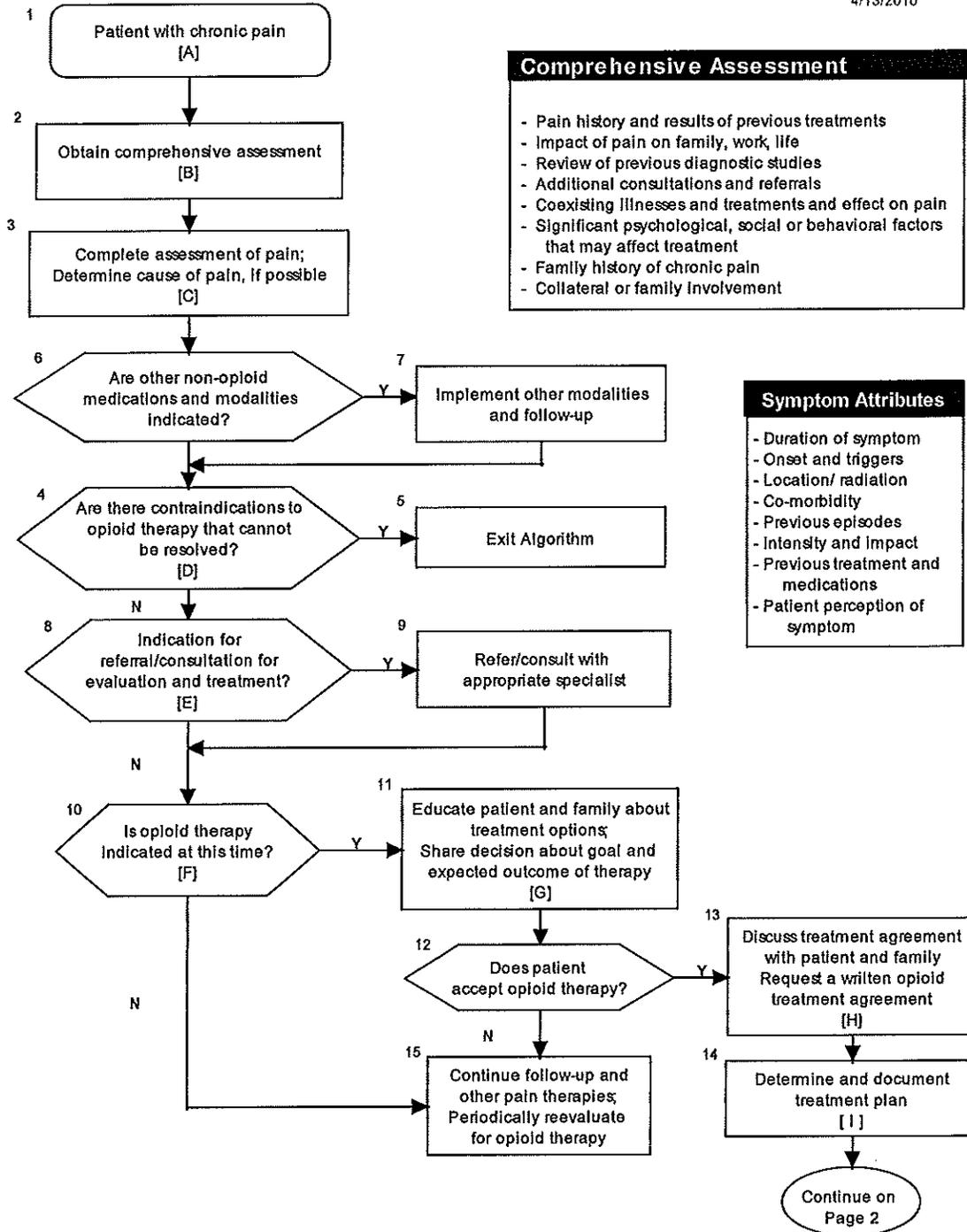
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Algorithms

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4/13/2010



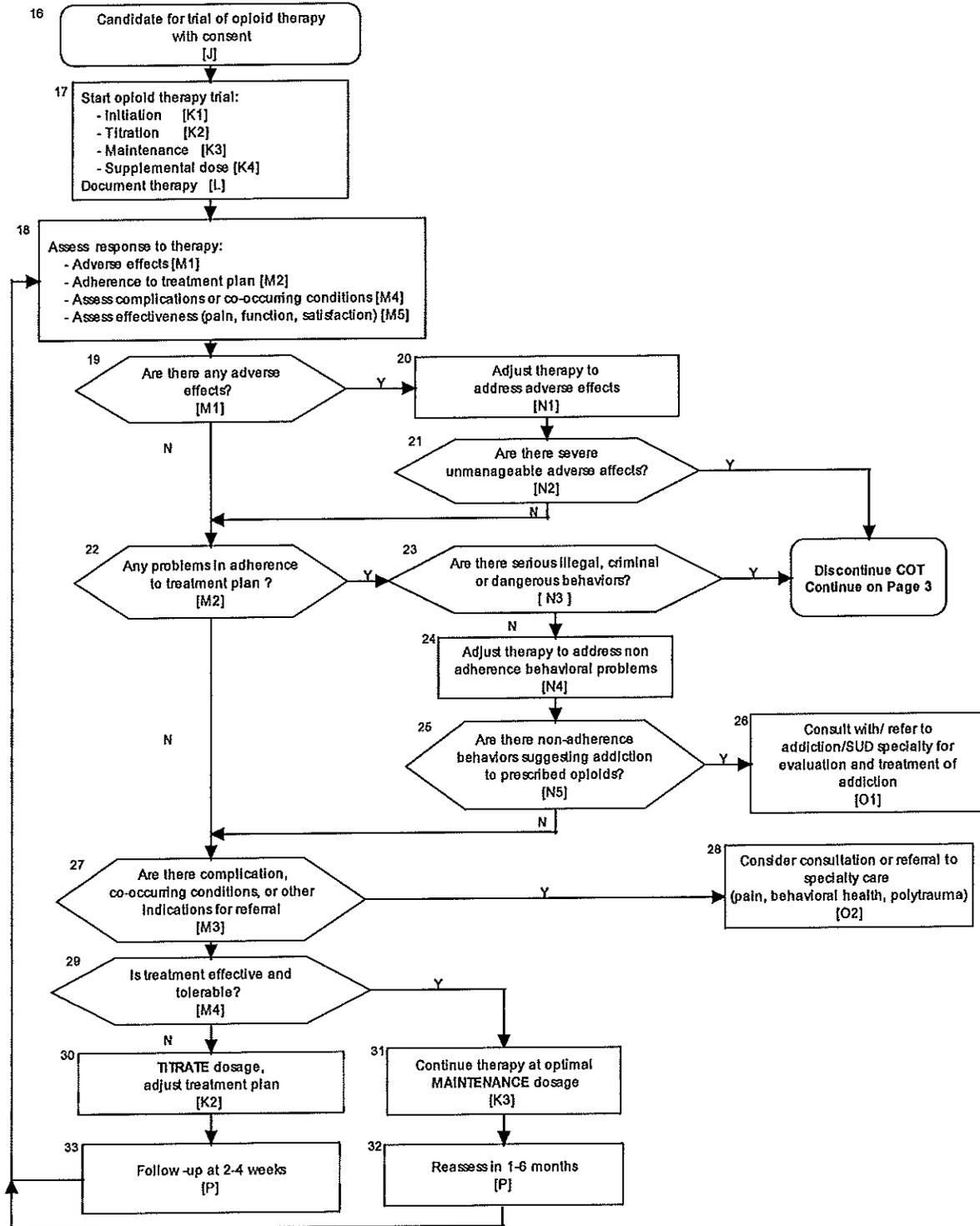
Comprehensive Assessment

- Pain history and results of previous treatments
- Impact of pain on family, work, life
- Review of previous diagnostic studies
- Additional consultations and referrals
- Coexisting illnesses and treatments and effect on pain
- Significant psychological, social or behavioral factors that may affect treatment
- Family history of chronic pain
- Collateral or family involvement

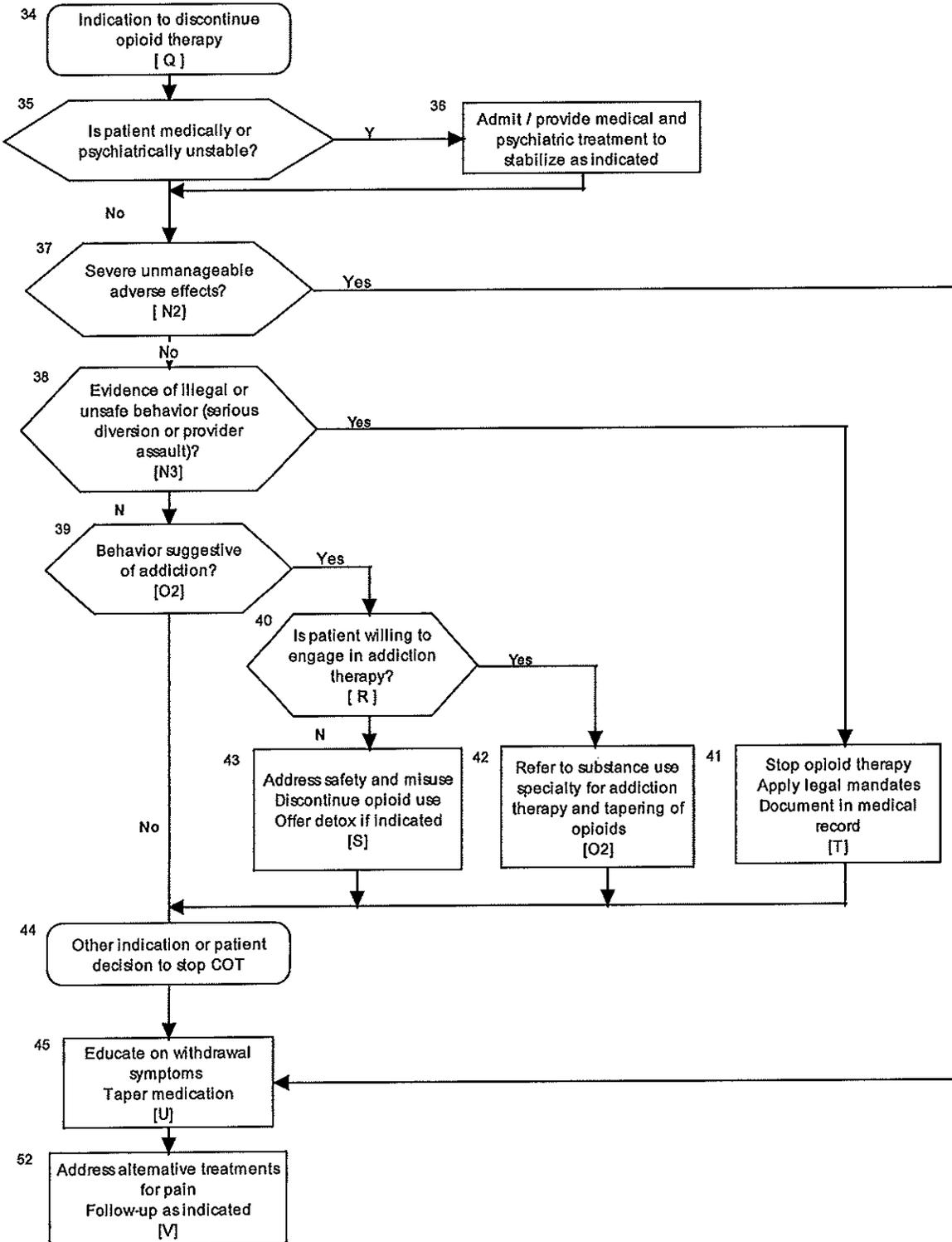
Symptom Attributes

- Duration of symptom
- Onset and triggers
- Location/ radiation
- Co-morbidity
- Previous episodes
- Intensity and impact
- Previous treatment and medications
- Patient perception of symptom

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Annotations

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 using long-term use of opioids for therapeutic or for non-therapeutic purposes. It does not, in and of itself, imply addiction (APS, 2004).

Use of the word "dependence" by itself is often used synonymously with addiction and should not be used to describe physical dependence.

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 (APS, 2004).

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 (APS, 2004)

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 to be inappropriately "drug seeking." Even such behaviors as illicit drug use and deception can occur in the patient's efforts to obtain pain 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. Distinguishing addiction from pseudoaddiction can be difficult and often takes time and multiple patient encounters.

Hyperalgesia

Hyperalgesia is an increased sensitivity to pain, which may be caused by damage to nociceptors, to peripheral nerves, or by changes in the central nervous system.

Opioid Induced Hyperalgesia

Opioid induced hyperalgesia clinically presents with increased pain or increased pain sensitivity without a change in the underlying medical condition. It is clinically confirmed by observing unremitting or perhaps increased pain to increases in opioid dose. Patients with opioid induced hyperalgesia may experience a paradoxical reduction in pain when opioids are discontinued. This is clinically complex, and difficult to diagnose.

1. Assessment

A. Patient with Chronic Pain

The patient managed within this guideline suffers from chronic pain, either chronic noncancer pain or chronic cancer-related pain in cancer survivors. 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 benefit, the patient is considered a candidate for a trial of opioid therapy.

Because opioid therapy carries risk and can cause harm in some individuals, this guideline addresses the needed actions and documentation required for the safe and effective use of opioid therapy.

Pain is defined as 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 physical, psychological, social, cultural, and hereditary factors.

In the absence of reversible pain-generating pathology, chronic pain (pain that persists beyond expected tissue healing time and generally persists longer than 3-6 months) is generally best viewed as a chronic condition for which cure is not likely. An opioid trial when indicated for chronic pain is best used as one component of a chronic care model treatment approach emphasizing active treatment modalities and collaborative self-management to maintain or improve long-term physical and psychosocial functioning.

There are limited data on the safety and efficacy of long-term opioid therapy for chronic pain and there are significant risks involved. Therefore, a "universal precautions" approach involving careful patient selection and risk management is recommended.

This guideline can also be used for patients with chronic cancer pain. Cancer survivors may benefit from use of opioid therapy in treatment of persistent pain caused by the cancer itself or by treatment for the cancer (e.g., surgery, radiotherapy, chemotherapy), as well as non-cancer related pain. Patients with cancer, who are increasingly living many years after diagnosis, can be better served using opioid therapy in a chronic pain model.

This guideline does not address patients who are at a terminal stage of their disease or who are undergoing end-of life care, patients with cancer who have been recently diagnosed, or patients with other serious or life threatening illnesses.

The classes of opioid medications that are included in this guideline are listed in Table 1: Classes of Opioid Medications. This guideline will not address the use of sublingual buprenorphine for the treatment of pain since it is not FDA approved for this purpose. There are studies underway looking at the efficacy of sublingual buprenorphine for pain management. The guideline will address the treatment of chronic pain for patients on sublingual buprenorphine for addiction treatment.

RECOMMENDATIONS

1. A trial of opioid therapy is indicated for a patient with chronic pain who meets all of the following criteria:
 - a. Moderate to severe pain that has failed to adequately respond to indicated non-opioid and non-drug therapeutic interventions
 - b. The potential benefits of opioid therapy are likely to outweigh the risks (i.e., no absolute contraindications)
 - c. The patient is fully informed and consents to the therapy
 - d. Clear and measurable treatment goals are established
2. The ethical imperative is to provide the pain treatment with the best benefit-to-harm profile for the individual patient.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Opioid therapy is indicated for moderate to severe pain that has failed other indicated therapeutic interventions	Breivik, 2001	III	Poor	I
2	Consider the ethical imperative of benefit-to-harm profile	Joranson et al., 2002 Laval et al., 2002	III III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = 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://vawww.sites.lrn.va.gov/pain/opioids>.

Table 1 lists the opioid medications from four different classes that are addressed in this guideline.

Table 1: Classes of Opioid Medications ^a

Phenanthrenes	Diphenylheptanes	Phenylpiperidine	Other
Codeine Hydrocodone Hydromorphone Morphine Oxycodone Oxymorphone	Methadone Propoxyphene	Fentanyl	Tramadol Tapentadol

^a for contraindication regarding specific medications (See Appendix E)

B. Obtain Comprehensive Assessment Including: History, Physical Examination, and a Review of Diagnostic Studies

OBJECTIVE

To perform and document a benefit-to-harm evaluation which includes history, physical examination, and appropriate diagnostic testing before initiating OT.

BACKGROUND

Most of the information needed to develop an effective pain therapy plan 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, cultural, spiritual, and hereditary factors as well as behavioral factors that contribute to suffering and 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", and intermittent re-evaluations should be considered to determine the pathophysiology of the pain complaint.

RECOMMENDATIONS

1. A comprehensive patient assessment should be completed to identify clinical conditions that may interfere with the appropriate and safe use of opioid therapy (OT).
The comprehensive assessment should include:
 - a. Medical History
 - Age, Sex
 - History of present illness, including a complete pain assessment (see Annotation C)
 - History of injury if applicable
 - Past Medical and Surgical history
 - Past Psychiatric history (including depression, anxiety, other emotional disorders, risk of suicide including family history and previous suicidal attempts)
 - Medications (including current and past analgesics, their effectiveness, side effects, and tolerability, as well as drugs that may interact with opioid therapy)
 - Substance use history (personal, family, peer group)
 - 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
 - Allergies
 - Abuse (sexual, physical and mental)
 - b. Physical examination
 - A general examination
 - A pain-focused musculoskeletal and neurologic examination
 - Mental Status Examination (MSE) (Including level of alertness, ability to understand and follow instruction, and suicidal ideation)
 - c. Review of diagnostic studies and assessments
 - d. 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 therapeutic trial of non-opioid medication therapies.
3. A urine drug test (UDT) (also referred to as urine drug screen (UDS)) should be used to screen for the presence of illegal drugs, unreported prescribed medication, or unreported alcohol use prior to starting therapy. [B]
4. Patients on chronic opioid therapy should be assessed for suicide risk at onset of therapy and regularly thereafter. High suicide risk is a relative contraindication for OT.
5. Opioid therapy should be used only after careful consideration of the risks and benefits.

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 with chronic pain being considered for opioid therapy, it should include several areas.

Pain-related History—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. It is important to evaluate not only which treatments have been tried but also to determine the dose and length of the treatment. Some patients may report treatment failure

when they have actually not experienced an adequate therapeutic trial of the treatment option. Of particular relevance is any information regarding past opioid treatment, including adherence, adverse effects, and outcomes, as previous opioid therapy failure may warrant strong consideration of not undertaking 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, 2002). Benzodiazepines have been shown to also increase the risk of central sleep apnea with methadone (Webster & Choi, 2008). Benzodiazepines have also been shown to be associated with an increased risk of death due to methadone toxicity. (McCowan et al., 2009; Caplehorn & Drummer, 2002) The use of fentanyl with CYP 3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil) may increase plasma fentanyl concentrations, increase or prolong adverse drug effects, and cause potentially fatal respiratory depression. Agents that prolong QTc intervals on electrocardiogram may increase the risk of QTc prolongation and torsades de pointe with methadone.

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 & Crombez, 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. Significant respiratory depression, particularly in unmonitored settings, and acute or severe asthma are relative contraindications to opioid therapy. Chronic Obstructive Pulmonary Disease (COPD) patients may have decreased respiratory drive with opioid therapy. This is not an absolute contraindication; however, extreme caution should be used. Obstructive sleep apnea patients who do not use Continuous Positive Airway Pressure (CPAP) are at increased risk of further desaturation with the use of opioids, which may cause central sleep apnea. Patients on CPAP with sleep apnea may experience additional opioid-induced central sleep apnea with opioids. Patients with sleep apnea should be adequately treated for their sleep apnea before the initiation of chronic opioid therapy (Javaheri et al., 2008). Patients with symptoms suggestive of sleep apnea should have a sleep study prior to initiation of OT. Risk factors for osteoporosis and the presence of sexual dysfunction should be noted. Renal failure and liver failure may alter the recommended dosing of opioids.

Allergies— True allergy to opioids is uncommon. In patients reporting adverse reactions 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.

Psychiatric History—Include the following:

Depression— Patients with chronic pain commonly have co-morbid depression, which can complicate treatment. In these patients, screening and concurrent treatment of depression may lead to improved results. Patients being treated for depression with MAOIs should not be treated with opioid therapy. Patients with depression should be asked about suicidality. Cross-sectional and longitudinal studies indicate an increased risk of suicide for patients with persistent pain. The additional risk of opioid therapy for patients with suicidal ideation/history needs to be carefully evaluated (Smith et al., 2004).

Anxiety Disorders—Anxiety disorders may complicate pain treatment and may necessitate ancillary treatment.

Other Emotional Disorders—Potentially unstable affective disorders such as bipolar disorder, 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 an 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— Current substance use disorder (SUD) is not a contraindication to OT. However, when treated with opioids, patients with a history of SUD are at higher risk of developing problematic use of drugs, addiction, or relapse. Physicians should be especially cautious about prescribing controlled substances to these patients. The degree of risk in opioid abuse forms a continuum that correlates to the history of SUD. 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. An alternative would be the provision of opioids in a structured setting (i.e., Opioid Pain Clinic) that can provide support and evaluation needed for this group of patients (Wiedemer, 2007).

Social History—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 vigilance may require special considerations. Consultation to occupational health providers and review of industry guidelines may be necessary (see Annotation E). Patients with occupations that require a high level of cognitive function or personal reliability (e.g. pilots) or occupations covered by individual state Departments of Transportation (e.g. bus drivers, truck drivers) require special consideration. When possible, consult with their occupational physician or industry guidelines about allowed medical therapies. 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. Research literature supports the prompt return to employment for acute back pain.

Cultural Background—In general, cultural factors are not an issue in response to opioid therapy. However, culturally driven belief systems may affect compliance with medication regimens.

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 drug related legal issues decrease the likelihood of pain treatment success and may predict opioid misuse.

Physical Examination—Include the following:

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

Age—Patient age is of special concern when prescribing opioids. In a literature review, Herr, (2002) cautions caregivers to be particularly aware of adverse effects that may be more severe in older patients. Older patients, who are often treated with multiple medications, tend to have co-morbidities; have a

greater frequency of hepatic, renal, or cardiac impairments; and are more likely to experience 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. 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 prevalence of cognitive impairment and sedation, there is no evidence that there is an increased frequency 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)

Race— One clinical study addressed the potential impact of race on the effects of codeine. Caraco et al., (1999) compared the effect of quinidine on the production of morphine 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 in response to codeine.

Gender—Zacny (2001), in a literature review of six studies, analyzed the differences in the subjective effects of morphine in women and men. Females were found to 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.

Risk Assessment for Aberrant Drug-related Behaviors:

Urine Drug Test (UDT)—UDT or other laboratory tests should be 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 UDT 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 UDT, however, have cut-off levels below which the test result is reported as negative (see Annotation M3). Providers should be aware of the fact that positive results may occur and confirmation done by different methodology may be appropriate before clinical decisions are made.

Risk Stratification Instruments—The Opioid Risk Tool (ORT), Screener and Opioid Assessment of Patients with Pain (SOAPP) Version 1, and Revised SOAPP (SOAPP-R) instruments may be useful for predicting risk of future aberrant drug-related behaviors. However, some caution in the interpretation of the results of these instruments is warranted. The evidence on risk stratification instruments to predict occurrence of aberrant drug-related behaviors is limited mainly to prospective studies (Akbik et al., 2006; Butler, 2004; Butler et al., 2008) with some methodological shortcomings, and evidence is sparse for each instrument. The SOAPP-R is associated with only modest likelihood ratios (Butler, 2004; Butler et al., 2008, 2009). In addition, evidence on methods for performing risk assessment before starting opioids, and for monitoring patients once on chronic opioid therapy, is limited. The evidence is based on a small number of diagnostic accuracy and prognosis studies that focused on prediction (Butler, 2004; Butler et al., 2008) or identification of variably defined aberrant drug-related behaviors (Chou, 2009; Butler, 2007; Compton et al., 1998; Holmes, 2006; Michna, 2004; Wasan et al., 2007; Eisenberg, 2006). All of these studies had some methodological shortcomings, including use of non-standardized definitions for aberrant drug-related behaviors with uncertain clinical significance. No reliable evidence was found on the diagnostic accuracy of urine toxicology testing, pill counts, or prescription drug monitoring programs, or on clinical outcomes associated with implementation of different monitoring approaches (APS/AAPM, 2009).

Risk of Suicide

Patients with chronic pain have an increased risk of suicide. This risk is increased during times of stress and loss. Often patients will choose to use lethal medication as a means of suicide. Patients with a family history of suicide are at an increased risk of suicide. Patients are also at an increased risk if they demonstrate impulsivity or medication misuse. It is important to assess frequently for suicide, refer as needed for treatment of depression, and provide patients supportive psychological therapy and safe drug treatment.

EVIDENCE TABLE

	Evidence	Sources of Evidence	LE	QE	SR
1	Epidemiological studies: Chronic pain is an independent risk for suicide.	Braden & Sullivan, 2008 Hakansson, Schlyter, et al., 2008 Ilgen et al., 2008 Magni et al., 1998 Ratcliffe et al., 2008 Theodoulou et al., 2005	II-2	Good	B
2	Patients with access to lethal drugs will often use them as part of their suicidal plan	Smith, Edwards et al., 2004	II-2	Good	B
3	Family history of suicide, poor impulse control, and medication misuse are risk factors for suicide	Hakansson, Schlyter, et al., 2008	II-2	Fair	C
4	Suicidal ideation associated with severe chronic pain, ongoing problems with street drugs, firearm ownership	Thompson et al., 2006	II-2	Fair	C

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of 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, diabetic neuropathy, radiculopathy, brachial plexopathy, phantom limb pain, complex regional pain syndrome type I (reflex sympathetic dystrophy) and type II (causalgia), and pain resulting from spinal cord injuries. Most chronic pain syndromes involve one or both of the above mechanisms.

RECOMMENDATIONS

1. Pain intensity should be evaluated at each visit.
2. Intensity of pain should be measured using a numeric rating scale (0-10 scale) for each of the following:
 - current pain,
 - least pain in last week
 - "usual" or "average" pain in last week
3. The patient's response to current pain treatments should be assessed using questions such as:

- “What is your intensity of pain after taking (use of) your current treatment/medication?”
- “How long does your pain relief last after taking your treatment/medication?”
- “How does taking your treatment/medication affect your functioning?”

(Note: some interventions may temporarily increase pain, so it may not be appropriate to ask these questions.)

4. Other attributes of pain should be assessed as part of the comprehensive pain assessment:
 - Onset and duration, location, radiation, description (quality), aggravating and alleviating factors, behavioral manifestations of pain, and impact of pain
 - Temporal patterns and variations (e.g., diurnal, monthly, seasonal)
 - Current and past treatments for pain
 - Patient’s expectations for pain relief
5. If possible, determine the type of pain:
 - Differentiate between nociceptive and neuropathic pain
 - Consider further evaluation if needed (such as imaging, Electro Diagnostic Studies (EDS) or consultation)
 - Ask specifically whether the patient suffers from headache
6. Assessment of function, to obtain a baseline, should include: (Consistent evaluation tool is helpful in providing evaluation of response to opioid therapy over time):
 - Cognitive function (attention, memory, and concentration)
 - Employment
 - Enjoyment of life
 - Emotional distress (depression and anxiety)
 - Housework, chores, hobbies, and other day to day activities
 - Sleep
 - Mobility
 - Self-care behaviors
 - Sexual function
7. 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; Farrar et al., 2000; 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) reported that in a group of elderly patients with moderate osteoarthritis, self-evaluations of general activity, sleep, enjoyment of life, and mood improved during treatment with controlled-release oxycodone therapy compared to placebo. 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 and screening tools for high-risk patients

EVIDENCE TABLE

	Evidence	Sources of Evidence	LE	QE	SR
1	Evaluate pain intensity using 0-10 scales	Breivik & Skoglund., 1998 De Conno et al., 1994 Farrar et al., 2000 Jensen et al., 1992 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

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

2. Determination of the Appropriateness of Opioid Therapy

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 opioid therapy, and should discuss them with the patient and family/care giver where appropriate. Patients with relative contraindications pose higher risk problems.

RECOMMENDATIONS

1. Opioid therapy trial should NOT be initiated in the following situations (absolute contraindications):
 - a. Severe respiratory instability
 - b. Acute psychiatric instability or uncontrolled suicide risk
 - c. Diagnosed non-nicotine Substance Use Disorder (DSM-IV criteria) not in remission and not in treatment
 - d. True allergy to opioid agents (cannot be resolved by switching agents)
 - e. Co-administration of drug capable of inducing life-limiting drug-drug interaction
 - f. QTc interval > 500 millisecond for using methadone
 - g. Active diversion of controlled substances (providing the medication to someone for whom it was not intended)
 - h. Prior adequate trials of specific opioids that were discontinued due to intolerance, serious adverse effects that cannot be treated, or lack of efficacy
2. Opioid therapy trial can be initiated with caution in the following situations. Consider consultation with appropriate specialty care to evaluate if potential benefits outweigh the risks of therapy.
 - a. Patient receiving treatment for diagnosed Substance Use Disorder (DSM-IV criteria). (See **Annotation P1**)
 - b. Medical condition in which OT may cause harm:
 - Patient with obstructive sleep apnea not on CPAP
 - Patients with central sleep apnea (See **Annotation P2**)
 - Chronic pulmonary disease (mild-moderate asthma, COPD)
 - Cardiac condition (QTc interval 450-500 milliseconds) that may increase risk of using methadone
 - Known or suspected paralytic ileus
 - Respiratory depression in unmonitored setting
 - c. Risk for suicide or unstable psychiatric disorder
 - d. Complicated pain
 - Headache not responsive to other pain treatment modalities
 - e. Conditions that may impact adherence to OT:
 - 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
 - Mental Health disorders
3. Consider consultation with an appropriate specialist if legal or clinical problems indicate need for more intensive care related to opioid management. (See Annotation E – Indications for consultation).

DISCUSSION

Absolute contraindications

a Acute psychiatric instability

Current serious suicidality, severe depression, 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).

b Meets DSM-IVR criteria for substance use disorder (SUD) not in remission and not in treatment

Current substance (other than nicotine) 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-R). 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 does not constitute a SUD when it results in improved function and quality of life. Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications. The proper response to pseudoaddiction is to adjust the dose of opioids, or other treatment, to provide effective pain relief.

It is not clear whether a history of SUD in a sustained remission (> 12 months) is predictive of increased risk for development of addiction or relapse 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. Opioid therapy may lead to abuse/addiction in a small percentage of chronic pain patients, but a larger percentage will demonstrate aberrant drug-Related behaviors (ADRBs) and illicit drug use (Fishbain et al., 2008). Providers should consider consultation with a SUD 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).

c True Allergy to opioid agents

Morphine causes the release of histamine that frequently results 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. When patients report an "allergy" to all but one agent, the presence of a substance use disorder should be considered. Consultation with an allergist may be helpful to resolve these issues.

d 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, methadone with benzodiazepines, fentanyl with CYP3A4 inhibitors, or propoxyphene and alcohol and other CNS depressants). (Note: meperidine is contraindicated for chronic pain because of this potentially fatal drug interaction and the potential for accumulation of the neurotoxic metabolite, normeperidine, with regular dosing.)

e QTc interval > 500 millisecond for using methadone

Methadone is a potent opioid receptor agonist with similar side effects compared with other strong opioids. It also has unusual pharmacodynamics, pharmacokinetics, and metabolism that must be considered in order to ensure safe use of methadone as an analgesic. Unlike most other commonly used opioids, methadone is associated with dose related prolongation of the QTc interval, and with torsades de pointes. In patients on methadone maintenance therapy for treatment of DSM-diagnosed opioid dependence, the estimated prevalence of QTc > 500 msec was 2%. The risk of QTc prolongation or torsades de pointes in patients treated with methadone for chronic pain is unclear. Nationally, increased use of methadone for pain management has been associated with increases in methadone associated overdose deaths (GAO, 2009).

f 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 sensitive urine drug test (UDT) is negative for the substance being prescribed in the absence of withdrawal symptoms. Routine UDT 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 SUD specialist may be warranted. Consider consultation with local risk management and/or counsel.

g Intolerance, serious adverse effects, or history of inadequate beneficial response to opioids, (lack of efficacy).

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

Relative contraindications (Initiate Trial with Caution)

a Chronic or recurrent headache

Headache is common in veterans, particularly in OEF-OIF veterans. Because of the potential for "transform" or "rebound" headache caused by regular frequent use of short-acting medications (including opioids), chronic daily or frequent use of opioid therapy is generally not indicated. Common diagnostic categories of headache include migraine (with or without aura), tension-type, occipital neuralgia and myofascial pain. As a general rule, chronic opioid therapy is not considered effective in this population, although occasional (less than 3 times weekly) use of short-acting opioids may become part of an abortive strategy or second-third line treatment for episodic headache in a complex patient where standard abortive treatments fail or are not tolerated.

b 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. The likelihood of these problems can be minimized by clearly specifying expectations prior to initiating therapy using the written opioid treatment agreement (See Appendix C). Many patients respond to reminders and clear limit setting at the first instance, but repeated occurrence makes continuing therapy difficult. In these cases, a more structured setting (e.g., opioid pain care clinic) may help. If a patient is cognitively impaired, assistance of a responsible caregiver may be required.

c Unwillingness or inability to comply with reasonable treatment plan

Treatment of chronic pain often requires an interdisciplinary approach (such as physical therapy, relaxation training, or behavioral health 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.

d Social instability

Patients living in chaotic or unsafe environments (e.g. homeless shelter, living with others who are using cocaine) should not receive an opioid supply until the environment is conducive to safe storage and use of these medications, or other social stability is achieved.

E. Indications for Referral /Consultation for Evaluation and/or Treatment?

BACKGROUND

Chronic opioid therapy can be managed in the primary care setting for most patients who adhere to their treatment agreement. However, some patients will present with complicating medical and social conditions or with complex pain problems, which will require integrated care with specialists outside of the primary care setting. In some cases, these more complicated cases may be treated successfully within primary care by involving specialists as co-managers. In other cases, treatment will require referral to specialists, clinics, or programs outside of the primary care setting. When significant psychosocial, emotional, behavioral, or cognitive factors complicate chronic pain treatment, referral for interdisciplinary pain care involving behavioral health specialists is appropriate. Special attention should be given to those patients who are at risk of misusing their medications and those whose living arrangements create a risk for medication misuse or diversion. The management of patients with a history of substance abuse or with a coexisting psychiatric disorder may require extra care, monitoring, documentation, and consultation with, or referral to, a SUD or behavioral health specialist.

RECOMMENDATIONS

1. Refer to an **Advanced Pain provider**, or interdisciplinary pain clinic or program for evaluation and treatment a patient with persistent pain and any of the following conditions:
 - a. Complex pain conditions or polytrauma
 - b. Significant medical comorbidities that may negatively impact opioid therapy
 - c. Situation requires management beyond the comfort level of the primary provider
2. Refer to **SUD Specialty Provider** for evaluation and treatment patient whose behavior suggests addiction to substances (excluding nicotine).
3. Consider consultation with a **SUD specialist** to evaluate the risk of recurrent substance abuse or to assist with ongoing management.
4. Refer to **Behavioral Health Specialty** for evaluation and treatment a patient with any of the following conditions:
 - a. Psychosocial problems or comorbidities that may benefit from behavioral disease/case management
 - b. Uncontrolled, severe psychiatric disorders or those who are emotionally unstable
 - c. Patients expressing thoughts or demonstrating behaviors suggestive of suicide risk
5. Refer patients with significant headache to a neurologist for evaluation and treatment.
6. Consider consultation with occupational health specialty if patient's occupation require a high level of cognitive function.

DISCUSSION

Studies show that patients do better when they have continuous access to a clinician who provides comprehensive care for the large majority of their health care needs and who coordinates care when the services of other health care professionals are needed (Chou et al., 2009).

EVIDENCE TABLE

	Evidence	Sources of Evidence	LE	QE	SR
1	Manage OT in Primary Care	Chou et al., 2009 APS/AAPM, 2009	II	Fair	C
2	Refer to interdisciplinary 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	II	Fair	C

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

F. Determine Appropriate Setting for Opioid Therapy

BACKGROUND

The appropriateness of opioid therapy as a treatment modality for chronic pain and the level of risk for adverse outcomes should be determined based on the initial and ongoing assessment of the patient. The level of risk and the treatment setting, according to the clinical condition or situation, are summarized Table 2.

RECOMMENDATIONS

1. The clinician should assess the ability of the patient being considered for opioid therapy to be able to adhere to treatment requirements, as these patients are likely to do well and benefit from OT.
2. The appropriateness of opioid therapy as a treatment modality for chronic pain and the level of risk for adverse outcomes should be determined based on the initial and ongoing assessment of the patient.
3. For patients with history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors, initiation of a trial of OT in the primary care setting should only be considered if more frequent and stringent monitoring can be provided. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist.
4. Young patients (less than 25 years old) are at higher risk for diversion and abuse and may benefit from more stringent monitoring.
5. The clinician should consider referring patients who have unstable co-occurring disorders (substance use, mental health illnesses, or aberrant drug related behaviors) and who are at higher risk for unsuccessful outcomes (see Annotation E).

The level of risk in certain clinical condition or situation, and the treatment setting are summarized in Table 2: Risks for Opioid Misuse of OT and Preferred Treatment Settings

DISCUSSION

“Proper patient selection is critical and requires a comprehensive benefit-to-harm evaluation that weighs the potential positive effects of opioids on pain and function against potential risks. Thorough risk assessment and stratification is appropriate in every case. This approach is justified by estimates of aberrant drug-related behaviors, drug abuse, or misuse in patients with CNCP, which range from 0% to 50%, depending on the population evaluated and methods used to define and identify these outcomes. Risk stratification pertaining to outcomes associated with the abuse liability of opioids—misuse, abuse, addiction and diversion—is a vital but relatively undeveloped skill for many clinicians. However, all clinicians prescribing opioids should be knowledgeable about risk factors for opioid abuse and methods for assessing risk. Assessment of risks for opioid-associated adverse effects also should be performed, given their high prevalence.

"A thorough history and physical examination, including an assessment of psychosocial factors and family history, is essential for adequate risk stratification. Implicit in the recommendation to conduct a comprehensive benefit-to-harm analysis is the recognition that an opioid trial may not be appropriate." (APS/AAPM, 2009)

Table 2: Risks for Opioid Misuse of OT and Preferred Treatment Settings

Risk opioid misuse	Condition/situation	Treatment Setting for OT
Low	<ul style="list-style-type: none"> - No history of SUD - No psychiatric co-morbidity - Prior good adherence to treatments with the primary care provider - Existence of social support system 	<ul style="list-style-type: none"> - Provide OT in primary care setting
Moderate	<ul style="list-style-type: none"> - History of substance use - History or co-occurring psychiatric disorder - History of suicide attempt - Any positive UDT - Any history of legal problems - Young age (less than 25) 	<ul style="list-style-type: none"> - Primary care with escalated monitoring and caution - Consider consultation with SUD or Behavioral health specialty
High	<ul style="list-style-type: none"> - Unstable or untreated substance use or mental health disorder - Persistent or repeated troublesome aberrant behavior or history of ADRB 	<ul style="list-style-type: none"> - Advanced structured pain clinic/ program - Co-managed with Substance Use Disorder or Mental Health Specialty

G. Educate Patient and Family about Treatment Options; Share Decisions about Goals and Expected Outcomes of Therapy

OBJECTIVE

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

BACKGROUND

The education of patients regarding their therapy is important for all patients with chronic pain. Helping patients gain a clear understanding of the nature of the treatment, expected outcome and possible adverse effects is an important element of management. Given the deeply rooted biases and prevalence of misinformation in our society regarding the medical use of opioids, the need for repeated education of patients and families can be expected. Some patients may harbor fears that use of opioids will cause more harm than benefit, while others may think of opioid therapy as a panacea. Unwarranted beliefs of this kind can lead to undesirable attitudes and behaviors that may increase dysfunction and retard the alleviation of pain. Total pain relief is rare. Relief of 2-3 points on 10-point scale is average.

RECOMMENDATIONS

1. Involve the patient and family/caregiver in the educational process, providing written educational material in addition to discussion with patient/family.
2. Discuss the *opioid pain care agreement (OPCA)* in detail, and reinforce in subsequent visits (See Annotation H).

3. Provide, and document in the medical record, patient education on the following topics:
- General Information: goals and expectations, addiction, tolerance, physical dependency, withdrawal symptoms
 - Patient responsibilities: prescriptions, adherence to treatment plan, obtaining medications from a single prescriber (or clinic) and single pharmacy, pain diary, feedback to the provider
 - Legal Issues
 - Instruction on how to take medication: importance of consistent dosing and timing, interaction with other drugs
 - Prophylactic treatment of adverse effects and management of constipation
 - Discussion of an individualized comprehensive care plan that may include, in addition to OT, physical therapy, occupational therapy, cognitive-behavioral therapy, acupuncture, manipulation, complementary and alternative medicine, other non-pharmacologic therapies, and other non-opioid agents.

DISCUSSION

There are no systematic reviews or randomized controlled trials concerning the role of patient education in opioid therapy. The review of the evidence by Chou et al., (2009) found no studies evaluating the effects of patient education methods, or different methods for providing or documenting informed consent, before initiating a trial of opioids. Valuable information, however, is available from ad hoc reviews of the medical literature, and from clinicians' day-to-day interactions with patients who take opioids or who are contemplating taking opioids. These sources indicate that some patients may experience considerable anxiety when contemplating opioid therapy. They fear outcomes such as 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 concerns, ask questions, and be appropriately informed about adverse effects, tolerance, risks of addiction and ways of preventing difficulties in opioid management. It is also important for clinicians to be aware of the potential for distorted 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 outcomes in patients on opioids, the literature review on this issue supports education of the patient and family before starting opioid therapy (Brown et al., 1996; Cohen et al., 2001; Hancock & Burrow, 2002; Jackman et al., 2008). 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; Goodwin et al., 2009), diversion, drug interactions, and adverse drug effects.

On a general level, Knight & Avorn, (2001) 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, a literature review by Cohen et al., (2001) addressed 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 that can contribute to overall reduction of the patient's pain. 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 & 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 & Pasero's review is a good source of common sense and 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 papers (Hancock & Burrow, 2002; Heidrich, 2001) address concerns about controlled-release oxycodone hydrochloride as an opioid particularly susceptible to abuse. Both papers address the need for a balanced portrayal of this drug in the media. Hancock & Burrow, (2002) call for an effort "to publicize the need for cautious handling and management of oxycodone controlled-release to help decrease the incidence of diversion and abuse without restricting its use as a legitimate analgesic for people experiencing pain."

In several other literature reviews, also with interspersed opinions of the authors, Miaskowski, (2008) and Palos, (2008) both describe the importance of communication between patients on opioid therapy and their providers. Jackman et al., (2008) concurs that a written treatment plan for OT should have clear objectives to determine success, monitor misuse, outline responsibilities, and state expectations that the patient will have periodic follow up with the provider. He also emphasizes the importance of one prescriber and one pharmacy to dispense the medications. Goodwin et al., (2009) highlights the importance of a comprehensive care plan for patients on chronic opioid therapy.

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 TABLE

	Evidence	Sources of Evidence	LE	QE	SR
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 Goodwin, 2009 Jackman et al., 2008	III	Poor	I
2	Discussion of the opioid agreement	Jackman et al., 2008 Miaskowski C, 2008	III	Poor	I
3	Documentation of patient and family education in the medical record	Working Group Consensus	III	Poor	I
4	One prescriber, one pharmacy for patients on OT	Jackman et al., 2008 Fishbain SM, 1999	III	Poor	I
5	Patients on OT should have a comprehensive care plan which includes patient education	Goodwin, et al., 2009	III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

H. Discuss a Written Opioid Pain Care Agreement with Patient and Family

OBJECTIVE

Define the responsibilities of the patient and the provider for the management of OT.

BACKGROUND

Opioid Pain Care Agreement (OPCA) is an agreement between the providers and the patient regarding provision of opioid therapy as part of care for chronic pain. This type of agreement is also named Treatment Agreement, Opioid Agreement, or Opioid Contract. The use of the term *contract* should be avoided, since it is not a legal document. The VA coined the term OPCA to emphasize the purpose of the treatment as

management of pain using opioids. The success of any therapies for chronic pain conditions largely depends on the patient's participation with all aspects of the treatment plan, including and not limited to opioid therapy. Before a trial of opioid analgesic is undertaken, the provider should obtain informed consent from the patient or the patient's guardian. Informed consent should include a discussion of the risks and benefits of therapy as well as the conditions under which opioids will be prescribed. Written treatment agreements are tools for educating patients (and providers) about the opioid treatment plan and documenting the patient's agreement to participate. Evidence supporting use of opioid pain treatment agreements is largely unremarkable but what is available appears to indicate that use of these agreements would be beneficial for patients and providers.

Patients on OT should have one designated provider who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe OT, but should coordinate consultation and communication among all clinicians involved in the patient's care.

RECOMMENDATIONS

1. Discuss a trial of opioid therapy with the patient, and obtain the patient's informed consent in a shared decision-making discussion. Document the informed consent discussion.
2. Review and discuss a written Opioid Pain Care Agreement (OPCA) with the patient who is expected to receive daily opioid therapy for the treatment of chronic pain. The signed agreement can serve as documentation of an informed consent discussion. (For a sample agreement, see Appendix C)
3. The responsibilities during therapy, of the provider and the patient, should be discussed with the patient and family. A discussion of patient responsibilities should be patient-centered and address the following issues :
 - Goals of therapy -- Partial pain relief and improvement in physical, emotional, and/or social functioning
 - The requirement for a single prescribing provider or treatment team
 - The limitation on dose and number of prescribed medications
 - Proscription against the patient changing dosage without discussing with provider
 - Monitoring patient adherence - discuss the role of random urine drug testing, the use of "pill counts"
 - A prohibition on use with alcohol, other sedating medications, or illegal drugs without discussing with provider
 - Agreement not to drive or operate heavy machinery until abatement of medication-related drowsiness
 - Responsibility to keep medication safe and secure
 - Prohibition of selling, lending, sharing or giving any medication to others
 - Limitations on refills: only by appointment, in person, and no extra refills for running out early (exceptions should be considered on an individual basis)
 - Compliance with all components of overall treatment plan (including consultations and referrals)
 - 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, with the patient's consent
 - Need for periodic re-evaluation of treatment
 - Reasons for stopping opioid therapy
 - Consequences of non-adherence with the treatment agreement.
4. Patient refusal to sign an agreement should be documented in the medical record. Consider patient's refusal to sign an agreement as part of the initial and ongoing assessments of the patient's

ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Table 2, Annotation F). The prescription of therapy, in such cases, should be based on the individual patient and the benefits versus harm involved with therapy. The rationale for prescribing opioids without a signed agreement should be documented.

DISCUSSION

No prospective experimental studies were found that evaluated whether an explicit or detailed informed consent process before initiating opioid therapy for CNCP is associated with improved clinical outcomes, better adherence to the treatment plan, greater patient satisfaction, or how the consent process affects patients' choices regarding use of opioids (Chou et al., 2009). 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 opioid therapy for patients with chronic 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 et al., 1994). Two of these studies showed that all or nearly all patients who signed a written treatment agreement as part of an opioid management plan for chronic pain had positive outcomes and that there was a low rate of drug tolerance and noncompliance with the treatment protocol (Burchman & Pagel, 1996; 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 be obtained.

A retrospective study (Wiedemer et al., 2007) evaluated the effects of a structured program in an opioid renewal clinic that included the use of opioid treatment agreements. The program was designed for prescribing opioids in patients with aberrant behavior, or "deemed" at risk for aberrant behavior or addiction by their primary care provider. The program eliminated aberrant behavior and abnormal urine tests in all "at-risk" patients and in 33% of patients with demonstrated aberrant behaviors.

Goldberg et al., (2005) measured the effect of an explicit pain management program on unscheduled patient visits, prescribing behavior, and opioid use. In a retrospective study, 91 VA patients who had a formal pain management contract and a matched comparison group of patients without evidence of such a contract were evaluated. The results of the study showed that implementation of a contract decreased visit frequency to the ED, the number of providers issuing prescriptions, the number of separate prescriptions for opioids, and the number of dispensed oxycodone tablets. The decrease was significant ($P < 0.001$) for each measure. In the matched group of 224 patients receiving opioids, ED visit frequency decreased during the observation period, but to a lesser degree. The number of separate providers issuing opioids to these patients and the number of unique prescriptions did not change over time, although the number of oxycodone tablets consumed increased steadily.

Fagan et al., (2008) surveyed 110 internal medicine physicians about their perception of the usefulness of agreements/contracts for opioid therapy in CNCP, and about their perception of whether using agreements was associated with a more positive attitude towards patients with CNCP. The survey showed that physicians believe that the use of agreements was associated with reducing multiple prescribers by 76%, requests for early refills by 67%, and calls from patients by 57%. They also believe that an agreement facilitated discussions on potential problems associated with OT and easier identification of patients who were abusing medications.

Hariharan et al., (2007) in a retrospective study of 330 patients from a single medical practice (majority with low back pain or fibromyalgia) reported that over 60% of patients adhered to their agreement.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Discuss opioid use issues with patient and obtain patient's consent	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 Goldberg et al., 2005 Kirkpatrick et al., 1994 Fagan et al., 2008 Hariharan et al., 2007 Wiedemer et al., 2007	II II III II II III III II	Fair	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of 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 (such as supervised therapeutic exercise, biofeedback, or 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 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 physical, psychological, and social contributors to their suffering. The Canadian Pain Society, (2002) guideline for the establishment of a treatment plan provides a valuable basis for the development of individualized treatment plans for suitable candidates.

OT Treatment Goals

Treatment goals should be relevant to the individual patient and may include the following domains:

1. Improvement of physical function (e.g., increase range of motion, standing, walking);
2. Improvement of general functional status (e.g., increase activities of daily living, social—recreational activities, home—domestic activities);
3. Increase in self-management of the persistent pain;
4. Improvement of vocational/disability status (e.g., improvement in work function, return to work, start job training; start classes);
5. Reduction/discontinuation of opioids and other pharmacologic medications;
6. Reduction of health care utilization for the chronic pain condition (e.g., reduce medical procedures, inpatient admissions, outpatient office and emergency room visits);
7. Reduction of pain level (e.g., reduce visual analog scale scores, verbal rating scores, verbal descriptor scores).
8. Reduction of emotional distress associated with chronic pain
9. Achieve above goals while reducing the risk of misuse, and optimize treatment to avoid harm.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	R
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, 2002 Gallagher, 1999 Dobscha et al., 2008	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 Fishbain, 1999	I	Good	A

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

3. STARTING THE OPIOID THERAPY TRIAL

J. Candidate for Trial of Opioid Therapy with Consent

Opioid therapy is a therapeutic trial. Prior to such a trial, the provider should determine that the potential benefits are likely to outweigh the potential harms, and the patient should be fully informed and should consent to the therapy. As treatment is administered, close monitoring of outcomes (pain reduction, physical and psychosocial functioning, satisfaction, adverse effects, or any aberrant drug-related behaviors) along with careful titration and appropriate management of adverse outcomes, can establish successful long-term therapy.

A trial of opioid therapy consists of three phases: initiation, titration, and maintenance. The **initiation** phase (See Annotation K1) 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 (see Annotation K2) involves adjustment of the dosage to achieve the desired clinical outcomes (pain relief, improved function, and patient satisfaction with minimal or tolerable adverse effects). The clinically appropriate dose is the dose that yields maximum pain relief with a minimum of intolerable or unmanageable adverse side 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 [Figure 1](#))

The patient has entered the **maintenance** phase (see Annotation K3) when the required daily dose remains relatively stable. This may be the longest phase of the opioid therapy trial. Worsening pain after a period of stable 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 Annotation K4).

Opioid Therapy - Titrate to Effect

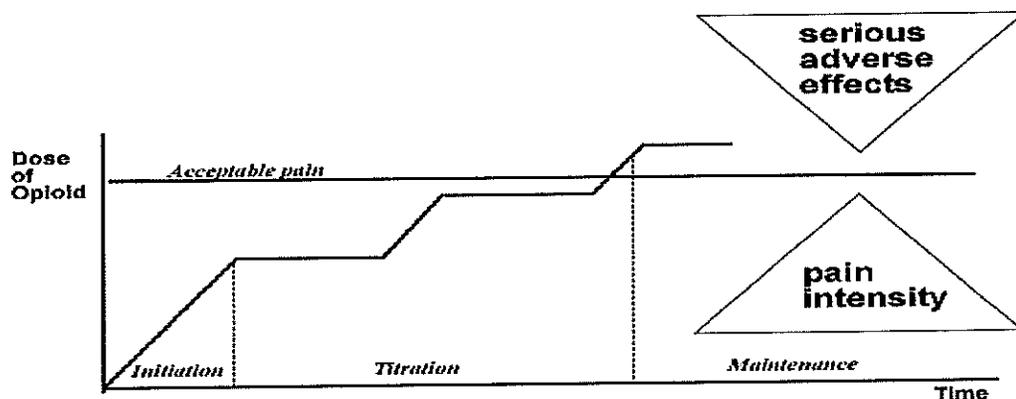


Figure 1 Opioid Therapy Titrate to Effect

K1. Initiation Phase

OBJECTIVE

To start opioid therapy using an appropriate drug and formulation for the patient at a relatively low dose to gauge initial response, minimize adverse effects, and allow the patient to develop tolerance before making further dosage increases.

BACKGROUND

A trial of opioid therapy may be indicated for patients who have failed to respond to a reasonable and documented course of non-pharmacological or non-opioid pharmacological modalities, or when the risks of those modalities outweigh the risks of opioid therapy. The trial involves a stepwise approach to the identification of the best agent, or agents, and the best dosage for the individual patient. All three phases of the opioid therapy trial (initiation, titration, and maintenance) require ongoing assessment of the patient and documentation regarding effectiveness and adverse effects.

The treatment of pain is guided by the premise that patients are unique in their perception of pain and in their response to medications. It is known that there is a huge interindividual variability in the responsiveness to opioids. Accordingly, the patient's response is the ultimate guide to treatment.

RECOMMENDATIONS

General strategy for OT initiation phase:

1. Chronic pain is often a complex biopsychosocial condition. Clinicians who prescribe OT should routinely integrate psychotherapeutic interventions, functional optimization, interdisciplinary therapy, and other adjunctive non-opioid pain therapies.
 2. Provide written and verbal education to the patient about the specific medication, anticipated adverse effects, dosing and administration, possible excessive sedation and symptoms of opioid withdrawal.
 3. With patient consent, obtain a urine drug test (UDT) prior to initiating an OT trial and randomly at follow-up visits to confirm the appropriate use of opioids. A patient can refuse urine drug testing. The provider should take into consideration a patient's refusal to undergo urine drug testing as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F, Table 2).
 4. There is no evidence to recommend for or against the selection of any specific opioid:
 - a. Using a shared decision-making process, select a specific opioid formulation, based on experience and knowledge that matches the individual's needs and specific medical conditions
 - b. Consider patient preference, and agent that allows administration by the least invasive route
 - c. Consider the ease of drug administration, patient's prior experience with, and level of tolerance to opioid medications, potential risk for misuse, abuse patterns, and local formulary guidance
 - d. Transdermal fentanyl should be avoided in opioid naïve patients.
 5. Start the opioid therapy trial with a low dose and with one medication at a time.
 6. Initiate a bowel regimen to prevent and treat constipation, which is anticipated with all opioids.
- For possible choices of opioids, see Table 3: Use of Opioids for Chronic Pain in Special Populations.

Initiation strategy for continuous, persistent daily pain:

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

8. Alternatively, short-acting opioids can be started, and later converted to long acting opioids. (See Annotation K2 - Titration)
9. Treatment of continuous chronic pain should be initiated with opioids on a defined and scheduled basis.

Initiation strategy for episodic pain (intermittent pain that occurs few times a week):

10. For episodic chronic pain, consider short-acting opioids (such as morphine, oxycodone, or hydrocodone), trying one medication at a time on a PRN (as needed) basis. Long-acting opioids should not be used on a PRN basis.

Cautions for use of Methadone in Patients with Chronic Pain:

Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously by clinicians who are familiar with its use and risks, or who can consult with clinicians experienced in dosing methadone. Only under these requirements should methadone be considered as an alternative first-line drug for OT in the primary care setting.

11. When using methadone:
 - a. Inform patients of the arrhythmia risk
 - b. Ask patients about heart disease, arrhythmia, and syncope
 - c. Obtain an electrocardiogram (ECG) to measure the QTc interval before starting methadone and once the dose is stabilized (maintenance phase). Measure the QTc annually thereafter if the patient history is positive for risk factors for prolonged QTc interval, or has known prolonged QTc interval. Perform additional electrocardiography if the methadone dosage exceeds 100 mg/day, or if the patient has unexplained syncope or seizures
 - d. If the QTc interval is greater than 450ms, but less than 500ms, reevaluate and discuss with the patient the potential risks and benefits of therapy, and the need for monitoring the QTc more frequently
 - e. If the QTc interval exceeds 500 ms, discontinue or taper the methadone dose and consider using an alternative therapy. Other contributing factors, such as drugs that cause hypokalemia, or QT prolongation should be eliminated whenever possible
 - f. Be aware of interactions between methadone and other drugs that may prolong QTc interval, or slow the elimination of methadone, and educate patients about drug interaction.

DISCUSSION

A trial of opioid therapy has been endorsed as a standard therapeutic approach to chronic pain by several professional organizations (APS/AAPM, 1996, 2009; Canadian Pain Society, 2002). The entire treatment with an opioid agent is a trial. During the trial, the clinician attempts to establish effective pain relief and improvement in function by prescribing opioid agents, and by making specific and well-documented dosage adjustments in response to feedback from the patient.

Choice of agent:

Very few well-designed studies 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 an opioid-naïve patient, a short-acting opioid or an equivalent dose of a long-acting opioid (other than transdermal fentanyl) may be used (see Appendix E, Drug 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 versus long-acting formulations:

There is insufficient evidence of the superiority of long- over short-acting opioids with respect to pain relief, adverse effects, or the rate at which tolerance develops (APS/AAPM, 2009). 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, and similar considerations are factors that can affect the choice of drug formulation.

The review of evidence for the VA/DoD guideline, (2002), identified 16 randomized controlled trials that directly compared the efficacy of long-acting opioids to short-acting opioids or to another long-acting opioid with shorter duration in patients with chronic non-cancer pain. Five 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 compared controlled-release (CR) with immediate-release (IR) oxycodone. The papers were all published in the same year and have several authors in common. Patients had chronic pain associated with osteoarthritis (Caldwell et al., 1999), low-back pain (Hale et al., 1999), or cancer or low-back pain (Salzman et al., 1999; two trials). Two papers had a double-blind phase (Caldwell et al., 1999; and Hale et al., 1999; N = 107 and 47, respectively). Both trials in the third paper were open-label (Salzman et al., 1999; 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 overall 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 addressed the issue of predetermined maximal dose versus to-effect dosing, 12 specifically state that long-acting formulations (codeine, fentanyl, morphine, oxycodone, or tramadol) were used.

One study addressed the use of twice daily versus once-daily administration of equivalent doses (30 mg per day) of extended-release morphine and showed 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:

Special Population Characteristics. See Table 3: Use of Opioids for Chronic Pain in Special Populations

Type of pain: There are no data to support basing the choice of opioid agent on the type of pain. Some 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), dispelling any prior perceptions that neuropathic pain does not respond to opioids.

In his literature review of the treatment of neuropathic pain with antidepressants and opioids, Watson, (2000) reported that for post-herpetic 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)

evaluated the effect of oral morphine in 12 patients with phantom limb pain. The authors showed 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, (2001) 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". Sindrup et al., (1999a, 1999b) also showed opioids to be useful in neuropathic pain. In a small study of tramadol for painful polyneuropathy the authors stated that "tramadol appears to relieve both ongoing pain symptoms and the key neuropathic pain feature allodynia in polyneuropathy."

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	A trial of opioids for chronic pain when other analgesic approaches are insufficient	Consensus Statement, AAPM & APS, 1997	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	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	Good	A
4	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	Good	A
5	Start with agent and dose that have been effective in the past	Canadian Pain Society, 2002	III	Poor	I
6	Increased overdose deaths with methadone involved in pain patients	GAO-09-341, 2009	III	Poor	C
7	Methadone causes QTc prolongation, a predecessor to torsades de pointes	Krantz et al., 2009	III	Fair	C
8	ECG testing reliably identifies QTc prolongation torsades de pointes	Bednar et al., 2002	I	Good	A
9	ECG should be obtained before initiation of methadone, after 30 days and yearly. ECGs should be repeated for dose increases above 100 mg/day, unexpected syncope, or seizures	Group Consensus Krantz et al., 2009	III	Poor/ Fair	C
10	Reevaluate benefit & risk of methadone if QTc > 450 ms	Bednar et al., 2002	II	Good	A
11	Discontinue methadone if QTc > 500 ms	Group Consensus	III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

Table 3: Use of Opioids for Chronic Pain in Special Populations

Medication	Swallowing difficulty	GI mal-absorption	Pregnancy Risk Category (a)	Lactation (a)	Hepatic dysfunction	Renal dysfunction	Renal Dialysis	Prolonged QTc	Seizures	Elderly or debilitated	Decreased CYP-2D6 activity
Codeine (b)			C**	◆°	×		×				Less effective
Fentanyl transdermal	+	+	C††	UC (c)	◆ and ↓		◆				
Hydrocodone			C††	PC		◆ and ↓	◆				? less effective
Hydromorphone	+ (OS, RS)	+ (RS)	B††	PC	◆ and ↓		◆ (RBD)				
Methadone (e)	+ (OS)		B††	PC	◆ and ↓		◆	◆			
Morphine	+ (OS, RS)	+ (RS)								◆ and ↓	
Morphine SR/CR (8-12h); ER (24h)			C††	PC		↓ or ×	◆ or × (RBD)				
Oxycodone	+ (OS)										
Oxycodone CR (12h)			B††	PC		◆ and ↓	× (ND)				? less effective
Oxymorphone											
Oxymorphone ER (12h)			B††	PC	×	◆ and ↓	◆ (RBD)				
Propoxyphene			C††	PC	×	×	×		◆	×	
Tapentadol			C†	×(f)	◆	↓ or ×	× (ND)		◆		
Tramadol											
Tramadol ER (24h)			C†	PC	◆ and ↓	◆ and ↓	× (RBD)		×	◆ and ↓	? less effective

- (a) Estimates of risk of opioid therapy in pregnancy and while breastfeeding may be based on expectations of intermittent or short-term use; use of chronic opioid therapy during pregnancy or while breastfeeding should be approached with caution.
- (b) Codeine is metabolized to morphine by CYP 2D6; both pass into breast milk in small amounts usually considered clinically insignificant; however, caution in known or suspected ultra rapid metabolizers of CYP 2D6 substrates; 2006 case report of death in a nursing infant of CYP 2D6 ultra rapid metabolizer mother associated with high morphine levels in breast milk (Koren et al., 2006).
- (c) Manufacturer does not recommend use while breast-feeding; classified as compatible by the American Academy of Pediatrics
- (d) Fentanyl citrate available as transmucosal lozenges, buccal tablets
- (e) Methadone is the only long-acting opioid available as an oral solution. See Appendix E, Tables E1 and E2 and Appendix F Methadone Dosing Recommendations for Treatment of Chronic Pain for further details and references.
- (f) Per product information.

CR = Controlled release
OS = Oral solution
RS = Rectal suppository
SR = Sustained release
TDS = Transdermal system
RBD = Removed by dialysis
ND = No data

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

Pregnancy Risk Categories

A = controlled studies show no risk
B = no evidence of risk in humans
C = Risk cannot be ruled out, but potential benefits may justify potential risk
D = Positive evidence of risk; however, potential benefits may outweigh potential risk
X = Contraindicated in pregnancy.
*human data suggest risk (Briggs et al., 2008)
† human data suggest risk in 3rd trimester (Briggs et al., 2008)
‡Risk category D if prolonged periods or high doses at term (Briggs et al., 2008)

Use while breast-feeding

UC = usually compatible; either not excreted into human breast milk in clinically significant amounts or not expected to cause toxicity in infant
PC = probably compatible; no or limited human data
◆ = potential toxicity; no or limited human data
✕ = not recommended due to potential toxicity; no or limited human data
CI = contraindicated; potential for severe toxicity based on animal and/or human data

REFERENCES

- Briggs R, Freeman R, Yaffe S. *Drugs in Pregnancy and Lactation*. 8th ed (2008). Lippincott Williams & Wilkins; Philadelphia.
- Dean M. Opioids in Renal Failure and Dialysis. *J Pain Symptom Management* 2004;28(5):497-504.
- Koren G, Cairns J, Chitayat D, Gaedigk A, Leader SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704

K2. Titration Phase

OBJECTIVE:

To adjust the dose of opioid in an individualized and safe manner to achieve satisfactory pain control and a tolerable adverse effect profile.

BACKGROUND

The goal of optimal opioid titration for a stable chronic pain condition is to find, incrementally, the lowest effective dose that achieves a satisfactory balance between benefits and harm. Effective therapy is achieved when the patient reports improvement in pain relief and/or function along with minimal or acceptable adverse effects. Depending on the situation and phase of opioid therapy, the titration phase can involve upward or downward adjustment of the dosage regimen, opioid rotation (i.e., downward titration of the old agent concurrently with upward titration of the new agent), or even discontinuation of opioids by tapering doses (i.e., titrating downward at a tolerable rate that minimizes withdrawal symptoms).

After initiation of opioid therapy, careful upward dosage titration is necessary to minimize toxicity, allow sufficient time for the patient to develop tolerance to opioid side effects, and to find the optimal dose for each patient. Too rapid upward titration may exceed the patient's level of opioid tolerance and lead to serious complications, such as respiratory depression.

Titration may also be necessary because it is not unusual for the patient's biopsychosocial, spiritual conditions, and pain to change after initiation of opioid therapy. Other circumstances may arise that require adjustments in the regimen or more aggressive clinical support. For example, increases in the patient's activity level (due to improved analgesia) may exacerbate the pain. New adverse effects may emerge or become more clinically significant with prolonged opioid administration, and their treatment may require dosage titration or the addition of adjunctive medications. The underlying condition causing pain may worsen, requiring new evaluation and therapeutic intervention. Furthermore, a patient may experience new medical or psychological symptoms, the evaluation and treatment of which are complicated by the medications to treat pain (See Table 4: Potential Reasons for Fluctuations in Pain).

Table 4: Potential Reasons for Fluctuations in Pain

Increases in pain may be due to:	Decreases in pain may be due to:
Increased activity level affecting current chronic condition Worsening or progression of pain condition Exacerbation of a different chronic medical condition A new acute medical condition Concurrent mental health condition (e.g. depression, anxiety, PTSD, SUD) Concurrent stressor Development of opioid tolerance Opioid induced hyperalgesia Drug interaction	Improvement of the underlying medical condition Improvement in the patients' biopsychosocial status secondary to an interdisciplinary approach to pain management

Clinicians should carefully titrate the dose until adequate levels of analgesia and / or function have been reached 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, opioids do not exert an appreciable analgesic effect until a threshold dose has been achieved. However, most patients who respond to opioid therapy achieve acceptable pain relief at low to moderate doses (*arbitrarily defined* as less than morphine-equivalent doses of 200 mg/day). Clinicians should

refrain from repeatedly escalating doses in an effort to achieve *complete* pain relief, as this is an unrealistic goal. In general, there is no pharmacological rationale for using a predetermined maximal dose for pure agonist opioids, although setting dosage limits is documented in the literature (see *Discussion*).

The incidence of common opioid-related adverse effects, except for constipation, can be expected to decrease during the titration period, either because of an effective adverse events management or because of the development of tolerance. Unmanageable and persistent adverse effects warrant a decreased dose or a change in therapy. Excessive sedation often precedes respiratory depression and indicates the need to withhold some doses and/or slow the rate of upward titration.

The eventual dose must be one at which the clinician can comfortably maintain the patient. If in the clinicians' judgment, the care of the patient is beyond their own expertise, then the patient should be referred to a clinician with the necessary expertise in chronic pain management. Once a medication has been found that provides pain relief, it is likely to continue to provide pain relief.

RECOMMENDATIONS

The general strategy for titration:

1. Maintain close communication with patients and families, explicitly discussing the criteria for evaluating the effects of analgesic medications; doing so can help in defusing the anxiety that often accompanies visits to the physician.
2. Ask the patient to keep records of the time and dose of medication, the degree of pain relief, and the occurrence of adverse effects.
3. Documentation is essential, and should demonstrate the evaluation process—including consultation, prescriptions, and periodic review of patient status. Any change and consequent patient response should be documented in the record.
4. Follow up with the patient in no longer than 2 to 4 weeks after dosage modifications, or other treatment adjustments, basing the frequency of follow-up on the clinical situation (also see Annotation K3 – Maintenance Phase).
5. Assess the patient for changes in biopsychosocial and spiritual domains but especially the diagnosis, trajectory of disease, and effect of adjuvant therapies.
6. As with initial opioid selection and dosing, titration should be individualized according to the patient's age, health status, previous exposure to opioids, level of pain, comorbidities, potential drug interactions, the particular opioid formulation, the level (setting) of care, attainment of therapeutic goals, and predicted or observed harms.
7. If necessary, the daily dose may be increased by 25%-100% at a time. In general, smaller increments are appropriate for elderly or frail patients, those with likely low opioid tolerance, and patients experiencing unsatisfactory pain relief in the presence of some adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance. If the new dose is well tolerated but ineffective, additional increases in dose can be considered.
8. To ensure that the full effect from a dosage change has been manifested, and to avoid potential toxicity due to rapid accumulation of a drug, do not increase the dose more frequently than every five half-lives. In the case of methadone, upward dosage titration should not occur more frequently than every 7 days and perhaps longer (e.g., every 1 to 2 months), and only if there is no problem with daytime sedation, taking into consideration that there is wide interpatient variability in half-lives and responsiveness. (See Appendices E1 and F)
9. If possible, titrate only one drug at a time while observing the patient for additive effects. Maintain patients on as few medications as possible to minimize drug interactions and adverse events. Discontinue medications, especially adjuvant medications, which do not add substantially to patient

function or comfort. Continue close assessment of patients prescribed multiple centrally acting/psychoactive medications.

10. If a medication provides less than satisfactory pain reduction despite increasing the dose as tolerated to a reasonable level (less than 200 mg/day morphine equivalent), evaluate for potential causes such as nonadherence and drug interactions (see Appendix E, Table E6– Drug Interactions), and consider changing to an alternate opioid medication.
11. Medication may be increased until limited by adverse effects or clear evidence of lack of efficacy. If a high dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function, consider consultation rather than further increasing the dose.
12. During the titration phase, reasonable supplemental (rescue) doses of a short acting opioid may be considered. (See Annotation K-4-Supplemental Dosing)
13. Consider one or more of the following adjustments in therapy when there is an apparent loss of analgesic effect
 - a. Further optimize adjuvant therapies
 - b. Re-titrate the dose
 - Increase dose by 25-100%.
 - **Do not** increase the dose more frequently than every 5 half lives (for methadone or fentanyl no more than once a week), to ensure that the full effect from a dosage change has been manifested and to avoid potential toxicity due to rapid accumulation of a drug
 - If possible, titrate only one drug at a time, while observing the patient for additive effects. Inappropriate or ineffective medications should be tapered while titrating an appropriate pharmacologic regimen
 - Medication may be increased until treatment goals are met, intolerable adverse effects occur, or there is clear evidence of lack of efficacy
 - c. Rotate to another opioid
 - Rotation between opioids may help to improve efficacy, reduce side effects and reduce dose escalation in some patients who are receiving long-term opioid therapy
 - Rotate to another agent based on equianalgesic table and titrate (see Appendix E, Table E6 for conversion factors)
 - d. Refer or consult with advanced pain care (pain or palliative care specialist/pharmacist)
 - If the dose of opioid is large (more than 200mg/day morphine equivalent)
 - If opioid induced hyperalgesia or opioid tolerance is suspected
 - e. Discontinue Opioid Therapy (See Annotation X).

Converting short-acting opioids to long-acting opioids:

14. For a patient with continuous pain, an agent with a long duration of action, such as controlled-release morphine or methadone, is recommended.
15. If short-acting opioids are effective and well tolerated, it may be possible to achieve equivalent pain relief with fewer daily doses of the medication by substituting an equivalent dose of long-acting opioid medication (such as methadone, morphine CR, oxycodone CR, or transdermal fentanyl). These long-acting medications may provide steadier serum levels and smoother pain control. They can be supplemented with doses of short-acting medication to control pain exacerbation.
16. 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.

A notable exception to this general rule is methadone, which has relatively little cross-tolerance with other opioids and should be started at a conversion dose that is based on the previous morphine-equivalent dose. Inexperienced clinicians should consult with an expert before initiating methadone; even in an opioid tolerant patient (see Appendix E, Table E-3, and Appendix F Methadone Dosing Recommendations).

General Recommendations for Opioid Rotation:

17. Base the method of rotating opioids on the clinical situation. Either of the following two methods may be used:
 - a. **Step-wise Rotation:** Reduce the old opioid dose by 25% to 50% decrements and replace the amount removed with an equianalgesic conversion dose of the new opioid. This method may be preferable when switching large doses of opioids. A disadvantage of this method is that the causative opioid(s) of new or worsening adverse effects during rotation would be difficult to identify.
 - b. **Single-step Rotation:** Stop the old opioid and start the new opioid in an equianalgesic conversion dose. This method may be preferable when the old agent must be stopped immediately because of a hypersensitivity reaction. A disadvantage of this method is that pain may worsen if the new agent has a delayed peak analgesic effect (e.g., methadone) while the old agent has a relatively short offset of effects.

See Appendix E, Table E3, for equianalgesic doses and conversion methods.

DISCUSSION

Dosage titration is necessary for every short- and long-acting opioid medication (see Appendix E: Drug Tables E1 and E2). Clinicians can avoid causing serious complications due to opioid toxicity by carefully titrating opioid doses at a rate that is appropriate for the patient's pain condition, circumstances, and risk factors that may affect opioid dosing, as well as the clinician's resources for patient monitoring.

Long- Versus Short-acting Formulation:

Clinicians can titrate opioids using either long-acting formulations from the start of therapy (Caldwell et al., 2002; Hale et al., 1999; Salzman et al., 1999; Roth et al., 2000; Rauck, 2008; Huse et al., 2001) or short-acting formulations, which are later switched to an equivalent dose of a long-acting formulation (Caldwell et al., 1999) (see Appendix E, Table E7: Equianalgesic Doses). For chronic, persistent pain, long-acting formulations of opioids provide better dosing convenience for the patient. Some pain experts believe that the use of an opioid with a long duration of action may have other advantages for treating chronic pain. Long-acting opioids may facilitate patient compliance with around-the-clock dosing and can provide a more consistent blood level (thereby potentially allowing better tolerability to adverse effects and may reduce the reinforcement of pain behavior that theoretically can occur with a PRN dosing regimen). However, short-term studies comparing long-acting and short-acting opioid formulations provide little support for these advantages (see Annotation K1). Evidence-based guidelines on the use of opioids for chronic noncancer pain concluded that there is insufficient evidence to recommend either formulation over the other (Chou et al., 2009). Clinicians may therefore consider patient preference when prescribing, as that may affect adherence to treatment.

Rescue Medication:

Titration can be done with (Peat et al., 1999) or without rescue opioid medication. If immediate-release rescue medication is used, 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, 2002). (See Annotation K4)

Time-contingent vs. As-needed (PRN) Dosing:

Time-contingent is preferred over as-needed (PRN) dosing in the treatment of chronic pain despite a lack of studies comparing these dosing methods. The literature review conducted prior to the VA/DoD, (2003)

guideline for opioid therapy identified 18 studies (RCTs) that addressed dosing issues. Of the 18 studies, 16 used time-contingent dosing for chronic pain and reported it to be effective and safe. It should be noted that many of the studies supplemented this baseline with additional medication for as-needed pain relief. Hale et al., (1999) concluded that CR oxycodone is appropriate for selected patients whose pain is inadequately controlled by use of as-needed therapy. In contrast, two studies by Palangio et al., (2000, 2002) used 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 analgesics. 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 of the aforementioned trials directly and/or indirectly addressed this issue. Fifteen of these made 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 between pain intensity and risk for adverse effects, 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. In addition, this (relatively high) predetermined ceiling was able to meet the analgesic needs of a large majority of the patients. Some examples of maximal titration dosages include codeine = 400 mg/day; fentanyl = 100 mcg/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. There is a subpopulation of patients who do not achieve adequate relief within these dose-limits, and do tolerate and function better on much higher doses.

Five of the 16 trials involved 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; Roth et al., 2000).

Opioid Rotation:

A retrospective study showed that rotation between long-acting opioids may help to improve effectiveness and reduce adverse effects without dose escalation (based on expected equianalgesic doses). Rotation from short-acting to long-acting opioids resulted in improved analgesia, but with a large (74%) increase in dose (Thomsen et al., 1999)

Stability of pain relief:

Stable pain relief can often be achieved with titration. Roth et al., (2000) reported 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 stated that the stability of dosage suggested that tolerance was 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 not affected over the course of the study. The authors therefore did not believe that chronic morphine use influenced 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).

Other Causes for Dose Escalation:

There are several pain or opioid-related phenomena that can lead to an apparent need to increase the opioid dose: hyperalgesia due to neural hypersensitization; opioid-induced hyperalgesia (sensitization of pronociceptive mechanisms); opioid tolerance (desensitization of antinociceptive mechanisms) or a combination of these. Identifying the development of hyperalgesia is of great clinical importance since patients receiving opioids to relieve pain may in fact experience more pain as a result of treatment. Whereas increasing the dose of opioid can be an effective way to overcome tolerance, doing so to compensate for opioid-induced hyperalgesia may worsen the patient's condition by increasing sensitivity to pain while escalating physical dependence. (See Annotation M4 - Assess and Identify any Complications.)

Adjuvant Therapies:

In a small RCT, Gilron et al., (2005) found that the combination of morphine and gabapentin for neuropathic pain was more effective than either agent alone.

EVIDENCE TABLE

	Evidence	Source of Evidence	LE	QE	SR
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, 2002	III	Poor	I
3	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	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	Titrate until an adequate level of analgesia is obtained	Jamison et al., 1998 Petrone et al., 1999 Ruoff, 1999 Rauck, 2008	I II-2	Good	A
6	During the titration phase, reasonable doses of rescue opioid may be provided	Canadian Pain Society, 2002 College of Physicians and Surgeons of Ontario, 2000	III	Poor	I
7	Individual dose titration: - Increase dose by 25-100%. - Do not increase more than every 5 half lives - Titrate only one drug at a time - Increase medication until limited by adverse effects or lack of efficacy	Roth et al., 2000 Caldwell et al., 2002	I I	Good	A
8	Rotate to another opioid based on equianalgesic table and titrate Further optimize or add other adjuvant therapies	Breitfeld et al., 2003 Thomsen et al., 1999 Gilron et al., 2005	III II II2	Poor Fair Fair	I B B
9	Long-acting agents are effective for continuous, chronic pain	Caldwell et al., 1999, 2002 Hale et al., 1999 Huse et al., 2001 Peat et al., 1999 Roth et al., 2000 Salzman et al., 1999	I I I I I I	Good	A
10	Time-contingent dosing schedule	Hale et al., 1999 College of Physicians and Surgeons of Ontario, 2000	I III	Good	A

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

K3. Maintenance Phase

OBJECTIVE:

Maintain reliable pain control and/or improvement in function by continuing the effective, satisfactorily tolerated dose in a routine schedule.

BACKGROUND

The goal during the maintenance phase is to maintain an effective, satisfactorily tolerated dose, keeping a positive balance between benefits and harms.

Although the opioid medication and dose are relatively stable during the maintenance phase, regular re-assessment is necessary (see Annotations M1–M4). Re-titration of the opioid dose may be necessary because of changes in the patient's biopsychosocial status, spiritual conditions, or pain level (see Annotation K2 – Titration Phase).

Emphasis should be given to capitalizing on improved analgesia by facilitating incremental gains in physical and social function. Opioid therapy should be considered complementary to other pharmacologic and rehabilitative approaches. Improving quality of life in the chronically medically ill patient is an acceptable goal of pain treatment.

Patients Transferred to Primary Care:

Patients may present to primary care, already in maintenance phase, for continuation of OT started by another provider. These patients may be on therapy that is different from what is recommended in this guideline. The clinician should perform a careful assessment, including potential risks versus benefits, and if clinically necessary adjust therapy following the recommendations in this section.

RECOMMENDATIONS

1. Maintain the lowest effective and well-tolerated dose. The optimal opioid dose is the one that achieves the goals of pain reduction and/or improvement in functional status and patient satisfaction with tolerable adverse effects.
2. Recognize that the dose may need to be titrated up or down on basis of the patient's current biopsychosocial situation. (See Annotation K2 – Titration Phase)
3. Assess patients *at least* every 1 to 6 months based on the following:
 - a. Individualize and adjust visit frequencies based on patient characteristics, comorbidities, level of risk for potential drug misuse (i.e., diversion, addiction, abuse, and aberrant drug-related behavior), type of pain, and type and dose of opioids. No specific visit frequency applies to all patients
 - b. 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. Any change in the efficacy of the maintenance dose requires a face to face encounter for assessment prior to modifying therapy
4. Monthly renewal of the prescription for opioid medication can be facilitated by:
 - a. Phone call, email, or mail-in requests; and/or
 - b. A structured program (e.g., opioid renewal clinic) staffed by advanced care providers (e.g., pharmacists, nurse practitioners, PA-Cs, psychologists, RNs) with appropriate co-signatures
5. In addition to the maintenance opioid analgesic, supplemental doses of short-acting opioids may be considered. (See Annotation K4 – Supplemental Therapy)
6. Assess and re-educate patient's adherence with safely storing opioid medications.

*DISCUSSION****Frequency of Assessments:***

Expert consensus opinion is the basis for the recommendation to assess patients at least every 1 to 6 months based on clinical needs of the patient and type and dose of opioids. Patients with a low risk for potential drug misuse may need to be monitored every 3 to 6 months and moderate risk patients more frequently, perhaps monthly, whereas high-risk patients may need weekly monitoring (APS/AAPM, 2009). Legal precedents for frequency of in-person (as opposed to phone) assessments of patients on opioid therapy should also be considered, although this issue is complex and beyond the scope of this clinical practice guideline.

K4. Supplemental Therapy*BACKGROUND*

Supplemental short-acting opioids may be considered in specific situations but their routine use in chronic pain is controversial. This guideline supports the use of long-acting opioids in a scheduled manner for chronic pain, rather than the use of supplemental or as-needed (PRN) opioids for exacerbations. Supplemental short-acting opioids arose out of the concept of breakthrough pain, which originated from cancer pain treatment and is defined in different ways in the literature. The preferred term is pain exacerbation. In chronic pain, exacerbations are common.

In chronic pain, supplemental opioids may be considered for rescue, breakthrough pain, and incident pain.

TYPE OF THERAPY	DESCRIPTION OF PAIN EPISODE
Rescue	Insufficient analgesia during dosage titration
Breakthrough pain	Unpredictable exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid
Incident pain	Predictable, activity-related exacerbation of chronic pain otherwise controlled on stable maintenance doses of opioid

Pain exacerbation at the end of the dosing interval does not call for supplemental opioids; rather, it requires either an increase in dose or shortening of the dosing interval of the around-the-clock dosing regimen.

RECOMMENDATIONS

1. Evaluate worsening or new pain symptoms to determine the cause and the best treatment approach.
2. Encourage the use of non-pharmacologic modalities (e.g., pacing activities, relaxation, heat, cognitive behavioral therapy).
3. Carefully evaluate the potential benefits, side effects, and risks when considering supplemental opioids.
4. Consider supplemental short-acting opioid, non-opioid, or a combination of both agents on an as-needed basis.
5. Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain, unless the time course of action of the preparation matches the temporal pattern of pain intensity fluctuation.

6. Avoid use of long-acting agents for acute pain or on an as-needed basis in an outpatient setting.
7. When using combination products, do not exceed maximum recommended daily doses of acetaminophen, aspirin, or ibuprofen.
8. Avoid the use of mixed agonist-antagonist opioids, as these agents may precipitate withdrawal in patients who have physical opioid dependence.
9. Whenever possible, use the same opioid for supplemental therapy as the long-acting opioid to avoid confusion about the cause of any adverse effects that may develop.
10. When using short-acting pure agonist opioids (alone or in combination with non-opioid analgesics) for supplemental therapy, give opioid doses equivalent to about 10-15% of the every four hourly equivalent, or 1/6th of the total daily opioid dose, as needed.

Rescue Therapy:

11. Use rescue short-acting opioids to assist with pain management during the titration process and to help determine the long-term daily opioid dose.

Breakthrough Pain Therapy:

12. Do not use routinely for chronic pain. If necessary, use breakthrough pain therapy sparingly.
13. Consider adjusting the long-acting opioid regimen if pain exacerbations are interfering with patient function due to severity, frequency, or diurnal variations in pain intensity.

Incident Pain Therapy:

14. Educate and reassure patient, emphasizing realistic expectations about limitations of chronic opioid therapy, the normal cyclic nature of chronic pain, and the importance of pacing activities.
15. Consider providing preemptive analgesia for preventing incident pain e.g., 8 to 12 doses per month of short-acting opioid preparation.

DISCUSSION

There is insufficient evidence to guide recommendations regarding optimal treatment strategies for breakthrough pain in patients with CNCP. Most of the trials evaluating supplemental opioid doses for exacerbation of pain were conducted in patients who were treated for end-of life care. This population is not addressed in this guideline.

Two trials supported the use of treating pain exacerbation (referred to as "breakthrough pain") using rapid-onset fentanyl buccal tablets on an as-needed basis in chronic noncancer pain (Portenoy et al., 2007; Simpson et al., 2007). These studies were short-term; therefore, there is no evidence to support the long-term safety and efficacy of supplemental opioid therapy for chronic noncancer pain. More studies are needed to evaluate the long-term benefits and harms of this strategy, and to compare effects of different short-acting or rapid onset opioids. Clinicians should weigh carefully the potential benefits versus risks when considering the addition of an as-needed opioid for treatment of breakthrough pain, and consider both non-opioid drug therapies and non-pharmacologic treatments as other options. Although there is no evidence on the risk of aberrant drug-related behaviors in relation to the availability of medication prescribed for breakthrough pain, it is reasonable to assume that access to a rapid-onset or short-acting drug may increase the risk of such behaviors in those already engaging in them or are at high risk to do so. In patients at low risk for aberrant drug-related behaviors, a trial of an as-needed opioid with routine follow-up and monitoring may be a reasonable strategy. In patients at higher risk for aberrant drug-related behaviors, a trial of an as-needed opioid should only occur in conjunction with more frequent monitoring and follow-up. In all cases, clinicians should carefully assess for aberrant drug-related behaviors and progress toward meeting therapeutic goals, and periodically reassess relative benefits to risks of the as-needed opioid to make appropriate decisions regarding continuation of this therapy.

No studies were found comparing supplemental opioid treatments to guide selection of an optimal approach. Short-acting opioids may not have a fast enough onset to adequately treat unpredictable pain exacerbations, may increase side effects, and may increase risk for ADRB.

EVIDENCE TABLE

	Evidence	Source of Evidence	LE	QE	RS
1	Use supplemental short-acting opioid, non-opioid, or a combination of both agents on an as-needed basis	Coluzzi et al., 2002 McCarberg B, 2007	I	Good	A
2	Do not give treatment for breakthrough pain to patients with poorly managed pain	Gomez-Batiste et al., 2002	I	Good	A
3	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)	Hagen et al., 2008 McCarberg B, 2007	I	Good	A
4	In patients being started on a new opioid, consider giving rescue medication Rescue therapy is often used when pain is severe or escalating	Markman et al., 2008 McCarberg B, 2007	I	Good	A
5	Avoid the use of rapid-onset opioids as supplemental opioid therapy in chronic pain	Working Group Consensus	III	Poor	I
6	Encourage the use of nonpharmacologic modalities (e.g., pacing activities, relaxation, heat, cognitive behavioral therapy)	Working Group Consensus	III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

L. Document Therapy**BACKGROUND**

Documentation should demonstrate the evaluation process, including consultation, prescription, checking for duplicate opioid prescriptions from other providers, and periodic review of patient status. Any change and consequent patient response should be documented in the record.

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. (In the case of methadone, indicate on the prescription that it is for pain as opposed to detoxification).
2. Follow local regulations.

4. Assessment of Patient Status and Response to Therapy

M1. Assess for Adverse Effects

OBJECTIVE

Identify adverse effects and tolerability problems that may potentially change the treatment plan.

BACKGROUND

Adverse effects are a common and predictable consequence of opioid therapy. Opioid-induced adverse effects may occur acutely or with long-term therapy. The most common adverse effects are constipation, drowsiness, nausea, pruritus, and confusion. Development of tolerance to adverse effects (with the exceptions of constipation, endocrine dysfunction, osteoporosis, and sleep disordered breathing) is commonly observed over time.

Generally, nausea and constipation can be minimized by the use of antiemetic and bowel regimens. When opioids are titrated and monitored appropriately, respiratory depression other than sleep-disordered breathing is relatively uncommon.

The long-term adverse effects of opioids are not well defined because studies are generally of short duration. Emerging studies suggest that opioid therapy can have relatively common effects on sleep architecture, respiration during sleep, and on the endocrine and immune systems.

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. Keep in mind that slowly titrating the opioid dose, modifying the dosage regimen, treating symptoms, and rotating the opioid agents may successfully treat most adverse effects.
5. Consider evaluation of possible drug-to-drug interactions with other medications that have been prescribed for the patient (see Appendix E: Drug Table E4 – Drug Interactions).

DISCUSSION

The incidence and severity of side effects can have a significant impact on the outcome of chronic opioid therapy. Typical opioid adverse effects are common (Caldwell et al., 2002; Mullican & Lacy, 2001; Roth et al., 2000; McNicol et al., 2003; APS/AAPM, 2009). Adverse effects include constipation, nausea, vomiting, somnolence, headache, dyspepsia, pruritus, dizziness, tiredness, dry mouth, sweating, sedation, osteoporosis, sexual dysfunction, and endocrine dysfunction. Patient discontinuation due to adverse events is often reported. Titration of dosage needs to be in balance with a tolerable level of adverse effects. Slower titration may minimize adverse effects. 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).

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; McNicol et al., 2003). 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. In McNicol’s review of 67 studies, the incidence of opioid induced nausea and vomiting was 10% to 40%, and this symptom was ranked as highly distressing by patients. McNicol’s review also estimated that constipation occurred in 25% to 50% of cancer patients and is the most common opioid related side effect in patients with advanced cancer. In a study by Roth et al. (2000), 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.

In a study by Daniell et al., (2006), endocrine function was measured in 54 patients on chronic opioid therapy and compared to 27 healthy controls. Hormone levels were much lower in the opioid users than in control patients and total testosterone levels were subnormal in 74% of the opioid group, with an apparent dose-response effect. Of the men who reported normal erectile function before opioid use, 87% reported severe erectile dysfunction or decreased libido after beginning opioid therapy. A recent study showed that women on chronic opioid therapy have a decrease in follicle stimulating hormone (FSH) and luteinizing hormone (LH) accompanied by a significant inhibition of ovarian sex hormones (estradiol) and adrenal androgen (testosterone and dehydroepiandrosterone sulfate [DHEAS]) production (Daniell, 2006).

Kinjo,(2005) observed in a cross-sectional analysis of a large US adult sample (N=14,646) significantly lower bone mineral density among participants exposed to opioids. Fortin et al., (2008) examined bone mass density in 81 male patients on opioid therapy and found that 44% of the subjects were osteopenic or osteoporotic; 11 patients were hypogonadal on testosterone blood level testing and 25 patients had a normal testosterone level. These results indicate that the osteoporosis is not solely due to hypogonadism and that testosterone is not lower in all patients treated with opioids.

A recent study by Mogri et al., (2009) evaluated 98 consecutive patients on chronic opioid therapy for sleep-disordered breathing. His findings showed 36% of patients had obstructive sleep apnea, 24% had central sleep apnea, and 21% had mixed disorder. Wang et al., (2005) compared 50 methadone maintenance treatment (MMT) patients to 20 matched normal subjects. Thirty percent of the MMT patients had central sleep apnea while all of the control subjects were normal.

EVIDENCE TABLE

	Evidence	Source of Evidence	LE	QE	SR
1	Evaluate patient for adverse effects and tolerability problems	APS/AAPM, 2009 Caldwell et al., 2002 McNicol et al., 2003, Mullican & Lacy, 2001; Peloso et al., 2000 Roth et al., 2000,	II	Good	B
2	Many adverse effects resolve spontaneously	Roth et al., 2000	II	Fair	C

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

M2. Assess Adherence

OBJECTIVE

Determine whether patient is adhering to the essential components of the treatment plan and the reasons for any nonadherence.

BACKGROUND

Though research confirmation is lacking, adherence to the treatment plan is likely to be associated with positive outcomes. Nonadherence may result from a variety of causes including poor provider-patient communication, addiction, pseudoaddiction, confusion and/or memory impairment, psychiatric disorders, emotional distress, or pursuit of financial gain (diversion). Taking less medication than prescribed can also be unsafe, e.g., leads to inconsistent dosing. Determination of the reasons for nonadherence requires a thorough evaluation by the care provider. The reasons for early refill requests should be sought since they may be due to undertreated pain (pseudoaddiction) or increased analgesic requirements because of new or worsening pathology.

Patients on OT for chronic pain can develop problems with adhering to the treatment plan. These problems frequently manifest as clinically problematic behaviors, often termed "aberrant behaviors", or also referred to as aberrant drug-Related behaviors (ADRBs). These can adversely affect the outcomes of treatment.

ADRBs vary widely in their clinical severity and clinical and public health importance. **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 predict more serious non-adherence. **Serious** variations are those that jeopardize the safety of the patient or society, or which are illegal.

Clinicians should emphasize to the patient the importance of not sharing or lending their opioid medications with others. Transferring opioid drugs to any person other than the patient for whom they were prescribed is a federal offense.

Lending and sharing opioid medications with anyone is potentially dangerous and is illegal. Although sharing opioid medications with friends or family is considered relatively minor nonadherence behaviors, the consequences of such behavior can be a serious public health problem. Medication supplies of friends and family are the primary source of drugs involved in cases of prescription drug abuse and overdoses. Misuse of opioids can lead to morbidity and mortality in the patient and the public via diversion. Prescription medications of family and relatives have become a major source of diverted drugs involved in drug abuse-related deaths. Diversion of prescribed opioids is a public health problem especially in the young. In the National Survey on Drug Use & Health (NSDUH, 2008) administered by SAMSHA, the majority of persons using prescription pain relievers for nonmedical indications report receiving their drugs for free from a friend or relative. They also reported that prescription painkillers have eclipsed marijuana as the first drug of abuse. In evaluating how to respond to evidence of nonadherence, it is useful to consider three types of nonadherent behaviors.

Level I: These relatively minor variations include non-adherence to prescribed medication schedules and other recommended treatments for pain, making calls to the clinic for early refills, misplacing medications, or lending and borrowing medications from family members or others. These behaviors can be managed effectively with education, clinical structure, and behavioral interventions in the primary care setting. Minor variations that occur frequently (more than 3 times a year) may be considered Level II variations; and may indicate a need for a more structured care environment.

Level II: Behaviors that are persistently demonstrating deviation from the treatment agreement, and represent manifestations of serious comorbidities such as addiction, mood disorders, personality disorder, PTSD, psychosis, or cognitive dysfunction. These behaviors require consultation or co-management with one or more specialists in pain management, mental health, or addictions.

Level III: Illegal, criminal, or dangerous behaviors. Behaviors that consist of criminal diversion require interaction with regulatory authorities outside, and within, the medical system and discontinuation of the OT.

RECOMMENDATIONS

1. At every visit and telephone contact for opioid renewal, assess and document adherence with appropriate use of opioid analgesics, and any evidence of misuse, abuse, or addiction.

- a. 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
 - b. Screening aids such as random pill counts, adherence checklists, or instruments such as the Screener and Opioid Assessment for Patients with Pain (SOAPP), may be used to assist the provider in assessing adherence
 - c. With patient consent, obtain a Urine Drug Test (UDT) before initiating opioid therapy trial and randomly at follow-up visits to confirm the appropriate use of opioids (See Annotation M3)
 - d. Assess and document adherence to other components of the treatment plan, such as follow up with referrals, tests, and other therapies
 - e. Assess patients for behaviors that are predictive of addiction including repeated minor variations in adherence that may indicate an increased likelihood of addiction or serious non-adherence
 - f. Assess patient's adherence and reeducate regarding the importance of safely storing opioid medications
 - g. Assess and document patient motivation and barriers to adherence
2. Based on the clinical assessment the provider should determine whether aberrant behavior is present and respond with appropriate action.
 3. If the clinician is not sure of the meaning of the behavior, more frequent clinic visits, addiction or mental health specialist consultations, or periodic drug screens might be employed.
 4. When aberrant behaviors are present, providers should not stigmatize or judge patients but instead simply inform the individual that the behavior is unsafe and needs evaluation and adjustment in treatment through increased structure and monitoring or referral.
 5. A continuing pattern of repeated episodes of non-adherence following treatment changes designed to maximize adherence should increase prescriber concerns and consideration of potential cessation of opioid therapy.
 6. Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include a change in the patient's living situation that would provide greater structure (e.g. nursing home, assisted living facility), potentially enhance compliance, and reduce nonadherence

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), less serious non-adherence to medication use is more common (Turk, 2008).

The importance of assessing for nonadherence / ADRBs is based on multiple interrelated observations. There is strong evidence from multiple, well-designed, level II-1 and II-2 epidemiology studies, both retrospective and prospective, for the high prevalence of psychiatric co-morbidity with chronic pain, the impact of psychiatric co-morbidity on the outcome of treatment of chronic pain, and the association of psychiatric co-morbidity with aberrant behaviors in patients taking opioid analgesics for chronic pain. There is moderate evidence (level II-2 studies) that substance abuse predicts poor outcome from OT for chronic pain. There is moderate evidence (level II-2 studies) that a substantial percentage of patients on OT for chronic pain have positive urine drug screens, suggesting that this procedure may be the only way to identify addiction, drug abuse and diversion. In consideration of the growing public health problems of ineffective pain management and its concomitant costs to society, despite a rapid rise in the use of opioid analgesics, and increase in prescription drug abuse, the Work Group felt that these recommendations deserved a "strong" designation.

Non-adherence may occur for a variety of reasons. It may be associated with undiagnosed addiction. Alternatively, it could be due to changes in concurrent disorders such as depression, psychosis, or dementia.

Otherwise, non-adherent behaviors may arise from a patient's misunderstanding of their responsibilities while receiving opioid therapy or from miscommunication between the patient and the prescriber.

When evaluating adherence 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. Providers should be aware of established predictors of opioid misuse as well as their strength of association with misuse (see Table 5: Predictors of Opioid Misuse).

Table 5: Predictors of Opioid Misuse (Turk, 2008)

Strong predictors	Moderate predictors	Weak predictors	Inconsistent predictors
History of alcohol and illicit substance abuse	- Younger age - History of legal problems - Positive UDT	- Family history of drug abuse - History of childhood sexual abuse - History of DUIs or drug convictions - Lost or stolen prescriptions - Obtaining opioids from alternate sources - High SOAPP or SOAPP-R scores	- Male sex - History of an anxiety disorder - History of prescribed drug misuse - Race (nonwhite) - Education - History of MVAs - History of schizophrenia

UDT=Urine Drug Test; MVAs=Motor Vehicles Accidents; SOAPP-R = Screener and Opioid Assessment for Patients with Pain (Revised)

Behaviors suggestive of opioid abuse or addiction include using opioids for reasons other than pain (such as to "get high" or "manage stress"), 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, borrowing, stealing or selling prescriptions.

One moderate sized prospective cohort study of a pain clinic sample on opioids (Wasan et al., 2009 [n=622]) demonstrated that drug craving predicts higher rates of opioid misuse and positive urine drug screens.

Urine drug tests (UDTs) are useful in documenting appropriate use of prescribed opioids or for detecting the presence of alcohol, illegal street drugs, or other prescribed pharmaceuticals that may interact with opioids and render them less effective or represent a danger to the patient. Results of UDT may also suggest the presence of a substance use disorder. (See Annotation M3)

Other tools may be useful in assessing adherence to the opioid treatment agreement, including aberrant behavior checklists, pill counts, and opioid misuse screening instruments such as the SOAPP. However, the final determination as to whether ADRBs are present should be based on all available information.

The SOAPP questionnaire contains the following questions for assessing medication adherence:

- How often do you take more medication than you are supposed to?
- How often have you taken medication other than the way that it was prescribed?
- How often have your medications been lost or stolen?
- How often has more than one doctor prescribed pain medication for you at the same time?

Adherence to other components of the treatment plan such as referrals, tests, and therapies (e.g., physical therapy) also is 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 regimen, or may lack transportation. Interviewing family members or other collateral sources is frequently helpful in determining adherence and barriers.

When non-adherence is present the clinician should determine whether the variation from the treatment plan is relatively minor and potentially amenable to educational intervention or adjustment of the treatment plan (Level I); more persistent and reflecting the influence of comorbidities where consultation or co-management is required (Level II); or serious, requiring termination of opioid therapy (Level III). Not every episode of variation from the agreed management plan warrants a diagnosis of addiction or reflects the presence of a serious comorbidity.

EVIDENCE TABLE

	Evidence	Source of Evidence	LE	QE	SR
1	Substance users die from overdose	Hall et al., 2008	II-1	Good	B
2	Prior history of substance abuse and presence of co-morbid psychiatric disorder predicts risk for ADRBs Patients who report 4 or more aberrant behaviors while on OT are likely to have a diagnosis of substance abuse disorder	Edlund et al., 2007 Fishbain et al., 2008 Wasan et al., 2007 Wasan et al., 2009 Fleming et al., 2008	I	Fair	B
3	Use of screening instruments reveals patients at risk for ADRBs	Chou et al., 2009 Compton et al., 2008			
4	Drug craving predicts abuse	Wasan et al., 2009	II-2	Fair	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

M3. Urine Drug Tests

BACKGROUND

Substance abuse, dependence, and diversion are risks of OT. The risk of opioid misuse in patients on OT is as high as 30% in some series. Self-report of drug use has limited validity, and monitoring behavior alone can fail to detect problems revealed by urine drug tests (UDTs). UDTs can identify patients using illicit substances and can assist in the diagnosis of SUD. Routine and random UDTs are recommended for all patients with chronic pain prior to and during opioid therapy. Providers should be familiar with the procedure for ordering UDTs at their local lab, in interpreting the results, and responding to the test results.

RECOMMENDATIONS:

1. Inform patients that drug testing is a routine procedure for all patients starting or on opioid therapy, and is an important tool for monitoring the safety of their treatment.
2. With patient consent, obtain a UDT in all patients prior to initiation of OT. [B]
3. With patient consent monitor all patients on OT with periodic random UDTs to confirm adherence to the treatment plan. Increase the frequency of UDTs based on risk level for aberrant drug-related behaviors and following each dose increase. [B]
4. Take into consideration a patient's refusal to take a UDT as part of the ongoing assessment of the patient's ability to adhere to the treatment plan and the level of risk for adverse outcomes (see Annotation F).
5. When interpreting UDT results take into account other clinical information (e.g., past SUD, other risk factors, aberrant drug-related behaviors, and other conditions indicating risk.)
6. Understanding of lab methods for drug testing and reporting are necessary to interpret UDT results (i.e., screen versus confirmatory test, substances tested, cut-off levels for tests). Maintain a close working relationship with the clinical laboratory to answer any questions about the UDT or for confirming the results.

DISCUSSION

The patient who misuses substance often gives inaccurate information regarding substance use and about the sharing or theft of their medications by family and friends. Providers cannot accurately predict which patients will misuse, abuse, or divert substances. Therefore, alternative sources of information regarding substance use need to be sought. Urine drug screens and confirmatory urine or blood drug testing may be useful in detecting illicit drug use, use of drugs not prescribed, and opioid malabsorption. Repeatedly negative opioid test results may strongly suggest diversion. When performed and interpreted properly, urine drug screens and confirmatory urine and blood drug tests can provide accurate and useful information that allows the clinician to tailor pain therapy, safeguards, and risk management strategies.

Substance abusers frequently have pain and die from overdose. Hall et al., (2008) reported that out of 295 decedents in West Virginia in 2006, pharmaceutical diversion was associated with 186 (63.1%) deaths, while 63 (21.4%) were accompanied by evidence of 'doctor shopping'. Substance abuse indicators were identified in 279 decedents (94.6%), with nonmedical routes of exposure and illicit contributory drugs particularly prevalent among drug diverters. Multiple contributory substances were implicated in 234 deaths (79.3%). Opioid analgesics were taken by 275 decedents (93.2%), of whom only 122 (44.4%) had ever been prescribed these drugs.

Urine Drug Test:

- In a study of UDTs in 470 consecutive patients referred to a university pain clinic (Michna et al., 2007) urine toxicology screens among patients prescribed opioids for pain revealed a high incidence of abnormal findings. Factors obtained by patients' clinical history, such as common patient descriptors, and number, type, and dose of prescribed opioids were found to be poor predictors of abnormal results, suggesting that UDTs identify patients at risk for ADRBs and addiction.
- In a study of 196 patients treated for at least 3 months with OT, 32% had abnormal drug screens. (Ives, Chelminski et al., 2006).
- In a three-year study at three university pain clinics, of 122 patients maintained on OT, 43% had a "problem" (21 % with positive urine toxicology and no behavioral issues and 11% with aberrant drug-taking behaviors but normal UDTs). Monitoring both urine toxicology and aberrant behavior in chronic-pain patients treated with opioids identified more problem patients than by monitoring either alone. The presence of active substance abuse predicts poor outcomes from OT.
- Substance users with pain often do not admit to using licit and illicit substances found in their urine. Schuckman et al., (2008) found a 32% discrepancy between self-reported illicit substances and the results of urine drug test in patients presenting to the emergency room requesting pain medication for treatment of headache, backache, and toothache.
- Manichikanti et al., (2006) found that in 80 out of 500 consecutive patients on opioid therapy, illicit drug use was evident. The prevalence of illicit drug abuse in patients with chronic pain receiving opioids continues to be a common occurrence.
- In a single-practice study, Atluri & Sudarshan ,(2003) examined urine drug screens in patients with pain who had suspicious behavior and denied using illicit substances. Of 89 patients with failed urine drug screens, 32% were using marijuana, 7 % were using cocaine and 7% were using both. In 39% of the patients, urine drug screens detected opioids not prescribed.
- Random and for-cause urine drug testing decreases illicit drug use (Manchikanti et al., 2006). Follow-on studies of 500 consecutive patients in a single practice who underwent random urine testing for illicit and licit drugs found substantially lower (16% compared to 23%) overall illicit drug use after random urine drug testing was instituted.
- Evidence on prediction and identification of aberrant drug-related behaviors is limited. Although several screening instruments may be useful, evidence is sparse and primarily based on derivation

studies, and methodological shortcomings exist in all studies. Studies that perform external validation, use standardized definitions for clinically relevant aberrant drug-related behaviors, and evaluate clinical outcomes associated with different assessment and monitoring strategies are needed. (Chou et al., 2009)

EVIDENCE TABLE

	Evidence	Sources of Evidence	LE	QE	SR
1	Use of screening instruments reveals patients at risk for ADRBs	Chou et al., 2009 Compton et al., 2008	II-2	Good.	A
2	Substance users with pain often do not admit to using illicit and illicit substances found in their urine	Schuckman et al., 2008 Alturi & Sudarshan, 2003	II-2 II-1	fair	B
3	Patients on OT have clinically significant rates of positive UDTs, even when they do not have aberrant behaviors	Michna et al., 2007 Ives et al., 2006	II-1	Good	B
4	Urine drug testing decreases illicit drug use	Manchikanti et al., 2006	II-1	Fair	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

M4. Assess and Identify Any Complications, Co-occurring Conditions, or Other Indications for Consultation or Referral

OBJECTIVE

To identify and assess any complications, co-morbidities, or other indications for consultation or referral that are not necessarily related to active nonadherence behaviors.

BACKGROUND

In addition to assessing and addressing any nonadherence problems (Annotations M2, M3, N3), patients may have complicated pain conditions, co-morbidities, or other conditions that affect the response to therapy and may warrant consultation with specialty care or referral to a higher level of care.

RECOMMENDATIONS

1. Evaluate and assess the patient for the following problems or other indications for consultation or referral:
 - a. Patient with complex pain conditions
 - b. Patient with significant medical comorbidities that may negatively impact opioid therapy
 - c. Patient with significant concurrent psychiatric illnesses
 - d. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued
 - e. Opioid induced hyperalgesia or opioid tolerance suspected (i.e., pain increases or changes while on chronic stable opioid dosing and with an unchanged underlying medical condition causing the pain)
 - f. Patient with conditions requiring management beyond the expertise level of the primary provider

DISCUSSION

Neurogenic Hyperalgesia:

Tissue injury can lead to nociceptor sensitization and subsequent central (spinal) neural sensitization and supraspinal mechanisms of pain amplification. Nociceptor and central sensitization processes are thought to be associated with development of hyperalgesia. Neurogenic hyperalgesia is probably more common than opioid-induced hyperalgesia.

Opioid-Induced Hyperalgesia (OIH):

OIH or opioid-induced abnormal pain sensitivity refers to a pharmacodynamic phenomenon typically associated with the long-term use of opioids.

In patients on opioid therapy, OIH clinically presents with increased pain or increased pain sensitivity without a change in the underlying medical condition (Angst & Clark, 2006; Chu et al., 2008).

The mechanisms of opioid-induced hyperalgesia are unclear but probably multifactorial, involving alterations in opiate receptor desensitization processes, receptor numbers, NMDA receptor activation, increases in pronociceptive excitatory neurotransmitters and adaptation of descending neuromodulatory systems. Clinically, opioid-induced hyperalgesia is manifested as increased sensitivity to noxious stimuli and/or allodynia (painful response to previously non-noxious stimuli).

An individual taking opioids who develops increased pain but cannot achieve effective pain relief despite increases in dose may be experiencing opioid-induced hyperalgesia. Opioid-induced hyperalgesia may be managed by tapering or discontinuing opioid therapy. A paradoxical reduction in pain would be expected to occur with reductions in opioid dose. This is seemingly rare in clinical practice.

Opioid-Induced Tolerance:

Opioid-induced tolerance refers to decreased sensitivity to opioids such that larger doses are required to achieve the same effect. Opioid tolerance would also present with decreased pain relief at a stable dose of medication. Tolerance can have a number of mechanisms, involving both psychological and physiological factors, which include:

- Innate tolerance: A genetically determined, preexisting relative insensitivity to a medication
- True tolerance:
 - Pharmacokinetic: (enzyme induction)
 - Learned: Behavioral modification by user
- Pharmacodynamic:
 - Reduction in number of receptors over time
 - Upregulation and resistance of cAMP pathways to opioid mediated decreases in activity

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

Patients who have developed tolerance will have improved pain control with increased doses. Medical providers may easily confuse opioid induced hyperalgesia with opioid tolerance. Opioid tolerance will also present with increased pain at a stable dose of medication. However, patients with OIH may have worsening pain with escalating doses of opioids, while patients who have developed tolerance will have improved pain control with increased doses. OIH may involve pronociceptor sensitization whereas tolerance may be due to antinociceptor sensitization (Chu et al., 2008). Testing of pain and sensory analgesia before and after initiating opioid therapy may help to distinguish between OIH and opioid tolerance (Angst & Clark, 2006; Chu et al.,

2008). Testing of different pain parameters of patients on opioid therapy, on non-opioid therapy, and not on medications has also supported the existence of OIH, but further testing needs to be done to elucidate better parameters for routine clinical providers to use (Chu et al., 2006; Ram et al., 2008; Hay, 2009).

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Consider opioid induced hyperalgesia if the effectiveness of the opioids decreases especially in the setting of increased pain	Angst & Clark, 2006 Chu et al., 2008	III	Fair	I
2	Opioid use may alter pain sensitivity as evidenced by clinical testing	Hay, 2009 Ram et al., 2008 Chu et al., 2008 Chu et al., 2006	II-2 II-2 III II-2	Fair Fair Fair Fair	C I I I
3	Testing of pain and sensory analgesia before initiating OT and at follow up visits may help distinguish between OIH and opioid tolerance	Chu et al., 2008 Angst & Clark, 2006	III	Fair	I
4	OIH may be due to pronociceptor sensitization and tolerance may be due to antinociceptor sensitization	Chu et al., 2008 Angst & Clark, 2006	III	Fair	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

M5. Assess Effectiveness (Pain, Function, and Satisfaction)

OBJECTIVE

To assess whether opioid therapy is meeting the patient's and clinician's expected goals of pain relief and/or functional improvement, and patient satisfaction, and whether opioid therapy should be continued.

BACKGROUND

Assessments of the patient for adverse effects or tolerability problems (Annotation M1) and adherence to the pain treatment plan (opioid and nonopioid therapies; Annotation M2) would be incomplete without a thorough assessment of whether opioid therapy is benefiting the patient. The three domains to assess for effectiveness of opioid therapy are pain, function, and patient satisfaction. Pain is subjective and there are no objective methods to verify the intensity of reported pain; pain is what the patient says it is. Functional ability can be verified using objective documentation, such as physical therapy progress notes, employment records, exercise diaries, family reports, or other supplemental clinical information and observations. Patients can be asked to perform, in clinic, specific tasks related to individualized goals of therapy (e.g., the ability to walk a certain distance).

Ideally, improvement in pain leads to gains in functional ability; however, many patients may experience reduction in pain without functional improvement, or functional improvement without substantial changes or even increases in pain level. Patients should also be asked about their overall satisfaction with opioid therapy. Evaluation of the three effectiveness domains forms the basis for the "positive" side of the equation when weighing risks and benefits and deciding whether the benefits outweigh the potential risks sufficiently to continue opioid therapy.

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. In addition, failure to maintain analgesia while on stable doses of chronic opioid therapy raises concerns about the presence of opioid induced hyperalgesia (OIH) or opioid tolerance, and the effectiveness of continuing the current opioid therapy.

Patient Assessments: 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 and quality of life, the provider also must assess for potential functional decline induced by treatment.

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.

RECOMMENDATIONS

1. Evaluate pain intensity at each visit.
 - a. Intensity of pain should be measured in the following manner using a Numeric Rating Scale (NSR) (0 to 10) and include the following:
 - Current pain
 - Least pain in last week
 - "Usual" or "Average" pain in the last week
 - b. The patient's response to current pain medications should be assessed each visit using questions such as:
 - "What is your intensity of pain after taking your current treatment/medication?"
 - "How long does your pain relief last after taking your medication?"
2. Evaluate pain-related function using objective documentation whenever possible, such as physical therapy progress notes, employment records, exercise diaries, family reports, clinician observations (e.g., walking distance), or validated instruments or NRS rating scales on a monthly basis during the titration phase and every six months after the patient is on stable opioids. Assessment of function may include:
 - Employment
 - Enjoyment of life
 - Emotional distress (depression and anxiety)
 - Housework, chores, hobbies, and other day to day activities
 - Sleep
 - Mobility
 - Self-care behaviors
 - Sexual function
3. Assess overall patient satisfaction with pain therapy at each visit
4. 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.

NOTE: The VA Pain Outcomes Toolkit recommends several optional instruments for functional status assessment. [Link to Web site http://www1.va.gov/pain_management/docs/Outcomes.doc]

DISCUSSION

Among patients with cancer pain, results of several studies from 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). Other research suggests that a rating of four, rather than five, indicates that pain significantly interferes with function. For example, Twycross et al., (1996) used the Brief Pain Inventory to assess 111 patients with advanced cancer. They found that, on a 0-10 scale, pain ratings of 4 or greater correlated with marked interference with activity, while scores of 6 and 7 correlated with marked increases in interference with enjoyment. This study and others, combined with

clinical experience, has led many clinicians to the conclusion that a pain rating greater than three 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 had been identified as optimal for cancer patients are optimal for persons with pain associated with amputation. The study also attempted to determine whether the optimal cutoffs replicate across pain types (phantom limb, back and general pain). Findings in patients with low back pain, using average pain, were consistent with those found in patients with cancer pain using worst pain, based on interference with function (i.e., mild pain 1–4; moderate 5–6; severe 7–10). However, in the other groups, the degree of pain interference appeared to vary as a function of pain type. At pain levels of 5 or higher (0–10 scale), the same level of pain was associated with greater interference with function in patients with back pain than in those with phantom limb pain (Jensen et al., 2001).

Zelman, et al., (2003) also found different cutoffs for pain severity for different types of pain (low back and osteoarthritis). Another study by Paul et al., (2005) suggests that pain severity cutoffs vary according to the type of pain.

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 four may not be attainable. Patients who set ongoing goals of greater than 3 need to be reminded that quality of life requires that they easily perform certain activities. Patients should be educated that satisfactory pain relief is a level of pain that is noticeable but not bothersome, and that a pain rating equal to or less than the goal should be maintained as much of the time as possible. The discussion should emphasize the activities that accompany the pain-rating goal. It is useful to ask the patient what pain rating would make it easy to sleep, eat, work, or perform other physical activities.

Not only does setting comfort and function goals 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 and function goals should be visible on all records where pain ratings are recorded (McCaffery & Pasero, 1999).

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 pain intensity 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) evaluated the treatment with controlled release oxycodone therapy versus placebo in a group of elderly patients with moderate osteoarthritis. The patients' self-evaluations showed improvement of general activity, sleep, enjoyment of life, and mood.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Evaluate pain intensity using 0-10 scales	Breivik & Skoglund, 1998 De Conno et al., 1994 Ogon et al., 1996 Serlin et al., 1995	II-1 III II-2 II-2	Fair	B
2	Evaluate function related to chronic pain after initiation of therapy	Caldwell et al., 1999 Peloso et al., 2000 Roth et al., 2000	I I I	Good	A
3	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	Fair	B
4	Emphasis should be given to capitalizing on improved analgesia by gains in physical and social function	McCaffery & Pasero, 1999	II	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

5. ADJUSTMENT OF THERAPY

N1. Address Adverse Effects

OBJECTIVE

Modify treatment to achieve effective pain control while minimizing adverse effects and medication intolerance.

BACKGROUND

Adverse effects to opioids may need only temporary symptomatic management because they often subside over time with the development of tolerance. Adverse events that usually do not diminish are constipation, endocrine dysfunction, and sleep-disordered breathing. Regular re-assessments and monitoring for these conditions are required.

Other less common adverse effects that are best treated by dose reduction during titration or opioid rotation include sweating, peripheral edema, urinary retention, myoclonus, and dyspepsia.

RECOMMENDATIONS

A general strategy to minimize adverse effects:

1. Adverse effects can usually be minimized through the use of low starting doses, slow titration rates, prophylactic and symptomatic treatments, and specific patient education provided at initiation of therapy.
2. Symptomatic treatment should be augmented with slow dosage titration, dose modification, and/or opioid rotation to minimize the adverse effects as follows:
 - a. Titrate slowly, temporarily reducing or holding doses if necessary, or modify the dosage regimen to allow the patient to develop tolerance to the adverse effects
 - b. If these measures fail to minimize the adverse effects, consider rotating to another opioid agent
3. If adverse effects are unmanageable and therapy is a greater detriment than benefit as determined by discussion with the patient and family, opioid therapy should be discontinued.

Constipation:

4. Initial bowel regimens should generally consist of a bowel stimulant and a stool softener as well as general measures, such as increased fluid intake, increased dietary fiber, and adequate exercise.
5. Routinely initiate a stimulant-based bowel regimen at commencement of chronic opioid therapy.
6. If the initial regimen is inadequate, mild hyperosmotic, saline, and emollient laxatives may be added.
7. If possible, reduce or discontinue other drugs that may cause or contribute to constipation.
8. Bulk-producing laxatives, such as psyllium and polycarbophil, are not recommended and are relatively contraindicated as they may exacerbate constipation and lead to intestinal obstruction in patients with poor fluid intake.
9. Assess patients for constipation symptoms at every office visit.

Nausea and vomiting:

10. Consider prophylactic antiemetic therapy at initiation of therapy.

11. Rule out other causes of nausea, and/or treat based on cause including
 - a. Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist
 - b. Slowed GI motility: metoclopramide
 - c. Nausea associated with motion: dimenhydrinate or scopolamine.

Itching:

12. Rule out an allergic reaction.
13. Itching may resolve spontaneously despite continuation of opioid therapy. If the itching does not spontaneously resolve, consider treatment with antihistamines.

Sedation:

14. Rule out other causes.
15. Reduce dose (with or without addition of a co-analgesic). Excessive sedation within the first few days of initiating opioids may require temporarily holding one or two doses and restarting at a lower dose to prevent respiratory depression.
16. Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.
17. If the above measures fail to relieve sedation adequately, consider rotating to another opioid agent.
18. Consider adding caffeine or a prescription psychostimulant medication.

Confusion or Minor deterioration of cognitive function:

19. Rule out other causes.
20. Consider reducing or stopping (tapering) the dose.
21. Add or increase non-opioid or non-sedating adjuvant for additional pain relief so that the opioid can be reduced.
22. Rotate opioid agent.
23. If patient continues to deteriorate during titration phase and presents with symptoms of delirium, opioid therapy should be discontinued.
24. If patient develops increased confusion or major cognitive changes (delirium) during the maintenance phase, consider hospitalization to investigate the cause and to continue treatment safely.

Opioid-induced-endocrinopathy:

25. Ask all patients on opioids for chronic pain about symptoms of opioid-induced endocrinopathy (i.e. hypogonadism) on each visit.
26. If opioid-induced endocrinopathy symptoms are present, and not accounted for by another disorder or illness (e.g., depression, chronic disease), laboratory evaluation and consultation with an endocrinologist should be considered
27. Insufficient data exists to recommend routine laboratory screening for endocrinopathy in asymptomatic patients on OT.

Immune Dysfunction:

28. There is insufficient evidence to make recommendations regarding OT and immune dysfunction.

**Osteoporosis:**

29. Consider monitoring bone density in patients at risk for osteoporosis (See Table 6: Risk Factors for Osteoporosis), as patients with fractures associated with hypogonadism often have no other symptoms associated with hypogonadism.

Table 6: Risk Factors for Osteoporosis

1. Increased age		
2. Female sex		
3. Family history		
4. Low body weight/small stature		
5. Caucasian, Asian and Latino heritage		
6. History of broken bones		
7. Females after menopause		
8. Inactive lifestyle		
9. Smoking		
10. Alcohol abuse		
Medical comorbidities that can lead to osteoporosis:		
<ul style="list-style-type: none"> • AIDS/HIV • Ankylosing spondylitis • Blood and bone marrow disorders • Breast cancer • Cushing's syndrome • Eating disorders • Emphysema • Female athlete triad • Gastrectomy • Gastrointestinal bypass procedures • Hyperparathyroidism • Hyperthyroidism 	<ul style="list-style-type: none"> • Idiopathic scoliosis • Inflammatory bowel disease • Diabetes mellitus • Kidney disease • Lupus • Lymphoma and leukemia • Malabsorption syndromes (e.g., celiac disease, Crohn's disease) • Multiple myeloma • Multiple sclerosis • Organ transplants • Parkinson's disease 	<ul style="list-style-type: none"> • Poor diet • Post-polio syndrome • Premature menopause • Prostate cancer • Rheumatoid arthritis • Severe liver disease (including biliary cirrhosis) • Spinal cord injuries • Stroke (CVA) • Thalassemia • Thyrotoxicosis • Weight loss
Certain drugs that can lead to osteoporosis:		
<ul style="list-style-type: none"> • Aluminum-containing antacids • Antiepileptic drugs, such as phenytoin, phenobarbital, carbamazepine, and possibly non-enzyme-inducing agents • Aromatase inhibitors, such as anastrozole, exemestane and letrozole • Cancer chemotherapeutic drugs • Cyclosporine A 	<ul style="list-style-type: none"> • Glucocorticoids, such as cortisone and prednisone • Gonadotropin releasing hormone (GnRH) such as leuprolide and goserelin • Heparin • Lithium • Medroxyprogesterone acetate for contraception • Methotrexate 	<ul style="list-style-type: none"> • Proton pump inhibitors (PPIs) • Selective serotonin reuptake inhibitors (SSRIs) • Tacrolimus • Tamoxifen (premenopausal use) • Thiazolidenediones (pioglitazone and rosiglitazone) • Thyroid hormones in excess

DISCUSSION

All 27 of the RCTs 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.

Nausea and sedation are generally short-term, and often resolve with continued therapy, although antiemetics may be necessary to control nausea during initial dose titration. Sedation can often be controlled by careful titration, as tolerance to this adverse effect will often develop. Rotating opioids may also provide benefits for patients. Proper patient screening, education, and preemptive treatment of potential side effects may aid in maximizing effectiveness while reducing the severity of side effects and adverse events (Benyamin et al., 2008) (See Annotation R3). One adverse effect that is not likely to be self-limiting is constipation. Every patient should receive prophylactic measures to ensure regular bowel movements.

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. 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."

Constipation:

Opioid-induced bowel dysfunction (OBD) is a constellation of gastrointestinal signs and symptoms that are often associated with the use of opioids for the management of chronic pain. OBD consists of constipation, decreased gastric emptying leading to gastroesophageal reflux disorder, abdominal cramping, spasm, bloating, delayed GI transit time and the formation of hard, dry stools. Constipation, often used as a surrogate measure of OBD, typically does not abate as a patient develops tolerance to opioids. Constipation is highly prevalent, being estimated to occur in 25% to 50% of patients treated with opioids for cancer pain and 15% to 90% of chronic noncancer pain patients treated with opioids. OBD can have a serious negative impact on the quality of life of the patient suffering with chronic pain. Oftentimes, these patients will decide on their own to decrease the dose or skip a dose of their medication to ease the distress of the chronic constipation. Constipation is a common problem associated with long-term opioid administration and this side effect should be anticipated, routinely treated prophylactically, and monitored regularly. There is a lack of RCTs evaluating therapies for constipation induced by chronic opioid therapy. Most of the literature consists of meta-analyses that assess the incidence of opioid-induced bowel disorder in patients on chronic opioid therapy with brief discussions of therapy, which are anecdotal opinions of the authors. Although most evidence is anecdotal, bowel regimens including increased fluid and dietary fiber intake, stool softeners, and stimulant laxatives are often used. There is insufficient evidence to recommend oral nonspecific opioid antagonists, and these agents can precipitate withdrawal. Peripheral opioid antagonists provide substantial relaxation benefits in hospice/palliative care patients with advanced medical illness. Presently, there is insufficient evidence to recommend peripheral opioid antagonists to prevent or treat opioid-induced bowel dysfunction in populations other than hospice/palliative care patients.

- A bowel regimen should be initiated for the patient at commencement of opioid therapy. It is commonly accepted that both a stimulant and a stool softener are required. Most frequently this combination involves the use of senna and docusate sodium, respectively. Osmotic laxatives such as lactulose are also commonly used.

- Bulk-forming laxatives should be used with caution because of the risk of exacerbating constipation, fecal impaction, and intestinal obstruction unless adequate fluid intake is maintained (Panchal et al., 2007; McNicol et al., 2003).

Nausea and Vomiting:

- Because of the high incidence of nausea, prophylactic antiemetic therapy is sometimes given (Canadian Pain Society, 2002; Cohen et al., 1992; Gan et al., 1997; Pitkanen et al., 1997; Wang et al., 1996).

Itching/Pruritus:

- Consider treatment with antihistamines (Cherny et al., 2001).

Sedation and Cognitive Dysfunction:

Sedation or clouded mentation most often occurs at the onset of opioid therapy, or with a significant dosage increase. These effects tend to resolve over a few days. Reassurance and education (such as warning the patient to avoid driving; and avoid alcohol, marijuana, illicit drugs, and additional sedating medications) should be provided. Sedation that does not resolve after a few days usually occurs when comorbidities or additional sedating medications are present. Treatment for patients whose symptoms persist should proceed in a logical progression to include assessment of the comorbidities, discontinuation, or dose reduction of the sedating medications to include the opioid agent, opioid rotation, and consideration of addition of a psychostimulant (McNicol et al., 2003).

Delirium (acute confusional state) is associated with mental clouding that leads to disturbance of consciousness and comprehension (McNicol et al., 2003). Mild cognitive impairment and hallucinations frequently occur at the onset of opioid therapy or with a significant dosage increase. The diagnosis of opioid-induced delirium can be complicated by the high prevalence of delirium and other mental status changes that can occur in opioid-treated patients with significant medical comorbidities. As with all opioid-induced side effects, delirium should be managed by first ruling out underlying causes and reducing the dose or discontinuing any non-essential centrally acting medications. If symptoms persist, dosage reduction, opioid rotation, or cessation of opioid therapy will need to be considered.

- Sedation usually decreases over time on stable doses (Jacox et al., 1994).
- Determine whether sedation is due to the opioid; eliminate nonessential CNS depressant medications (Passik & Weinreb, 2000).
- Add caffeine or a prescription psychostimulant medication during the day.
- Change opioid (Cherny et al., 2001).

Hallucination/Dysphoria:

Evaluate underlying cause; consider role of primary therapy. Hallucinations 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).

Reevaluate and treat underlying process if appropriate.

Dysphoria is more common with mixed opioid agonists/antagonists and antidopaminergic medications.

If hallucination or dysphoria persists:

- Consider a trial of an antipsychotic in consultation with behavioral health specialty

- Switch to another opioid.

Opioid-induced-endocrinopathy:

Evidence indicates that a significant percentage of patients treated with OT develop opioid-induced endocrinopathy. This side effect of OT is responsive to therapy if it is appropriately recognized and diagnosed. Symptoms of opioid-induced-endocrinopathy include, but are not limited to, decreased libido, erectile dysfunction (men), infertility, depression and anxiety, decreased muscle mass and strength, tiredness or fatigue, hot flashes and night sweats, amenorrhea, irregular menses, galactorrhea (women), osteoporosis and fractures. (Katz & Mazer, 2009)

Laboratory studies should include total and free testosterone (or sex hormone binding globulin), luteinizing hormone (LH), follicle-stimulating hormone (FSH) (optional), and dehydroepiandrosterone sulfate (DHEAS) in both men and women, and estradiol in women. (Katz & Mazer, 2009)

- Daniell, (2002) compared 54 community patients on sustained action opioids versus 27 similar men for control. Free testosterone, total testosterone, estradiol, dihydrotestosterone, LH and FSH; were all significantly lower ($p < .001$) in patients on opioid therapy. Free testosterone, total testosterone and estradiol were subnormal in 56%, 74% and 74% of subjects, respectively. Total testosterone was subnormal in all patients on >100mg of methadone and in 19 of 26 (73%) consuming lower doses. Of opioid patients who had normal sexual function prior to therapy, 87% reported severe erectile dysfunction or diminished libido after beginning opioid therapy.
- Another study (Daniell, 2008), compared 47 females on OT with 68 females not on opioid therapy and recorded menstrual histories and measured gonadotrophin, androgen and estradiol levels. Testosterone, estradiol and DHEAS values were 48% and 57% lower in opioid consuming women with intact ovarian tissue than control subjects ($p < .001-.05$). Menses had often ceased soon after beginning sustained-action opioid therapy.
- Long-acting opioid preparations suppress the hypothalamic-pituitary-gonadal axis in some men and produce a symptomatic state of androgen deficiency. Testosterone therapy normalizes hormone levels and appears to improve a number of quality of life parameters (sexual function, well-being, and mood) (Daniell, Lentz, & Mazer, 2006).
- Dehydroepiandrosterone (DHEA) deficiency often produces fatigue, depression, weakness, and sexual dysfunction, all of which improve with replacement therapy. In one study (Daniell, 2006), DHEAS levels were lower in opioid-treated (34 males and 32 females) than in control subjects (33 males and 53 females) in a dose related pattern ($p < .01$). DHEAS levels were below age-specific norms in 67% of opioid consumers and 8% of controls ($p < .001$). The levels were below the laboratory's lowest detection limits in 29% of opioid users and 1% of controls ($p < .001$).
- Osteoporosis is an important risk factor for many types of fractures. Complex patient populations with chronic pain, not usually on opioid as monotherapy, and exercising poorly may contribute to osteoporosis. Chronic opioid use has been recognized as a risk factor in the development of osteoporosis through reducing bone mineral density.
- Kim et al., (2006) examined the frequency and severity of low bone mineral density (BMD) among patients enrolled in a methadone maintenance treatment (MMT) program. Dual energy x-ray absorptimetry (DXA) results were below normal in 83% (76/92) of the study sample with T-scores < -2.5 (osteoporosis range) in 35% [32/92] and between -1.0 and -2.5 (osteopenia range) in 48% [44/92].
- Decreased bone mineral density defines osteoporosis according to the World Health Organization and is an important predictor of future fractures. Kinjo et al., (2005) analyzed data on adults aged 17 years and older from the Third National Examination Survey. Total femoral bone mineral density of 7114 male and 7532 female participants was measured by DXA. In linear regression models,

significantly reduced bone mineral density was found in subjects taking opioids compared to nonusers.

- Fortin et al., (2008) examined serum testosterone levels and bone mass density on 81 male patients on opioid therapy (average duration of therapy 2.5 years, average patient age 45 years). Thirty-six patients (44%) had bone mass densities in the osteopenic and osteoporotic ranges. Of these thirty-six, only eleven were hypogonadal, therefore monitoring the total testosterone blood level is not a reliable method to determine the risk for developing opioid-associated osteoporosis.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Recommend modifying the dose or rotating the opioid agent to minimize adverse effects	Ruoff, 1999 Cherny et al., 2001	I	Good	A
2	For constipation: Initial bowel regimens should generally include a stimulant laxative and a stool softener	Panchal et al., 2007	III	Poor	C
	A bowel regimen should be initiated at the start of opioid therapy.	McNicol et al., 2003	III	Fair	B
	Don't use bulk forming agents, as they may cause intestinal obstruction	Panchal et al., 2007 APS/AAPM, 2009	III	Fair	B
3	For nausea and vomiting: Consider prophylactic antiemetic therapy Add or increase non-opioid adjuvants If analgesia is satisfactory, decrease opioid dose by 25% Base treatment on cause: Stimulation of chemoreceptor trigger zone: dopamine or serotonin antagonist Slowed GI motility: metoclopramide Nausea associated with motion: dimenhydrinate or scopolamine	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, 2002 Jacox et al., 1994 Cherny et al., 2001	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 delirium: Delirium should be managed by first ruling out or eliminating other causes (metabolic disturbances,	McNicol et al., 2003 Davis et al., 2003	II	Poor	C

	hypoxia, and dehydration), offending antipsychotic agent (phenothiazines or tricyclic antidepressants) and reducing doses of or discontinuing nonessential, centrally acting medications, if pain is under control.	Ersek et al., 2004			
	Opioid switch rather than opioid reduction is a reasonable option if pain is not well controlled.	Davis et al., 2003 Ersek et al., 2004	II	poor	C
	Reduction in the dose of opioid, and the addition, if needed, of an adjuvant analgesic may resolve symptoms.	McNicol et al., 2003 Davis et al., 2003	II	poor	C
	If additional management is needed, changing the route of opioid administration may be beneficial.	McNicol et al., 2003 Davis et al., 2003	II	poor	C
	If pharmacologic treatment is deemed necessary, haloperidol may be considered for patients who have agitated delirium, because of its efficacy and low incidence of cardiovascular and anticholinergic side effects.	McNicol et al., 2003 Davis et al., 2003 Ersek et al., 2004	II	poor	C
8	For opioid Induced Endocrinopathy: 87% of males with c/o severe erectile dysfunction, >100mg methadone resulted in 100% of subjects with subnormal testosterone	Daniell, 2002	II-2	Good	A
	Menses had often ceased soon after beginning sustained action opioid therapy in females indicating opioid induced menopause	Daniell, 2008	II-2	Good	B
	Testosterone patch therapy in 23 men with OPIAD. Androgen deficiency symptoms, sexual function, mood, depression and hematocrit levels showed improvement during treatment.	Daniell, Lentz & Mazer, 2006	II-2	Good	A
	OT patients had significantly lower levels of DHEAS (p<.01) than non-opioid consumers	Daniell, 2006	II-2	Good	B
9	For Immune Dysfunction: Decreased Ig in chronic pain patients before starting treatment and further decreased during OT.	Palm et al., 1998	II-2	fair	C

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

N2 Severe Unmanageable 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 and advise 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. (See Annotation T)

RECOMMENDATIONS

1. If a medication causes unmanageable adverse effects, consider changing to an alternate opioid medication.

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

DISCUSSION

One situation that calls for strong consideration of discontinuing opioid therapy is the presence of unmanageable sleep-disordered breathing. Recent studies identifying sleep-disordered breathing as a potentially serious adverse effect of OT challenges previous beliefs that patients usually develop rapid tolerance to the respiratory depressant effects of opioid therapy (see Annotation P1) and that discontinuation for respiratory depression is rarely indicated (Joranson et al., 1992). Development of sleep apnea (central or otherwise) while on opioid therapy is a relative contraindication to continuing therapy (See Annotation D).

N3. Serious Non-Adherence – Illegal, criminal, or dangerous behaviors**OBJECTIVE**

Address serious nonadherence behaviors promptly.

BACKGROUND

Illegal, 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 or provider. Behaviors that jeopardize the safety of the patient or society or are illegal may require the immediate cessation of the opioid with appropriate treatment of potential withdrawal symptoms. In addition, prompt documentation is mandated and consideration of notifying police authorities.

Table 7: Types of Serious and Dangerous Behaviors

Illegal or Criminal behavior
- Active diversion (selling or provision of drugs to others)
- Prescription forgery
- Stealing, "borrowing", or buying drugs from others
Dangerous behavior
- Motor vehicle crash /arrest related to opioid or illicit drug or alcohol intoxication or effects
- Intentional or unintentional overdose or suicide attempt
- Assaultive behaviors
- Aggressive/threatening/belligerent behavior in the clinic

RECOMMENDATIONS

- Address safety issues immediately and apply legal mandates as appropriate.
- Dangerous or Illegal behaviors may require immediate cessation of the opioid therapy with consideration of appropriate treatment of potential withdrawal symptoms.
- Document and refer to behavior health specialty those patients demonstrating behaviors suggestive of suicide.
- For a patient with evidence of diversion or dangerous or suicidal behavior the clinician should discontinue OT, refer as appropriate for emergency psychiatric evaluation, and flag the chart.
- Consider notifying law enforcement about suspected criminal behaviors such as prescription fraud or diversion. Consult with counsel prior to doing so to clarify current confidentiality laws and regulations (e.g., VA /military police, risk manager, and/or regional counsel).

6. Carefully document the details of the situation in the clinical record, or not, as advised by risk management and/or legal counsel.

DISCUSSION

The opioid management plan or agreement instituted between the patient and the provider creates a structure to guide and evaluate adherence. 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 should ensure that the patient understood the directions for proper use of opioids and rule out the possibility that serious nonadherence was due to under-medication (pseudoaddiction). 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.

N4. Minor Non-adherence or Medication Misuse

OBJECTIVE

Educate patient, adjust clinical structure and behavioral interventions, and otherwise revise treatment to address relatively minor behavioral problems so that appropriate opioid therapy can be continued.

BACKGROUND

Minor nonadherence behaviors (Level I) are generally those that can be managed in the primary care setting. Once a relatively minor variation in adherence to the treatment plan has been identified, a more structured response to treatment may eliminate the aberrant behaviors, increase compliance with the treatment plan, and improve treatment outcomes.

The decision to continue therapy should rest on the resolution of the immediate issue coupled with implementation of any needed revisions in the treatment plan following discussion with, and agreement by, the patient.

RECOMMENDATIONS

1. Consider adjustment of the initial treatment agreement, with emphasis upon specific adherence issues that have been identified; a more structured approach may be required. Possible responses to minor nonadherence might include:
 - a. Reviewing, discussing, and restating the treatment plan
 - b. Reviewing the written opioid treatment agreement and incorporating any needed revisions
 - c. Recommending consultation with a pain, addictions, or behavior health specialist
 - d. Administration of medications under supervision or with the assistance of others
 - e. Change of medication, medication dose, or amount dispensed
 - f. More frequent clinic contacts (telephonic, physician extenders, or clinic visits)
 - g. Instituting periodic or random urine toxicology screens
2. Consider setting up a grievance procedure with the patient.
3. Consider involving family members or significant others in identifying solutions to non-adherence and in monitoring future adherence when possible. This may include change in the patient's living situation that would provide greater structure (e.g. nursing home, assisted living facility) and might enhance compliance and reduce nonadherence.

DISCUSSION

Minor nonadherence or misuse should result in the prompt review of the treatment agreement, modification of the management plan as indicated, and documentation of these actions. Involvement of the patient's family may be an important strategy in addressing non-adherence. 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 opioid therapy, a diagnosis of "substance dependence" (i.e. prescription opioid dependence) should not be based on the two DSM-IV 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 who exhibit aberrant behaviors associated with possible substance addiction/abuse, consultation with an addiction specialist knowledgeable about the treatment of pain may be helpful. The goal is, not only to more carefully identify opioid abuse or addiction behaviors arising out of the context of opioid therapy for chronic pain, but also to consider whether the patient's addiction/abuse non-adherent behaviors can be reduced or eliminated to allow for continued opioid treatment for chronic pain. Note also that medically undertreated pain may increase the risk for ADRBs.

A grievance procedure with the patient in the event that a disagreement may occur between the patient and the provider about the patient's treatment plan, can be presented either before or during ongoing therapy. The Joint Commission (TJC) has specific recommendations that may be helpful in this regard. The provider may alert the patient representative of the hospital in advance about possible treatment disagreements and other treatment providers about any controversy so that a coordinated approach is used among different providers.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Adjust the treatment plan to include specific adherence issues that have been identified; a more structured approach may be required	Working Group Consensus	III	Poor	I
2	Consult/refer to behavioral health specialist if nonadherent behaviors may be associated with changes in mood or emotional stability	Working Group Consensus	III	Poor	I
3	Set up a grievance procedure with the patient	The Joint Commission Behavioral Health Standards	III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

N5. Moderate Non-Adherence: Persistent Aberrant Behavior, Comorbidities or other Indications for Consultation or Referral for Evaluation and Management

OBJECTIVE

Address moderate (Level II) nonadherence behaviors.

BACKGROUND

Level II nonadherence behaviors are persistent and represent manifestations of serious comorbidities such as history of or co-occurring substance abuse or addiction; psychiatric disorders, such as mood disorders, personality disorder, PTSD, psychosis, or cognitive dysfunction. These behaviors require consultation or co-management with one or more specialists in pain management, mental health, or addictions.

RECOMMENDATIONS

1. Consider consultation with, or referral to, a behavioral health specialist if exacerbation of an underlying psychotic disorder is an issue, if the nonadherent behaviors may be due to changes in mood or increased suicidality, or if there is evidence of increased and poorly controlled anger and tendency to violent behaviors (see Annotation O2).
2. Consider referral to an addiction specialist if the nonadherent behaviors are those associated with possible addiction (see Annotation O1).
3. Patients presenting with persistent or troublesome aberrant behavior who do not respond to intervention by primary care should be referred for evaluation and management of OT to a more structured care environment (e.g., Pharmacy Pain Management Clinic / Opioid Renewal Pain Care Clinic/ Pain Medicine Clinic).
4. If such programs are not available, consider continuing OT with increased frequency of monitoring and screening, performing a comprehensive behavioral assessment, and addressing co-morbidities.

EVIDENCE TABLE

	Recommendation	Sources of Evidence	LE	QE	SR
1	Consider referral to a more structured program: patient with substance abuse history and/or psychiatric comorbidity	Edlund et al., 2007 Wasan et al., 2007 Schieffer et al., 2005 Meghani et al., 2009 Wilsey et al., 2008	II 2	Good	B
2	Referral to structured program: persistent or troublesome aberrant behavior	Edlund et al., 2007 Wasan et al., 2007 Schieffer, Pham, et al., 2005 Meghani et al., 2009 Wilsey et al., 2008	II2	moderate	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

6. CONSULTATION/REFERRAL

O1. Consultation or Referral to *Substance Use Disorder/Addiction Specialty* for Evaluation and Treatment of Non-Adherence Behaviors, or Misuse Suggestive of Addiction to Prescribed Medication, Including Addiction

BACKGROUND

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, borrowing, stealing or selling prescriptions. It is important to emphasize that although they may be associated, addiction behaviors and criminal activities should be clearly distinguished and identified, as there are significantly different implications for the prescriber to consider.

RECOMMENDATIONS

1. Consider consultation or referral to **addiction specialty** for evaluation and treatment in the following conditions:
 - a. Demonstration of behaviors suggesting addiction to prescribed opioids or substance use disorders
 - b. Patients with a significant chronic, or substantiated pain, who develop addiction behaviors in the context of chronic opioid therapy
 - c. Uncontrolled substance use disorder (excluding nicotine)
 - d. Behaviors characteristic of compulsive drug use (addiction) to either opioids or other drugs or alcohol should be referred to an addiction specialty
 - e. Complex conditions who manifest behaviors characteristic of addiction with multiple co-occurring psychiatric disorders
 - f. Need for tapering of opioids or unable to tolerate tapering after discontinuation of OT.
2. Consider consultation with a **SUD specialist** to evaluate the risk of recurrent substance abuse or to assist with ongoing management.
3. Refer patient for psychosocial treatments specific to prescription medication addiction/abuse. These can include addiction counselors comfortable with such topics, and self-help organizations (Pills Anonymous/PA, the National Chronic Pain Outreach association, and other similar organizations).

Table 8: Positive and negative predictors for continuation of OT in patients manifesting addictive behaviors

Positive predictors	Negative predictors
<p>Prior good adherence and motivation with the primary care provider</p> <p>The addiction/abuse behaviors are limited in both severity and number</p> <p>Absence of other pre-existing or concurrent substance abuse/addiction</p> <p>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)</p> <p>Opportunities for improvement exist in the management of the chronic pain; including the use of: (1) non-opioid pharmacotherapy; (2) non-medication physical therapies (i.e. TENS, ultrasound/deep heat, massage, physical therapy); and (3) the provision of psychosocial therapies (i.e. biofeedback, formal relaxation techniques, supportive and cognitive psychotherapy)</p> <p>Patient education by the addiction specialist regarding addiction/abuse behaviors results in significantly improved insight regarding addiction/abuse behaviors and their harm</p> <p>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)</p> <p>A supportive recovery environment (e.g., spouse, partner, family, supervisor) where someone is willing to assist (with patient's consent) in monitoring compliance issues</p>	<p>Prior poor or questionable adherence and motivation with the provider (weak therapeutic relationship)</p> <p>The addiction/abuse behaviors are significant in severity or number</p> <p>Pre-existing or concurrent other substance abuse/addiction</p> <p>Patient unwilling to comply with heightened compliance supervision measures</p> <p>Chronic pain management is already biopsychosocially maximized</p> <p>Patient education by the addiction specialist regarding addiction/abuse behaviors results in only mildly improved insight regarding addiction/abuse behaviors and their harm</p> <p>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</p> <p>An unsupportive recovery environment, including active substance abuse by others in the home</p>

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Consultation/referral to SUD specialty for redirecting addiction behaviors and continue opioid therapy	Dunbar & Katz, 1996 Pappagallo & Heinberg, 1997	I III	Fair	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

02. Consider Consultation or Referral to Specialty Care for Complications, Co-occurring Conditions, or Other Indications

BACKGROUND

Any complications, co-occurring conditions, or other indications requiring consultation or referral should be appropriately addressed according to the nature of the problem and needs of the patient.

Patients on OT should have one designated provider who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe OT, but should coordinate consultation and communication among all clinicians involved in the patient's care.

RECOMMENDATIONS

1. Consider referral to a **Pain Medicine Specialist** in the following situations:
 - a. Patient with complex pain conditions or polytrauma
 - b. Patient with significant medical comorbidities that may negatively impact opioid therapy
 - c. Patient who is unable to tolerate increased pain or physical withdrawal symptoms arising from opioid tapering when OT is being discontinued
 - d. Opioid induced hyperalgesia or opioid tolerance is suspected
 - e. High dose of medication (greater than 200 mg/day morphine equivalent) provides no further improvement in function
 - f. Patient requiring management beyond the expertise of the primary provider
2. Consider Referral to/consultation with a **Behavioral Health Provider** for evaluation and treatment in the following conditions:
 - a. Exacerbation of an underlying psychotic disorder
 - b. Uncontrolled, severe psychiatric disorder or those who are emotionally unstable
 - c. Demonstration of high-risk behaviors suggestive of suicide ideation
 - d. Psychosocial problems or comorbidities that may benefit from disease or case management
 - e. Adverse behavioral or cognitive effects of OT
 - f. Co-occurring trauma related conditions (mTBI, TBI, PTSD)

DISCUSSION

The provider should be aware that there may be patients with psychiatric disorders, including personality disorders, whose conditions may become manifest during therapy. These patients should be referred to the appropriate mental/behavior health clinic if simple strategies ordinarily used by the primary care provider 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, PTSD, personality disorders, substance use/gambling disorders, in panic disorder, and in patients with chronic pain.

Studies show that patients do better when they have continuous access to a clinician who provides comprehensive care for the large majority of their health care needs and who coordinates care when the services of other health care professionals are needed (Chou et al., 2009).

"Having a clinician who accepts primary responsibility for their overall medical care is likely to be particularly important for patients with CNCP, as they use health care services more frequently and have more comorbidities than those without CNCP. US adults with a primary care clinician, rather than a specialist, as their main health care provider had 33% lower costs of care and were 19% less likely to die at a given age compared with a matched cohort, after adjusting for demographic and health characteristics. Having a primary care clinician is a powerful predictor of longevity." (APS/AAPM, 2009)

7. FOLLOW-UP**P. 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. Schedule follow-up visits at least every 2-4 weeks after any change in medication regimen and at least once every 1-6 months for the duration of the therapy (maintenance).
2. Assess at each visit:
 - a. Comfort (degree of analgesia)
 - b. Opioid-related adverse effects
 - c. Functional status (physical and psychosocial)
 - d. Adherence to opioid treatment agreement and other aspects of treatment plan
 - e. Obtain laboratory studies (especially liver or kidney function screens), and/or order drug screens as indicated
 - f. 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.

EVIDENCE TABLE

	Recommendations	Sources of Evidence	LE	QE	SR
1	Evaluate and document comfort, adverse effects, functional status, and aberrant behaviors at each visit	College of Physicians and Surgeons of Ontario (CPSO), 2000	III	Poor	I
2	See the patient every 2-4 weeks after any change in medication regimen, then every 6-8 weeks	College of Physicians and Surgeons of Ontario, 2000	III	Poor	I
3	Request a consultation, as indicated	Working Group Consensus	III	Poor	I
4	Laboratory studies and/or drug screens, as indicated	College of Physicians and Surgeons of Ontario, 2000	III	Poor	I

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

8. Discontinue Opioid Therapy

Q. Indication to Discontinue OT

BACKGROUND

An opioid treatment trial should be discontinued if the goals are not ultimately met, and opioid treatment should be discontinued at any point if adverse effects outweigh benefits or if dangerous or illegal behaviors are demonstrated. At this point, the clinician will have reached the decision to discontinue opioid therapy for one of the following reasons:

- (1) Severe unmanageable adverse effects
- (2) Serious non-adherence to the treatment plan or unsafe behaviors
- (3) Misuse suggestive of addiction to prescribed medication
- (4) Lack of effectiveness of therapy or a desire on the part of the patient to discontinue therapy

The decision to discontinue opioid treatment should ideally be made jointly with the patient and, if appropriate, the family/caregiver. This decision should include careful consideration of the outcomes and ongoing monitoring.

RECOMMENDATIONS

1. Opioid therapy should be tapered off and discontinued if any of the following situations occur:
 - a. The medication fails to show partial analgesia with incremental dose titration
 - b. Trials with different agents provide inadequate analgesia
 - c. There is other evidence that the pain may not be opioid responsive
 - d. Real or potential harms outweigh real or potential benefits
 - e. Patient request.
2. Consider decreasing the opioid dose when pain level decreases in stable patients. (See Annotation X – Tapering)

DISCUSSION

Reviews of open-label follow-up studies have shown that up to 56% of patients abandon the treatment because of lack of analgesic efficacy or side effects (Furlan et al., 2006). Lack of analgesic efficacy may be due to predetermined dose limits, and thus failure of dose titration.

Severe Unmanageable Adverse Effects:

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. *See Annotation N2.*

Evidence of Illegal, criminal, or Unsafe and Dangerous Behavior:

Behaviors that consist of criminal diversion for financial profit require interaction with regulating authorities outside and within the medical system. These behaviors may also occur with active substance abuse or persistent or troublesome aberrant behavior. *See Annotation N3.*

Misuse suggestive of addiction to prescribed medication:

Opioid dependence is a cluster of cognitive, behavioral, and physiological symptoms characterized by repeated self-administration and usually results in opioid tolerance, withdrawal symptoms, and compulsive drug taking, despite negative consequences. While federal regulatory language uses the term "opiate addiction," the diagnostic term opioid dependence is used here for consistency. Opioid dependence may occur with or without the physiological symptoms of tolerance and withdrawal.

Currently, the Food and Drug Administration (FDA) has approved pharmacotherapy for patients diagnosed with opioid dependence. Recent scientific advances have encouraged the use of pharmacologic treatments. Opioid agonist therapy for opioid dependence consists of administering methadone or sublingual buprenorphine, in combination with a comprehensive range of medical, counseling, and rehabilitative services. Opioid therapy is not recommended in the setting of buprenorphine use. A SUD specialist may be better able to evaluate the risks and benefits of continuing opioid therapy in such a situation. See Annotation O2.

R. Is Patient Willing To Engage In Addiction Therapy**BACKGROUND**

Patients manifesting behaviors characteristic of compulsive drug use (addiction) to either opioids, other drugs, or alcohol should be offered referral to an addiction specialist. If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal should be 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 parallel management along with their ongoing pain management.

RECOMMENDATIONS

1. Document, and offer referral to addiction specialty for patients demonstrating behaviors suggesting addiction to prescribed opioids or substance use disorders.
2. Discuss pharmacotherapy options with all patients with opioid and/or alcohol dependence.
3. If there are clearly unsafe or illegal behaviors, opioid prescribing should stop immediately and withdrawal should be addressed.

Case Examples		
	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 day Day 1: 2 tab every 8 hrs Day 2: 2 tab every 12 hrs Day 3: 1.5 tab every 12 hrs Day 5: 1 tab every 12 hrs Day 6: 1/2 tab every 12 hrs Day 7: Discontinue oxycodone/acetaminophen

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

BACKGROUND

The provider may refer to a grievance procedure or treatment agreement if one has previously been discussed with the patient. The Joint Commission has specific recommendations that may be helpful in this regard. In addition, 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. Attempt to 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.
3. Identify and document any co-occurring disorders (CODs) in patients with substance use disorders;
 - a. Psychiatric history, including symptoms and their relation to substance use, current and past diagnoses, treatments and providers
 - b. Infectious diseases (HIV, Hepatitis C, sexually transmitted disease)
 - c. For patients using nicotine offer and recommend tobacco use cessation treatment
 - d. Medical CODs that may be related to or affected by substance use (e.g., diabetes, cardiovascular disease, digestive disorders, skin infections, respiratory disorders, dementia, cerebrovascular disease)
4. Individuals with SUD should be assessed for any significant, unmet psychosocial needs or situational stressors. These include but are not limited to:
 - a. Inadequate or no housing
 - b. Financial difficulties, especially if unable to meet basic needs
 - c. Problematic family relationships or situations (including caregiver burden or domestic violence)
 - d. Poor social support
 - e. Religious and spiritual problems
 - f. Occupational problems
 - g. Difficulties with activities of daily living or instrumental activities of daily living

DISCUSSION

The patient may not understand or agree with the decision to withdraw 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.

T. Discontinue Opioid Therapy; Taper Medication

OBJECTIVE

Maintain patient safety and comfort during the initial phase of opioid abstinence.

BACKGROUND

The decision to discontinue opioid treatment should ideally be made jointly with the patient and, if appropriate, the family/caregiver and needs to include careful consideration of the outcomes. Follow-up after discontinuation should include monitoring and consideration for consultation or referral to help maintain patient safety and comfort during the initial phase of opioid abstinence.

RECOMMENDATIONS

1. Decisions regarding tapering schedule should be made on an individual basis. Sometimes faster or slower tapering may be warranted.
2. For those patients who are at high risk of aberrant behaviors (parasuicidal acts, dealing/selling medications, or those with severe impulse control disorders), tapering opioid in a primary care setting is not appropriate and those patients should be referred to an addiction or pain specialist with expertise dealing with difficult cases.
3. Patients with complicated withdrawal symptoms should be referred to a pain specialist or a center specializing in withdrawal treatment.
4. Patient being tapered due to development of addiction should be referred for SUD treatment. Opioid detoxification in a primary care setting followed by ongoing substance use treatment may be appropriate.

U. 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 choose to stop therapy for elective reasons 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. Since alternate pain management strategies have usually already been exhausted, one may have to acknowledge that the patient is likely to experience increased pain.

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 and verbal 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. Withdrawal management 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.
- Consider using adjuvant agents, such as antidepressants to manage irritability, sleep disturbance, or antiepileptics for neuropathic pain. (Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain. (2007) available at: <http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf>)
- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids. (Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain (2007) available at: <http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf>)

DISCUSSION

Opiate withdrawal can develop within hours of cessation of the drug. While it is not life threatening, in patients without significant comorbidities, 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. In patients with significant comorbidities withdrawal should be medically managed.

According to Mattick & Hall, (1996), medically managed withdrawal 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 tapering 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 use a similar schedule
- Clonidine 0.1 mg twice, or three times daily may be used to control any withdrawal symptoms if there are no contraindications. Supplemental medications will often be required as clonidine will not address all withdrawal symptoms (e.g., muscle and joints aches, nausea, diarrhea, anxiety).
- The patient on fentanyl should be rotated to a different opioid, either long-acting morphine or methadone. Once the patient is converted, the same guidelines will apply.
- Alternately, with the availability of transdermal fentanyl 12 mcg/hr patches, some patients may be tapered down on fentanyl patches and then given a brief supply of oral short acting opioid to complete the taper.

Case Examples for Opioid Tapering

1. Unmanageable 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 morphine
2. Serious Adverse effect	Action		
50 year old male obese patient on morphine controlled-release 30 mg three times per day 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 Educate on withdrawal symptoms Referral for sleep evaluation and possible CPAP. Consider restarting opiate after evaluation and CPAP.	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	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: 80 mg bid Week 3: 60 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% - 50% 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 25%-50% every 3 days Day 1-3 2 every 8 hrs Day 4-7 2 every 12 hrs Day 8-11 1 every 12 hrs Day 12-14 1/2 every 12 hrs Day 14 DC oxycodone/ acetaminophen

V. 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.

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.

9. MANAGEMENT of OT in SPECIAL POPULATIONS**W. OT in Patient with History of Substance Use***RECOMMENDATIONS*

1. Use caution when using opioids in patients with history of substance use disorders. [B]
2. Use an integrated treatment approach addressing both pain [B] and SUD issues with appropriate information sharing. [C]
3. Patients on opioid agonist therapy for DSM-IV diagnosis of opioid dependence who have a co-occurring chronic pain disorder should be treated for pain considering the following options:
 - a. Use non-pharmacologic interventions
 - b. Use other non-opioid pharmacologic treatment modalities
 - c. Cautious use of opioid therapy by using another opioid agonist with slow titration and careful communication with the SUD opioid agonist therapy prescribers. [B]
4. Perform urine drug testing as an adjunctive tool at regular intervals. [B]

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	History of substance abuse is associated with opioid misuse	Schieffer et al., 2005	II-2	Good	B
2	A substantial number of patients do not take opioid medications as prescribed	Atluri & Sudarshan, 2003	II-1	Good	B
3	Acute pain can be managed in patients receiving chronic opioid agonist therapy	Alford et al., 2006	III	Poor	I
4	Chronic pain can be managed in patients receiving chronic opioid agonist therapy	Clark et al., 2008	III	Poor	I
5	Persons with concurrent chronic pain, SUD, and a history of SUD benefit from an integrated treatment model of pain management and relapse prevention	Currie et al., 2003	II-1	Good	B
6	Patients who are focused on; opioids, opioid overuse, other substance use, nonfunctional status, unclear etiology of pain, exaggeration of pain, legal problems, and mood swings have a tendency to misuse in chronic opioid therapy	Akbik et al., 2006 Atluri et al., 2004	II-1	Good	B

LE=Level of Evidence; QE = Quality of Evidence; SR = Strength of Recommendation (See Appendix A)

Management of buprenorphine-treated patients transferred from another provider:

1. Management of OT in patients on sublingual (SL) buprenorphine (with or without naloxone) for DSM-IV diagnosis of opioid dependence:
 - a. SL buprenorphine is FDA-approved for treatment of opioid dependence and can only be prescribed by a qualified and DEA-waivered physician for this purpose
 - b. Patients on SL buprenorphine should not receive full agonist opioids concomitantly for routine pain control
 - c. Nonopioid and nonpharmacologic strategies for pain management should be maximized

- d. In the event of anticipated pain (i.e., an elective procedure or surgery) SL buprenorphine should be stopped for 48 hours before the scheduled event
- e. For unanticipated pain (trauma, emergency surgery or procedure) the care team managing the acute pain should be notified that the patient is prescribed SL buprenorphine and when the last dose was taken.

DISCUSSION

SL buprenorphine is not FDA approved for pain management. In the event that a patient transfers care and requests to be continued on SL buprenorphine that was prescribed for pain by another provider, the recommendations for comprehensive assessment (see Annotation B) should be followed. In addition, permission should be obtained from the patient to speak with the provider who has been prescribing SL buprenorphine. If it is determined that the patient was receiving SL buprenorphine for addiction, the patient should be referred to an appropriately DEA-waivered Buprenorphine certified physician for further Buprenorphine treatment. If SL buprenorphine was being prescribed solely for pain, then an opioid rotation to a full-agonist opioid should be undertaken if opioid therapy is indicated. It is recommended that SL buprenorphine be stopped for 24 hours before a full-agonist opioid is started.

REFERENCE:

Clinical Guidelines for the use of buprenorphine in the treatment of opioid addiction. TIP 40. (2004) US Department of health and Human Services, Substance Abuse and Mental health Services Administration Center for Substance Abuse Treatment. Laura McNicholas, MD chair of consensus panel

X. OT and Risk for Sleep Apnea

BACKGROUND

OT is implicated in inducing central sleep apnea, ataxic breathing, and hypoxic / apneic episodes, and worsening sleep fragmentation. Daytime sleepiness may indicate severe sleep-disordered breathing or concurrent depression. Sleep-disordered breathing shows a dose-related effect and is more prevalent in patients taking daily morphine-equivalent doses of about 200 mg or higher; however, it may be prevalent at lower doses as well.

RECOMMENDATIONS

1. Be vigilant for sleep apnea during OT. If clinical suspicion exists for the presence of sleep apnea in a patient on OT, sleep study should be considered. [B].
2. Patients on OT who present with sleep disorder confirmed by a sleep study should be assessed for the appropriateness of continuing OT and should be evaluated for the risks (based on the severity of the sleep-disordered breathing) versus benefits of OT. If OT is continued, it should be titrated cautiously. Patients found to have sleep-disordered breathing should be followed with a repeated sleep study. [C]
3. Patient with abnormal sleep study should be educated about the significant additional risks including breathing disruption, and instructed to avoid alcohol, or any CNS-depressant medication. [A]
4. The type of sleep apnea should be evaluated to determine if it is obstructive or central. CPAP may worsen central sleep apnea. [D]
5. Patients with sleep apnea who are on OT may benefit from a reduction in the dose of their opioids.
6. Discontinuation of opioid therapy should be considered if the sleep apnea is severe or life threatening.

7. Consider more careful monitoring of OT in patients treated with methadone and/or benzodiazepines. [B]

DISCUSSION

In an observational study of 140 chronic pain patients on opioid therapy who received overnight polysomnographies regardless of whether they showed symptoms of sleep apnea, sleep-disordered breathing (i.e., apnea-hypopnea index ≥ 5 per hour) was common, occurring in 75% of patients (25% had no sleep apnea). Of those with sleep-disordered breathing, 39% had obstructive sleep apnea, 24% had central sleep apnea, 8% had both central and obstructive sleep apnea, and 4% had sleep apnea of indeterminate type. A relationship was observed between the central apnea index and methadone dose as well as with benzodiazepines (Webster, et al., 2008). More studies are needed to further evaluate risk factors and mechanisms for opioid-related sleep disordered breathing.

In a retrospective case series of 98 consecutive patients on OT sent for sleep studies regardless of whether they had symptoms of sleep apnea, 36% had obstructive sleep apnea (OSA), 24% had central sleep apnea (CSA), 21% had combined obstructive and central sleep apnea, 4% indeterminate, and 15% were negative (Mogri et al., 2009). Of 83 patients, 45 (54.2%) had sleep related hypoxemia. Hypoxemia during wakefulness was seen in 10% of patients, and hypoxemia during sleep not clearly associated with apneas/hypopneas was seen in 8% of patients. Sleep-related hypoxemia, in the absence of sleep apnea, or hypoxemia during wakefulness was observed in two patients (2%, 95% CI 0-7%). The results of this study suggested that patients on OT might be at risk of hypoxemia during quiet wakefulness with or without sleep apnea.

In a small case series of 6 patients who were on morphine-equivalent doses of 120–420 mg/day and were referred for sleep studies because of excessive daytime sleepiness, all patients had abnormal apnea-hypopnea indices, ranging from 28.4–106 per hour (Alattar & Scharf, 2009). Bilevel treatment of CSA corrected nocturnal hypoxemia and reduced sleep fragmentation. These treatment results require confirmation in randomized controlled trials.

In another small case report, Mogri et al., (2008) described three cases of patients who were using sustained release opioids for chronic non-malignant pain. These individuals had normal sleep studies at the beginning of the evening then developed severe central sleep apnea after the ingestion of a single dose of opioids during the night for their pain symptoms. The authors concluded that, “short-term ingestion of opioid analgesics can precipitate central sleep apnea in patients with chronic pain receiving long-term opiate therapy who otherwise show no evidence of central sleep apnea.”

In a case report, a 41-year-old on long-acting opioid therapy was diagnosed with moderate obstructive sleep apnea. On initiation of CPAP, she manifested severe central sleep apnea that was unresponsive to supplemental oxygen and interfered with CPAP titration. (Glidewell, 2009).

In a case study of 5 patients, Javaheri et al., (2008) reported that with CPAP administration their average apnea-hypopnea index improved, however their central apnea index increased from 26 to 37/hour. These patients were then successfully trialed on servoventilation. The authors stated, “treatment with CPAP eliminates obstructive apneas but increases central apneas.”

Sleep apnea has also been observed in patients on methadone for opioid addiction. In one study of 50 stable patients on methadone maintenance therapy, 30% had central sleep apnea, with 12% of the variance explainable by methadone blood concentration (Wang et al., 2005).

EVIDENCE TABLE

	Evidence	Source	LE	QE	SR
1	Patients on OT or methadone maintenance therapy (MMT) are at risk of developing central and obstructive sleep apnea	Wang et al., 2005 (MMT) Alattar & Scharf, 2009 (OT) Webster et al., 2008 (OT)	I III II-3	Good	A
2	Patients on chronic opioid therapy may be at risk of hypoxemia with or without sleep apnea	Mogri et al., 2009 (OT)	II-3	Good	B
3	Patients on opioid therapy may be at risk of central sleep apnea	Mogri et al., 2008 Glidewell, 2009 Javaheri et al., 2008			
4	Consider more careful monitoring in OT patients treated with methadone or benzodiazepines	Webster et al., 2008	II-3	Fair	B
5	Daytime sleepiness and fatigue in OT patients is suggestive of sleep disorder (Central Apnea or apnea) or depression	Wang et al., 2008 Walker & Farney, 2009	II III	Fair	B
6	Co-morbidities, such as cardiovascular disease, pulmonary disease, obesity, neuromuscular disorders may increase the likelihood of developing sleep apnea in patients treated with OT.	Webster et al., 2008	II	Good	B

LE = Level of evidence; QE = quality of the evidence; SR = strength of recommendation see Appendix A

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Appendix A: Guideline Development Process

The update of the VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain was developed following the steps described in "Guideline for Guidelines," an internal working document of the VA/DoD Evidence Based Practice Working Group, that requires an ongoing review of guideline works in progress.

The Offices of Quality and Performance and Patient Care Services of the VA, the U.S. Deputy Assistant Under-Secretary for Health, and the Army Medical Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD to form the Opioid Therapy (OT) for Chronic Pain Working Group (WG). For this guideline these WG participants were drawn from the fields of primary care, pain management, physical medicine (PM&R), anesthesiology, internal medicine, rheumatology, neurology, psychiatry, psychology, pharmacy, nursing, social work, and addiction specialists from diverse geographic regions, and both VA and DoD health care systems.

The WG participated in two face-to-face meetings to reach consensus about the guideline algorithm and recommendations and to prepare a draft update document. The draft continued to be revised by the Working Group through numerous conference calls and individual contributions to the document.

Recommendations for the performance or inclusion of specific procedures or services were derived through a rigorous methodological approach that included the following:

- Determining appropriate criteria such as effectiveness, efficacy, population benefit, or patient satisfaction
- Reviewing literature to determine the strength of the evidence in relation to these criteria
- Formulating the recommendations and grading the level of evidence supporting the recommendation

The WG developed a set of researchable questions within the focus area of the guideline and identified associated key terms after orientation to the guideline scope and to goals that had been identified. This ensured that the guideline development work outside of meetings focused on issues that practitioners considered important and produced criteria for the literature search and selection of included studies that formed the body of evidence for this guideline update.

An initial global literature search identified a few comprehensive systematic reviews (SRs) that employed a rigorous and methodical search for evidence on the key questions related to OT in adults. The WG decided to adopt the results of these systematic reviews and to focus the additional searches on topics that were not addressed by the published SRs. Therefore, the Search Questions developed by the WG were divided into two (2) categories. First were comprehensive (full) searches of topic areas that had either not been addressed in the previous version of this guideline or had been included but not fully developed. The search for these questions covered the period since the last VA/DoD CPG (2002 through 2009). The second group was limited (update) searches on topics which had been adequately addressed by the published SR of APS/AAPM, (2009) and for which new research findings were probable. The updating search for these questions covered the periods from June 2008 to March 2009.

Generally speaking, full searches were conducted on specific topics concerning potential adverse effects and their management, sub-populations with higher risk of harm caused by OT, and specific interventions involved in providing an opioid therapy trial. These included:

- Risks and benefits of OT for patients with sleep apnea, cardiac disease, substance use disorder and suicidal potential

- Approaches to addressing common adverse effects
- Breakthrough pain in non-cancer versus cancer, pre-medication
- Benefits & harms of OT in patients with comorbidities (e.g., TBI, PTSD)
- Enhancements of care and Care Models

Limited (update) Searches were conducted on:

- Risks & benefits of OT for patients with SUD
- Patient education
- Treatment and consent agreements
- Aberrant behavior: evaluation, predictors, and treatment
- Discontinuing or tapering OT
- Breakthrough pain; acute exacerbations or new acute pain
- Long acting opioids

All questions specified (adapted from the Evidence-Based Medicine toolbox, Center for Evidence-Based Medicine, [<http://www.cebm.net>]):

- Population – Characteristics of the target patient population
- Intervention – Exposure, diagnostic, or prognosis
- Comparison – Intervention, exposure, or control used for comparison
- Outcome – Outcomes of Interest

These specifications served as the preliminary criteria for selecting studies. See *PICO Questions to Guide Literature Search (page 101)* for a complete listing and categorization of the questions.

Selection of Evidence

The evidence selection process was designed to identify the best available evidence to address each key question and ensure maximum coverage of studies at the top of the hierarchy of study types. Published, peer-reviewed RCTs, as well as meta-analyses and systematic reviews that included randomized controlled studies, were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, most scientifically sound basis for judging comparative efficacy. The WG made this decision while recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and AHRQ systematic evidence reports.

In addition to Medline/PubMed, the following databases were searched: Cinahl/Medline/Embase/PsycINFO (OVID), Database of Abstracts of Reviews of Effectiveness (DARE), and Cochrane Central Register of Controlled Trials. For Medline/PubMed searches, limits were set for language (English), and type of research (RCT, systematic reviews and meta-analysis). For prognostic and diagnostic questions (e.g., does test improve outcome?); cohort or other prospective non-RCT designs were considered.

The following inclusion criteria were used to select the articles identified in the literature search for possible inclusion:

- Published in United States, United Kingdom, Europe, Australia, Japan, New Zealand
- Full articles only published in English
- Study populations: age limited to adults 18 years of age or older; all races, ethnicities, and cultural groups

Since the initial global search revealed only a limited number of randomized trials, the inclusion criteria were expanded to include prospective trials, cohort studies and in some cases, where these were not available, also epidemiologic and observational studies.

Preparation of Evidence Tables (Reports) and Evidence Rating

The results of the searches were organized in evidence reports, and copies of the original studies were provided to the WG for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the VA and DoD health care systems.

Recommendation and Quality Rating

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research.

A group of research analysts read and coded each article that met inclusion criteria. The articles were assessed for methodological rigor and clinical importance. Clinical experts from the VA and DoD WG reviewed the results and evaluated the strength of the evidence, considering quality of the body of evidence (made up of the individual studies) and the significance of the net benefit (potential benefit minus possible harm) for each intervention.

The overall strength of each body of evidence that addresses a particular Key Question was assessed using methods adapted from the U.S. Preventive Services Task Force (Harris, 2001). To assign an overall quality [QE] (see Table A-2) of the evidence (good, fair, or poor), the number, quality, and size of the studies; consistency of results between studies; and directness of the evidence were considered. Consistent results from a number of higher-quality studies [LE] (see Table A-1) across a broad range of populations; supports with a high degree of certainty that the results of the studies are true and therefore the entire body of evidence would be considered “good” quality. A “fair” quality was assigned to the body of evidence indicating that the results could be due to true effects or to biases present across some or all of the studies. For a “poor” quality body of evidence, any conclusion is uncertain due to serious methodological shortcomings, sparse data, or inconsistent results.

The Strength of Recommendation [SR] was then determined based on the Quality of the Evidence [QE], and the clinical significance of the net benefit [NE] (see Table A-3) for each intervention, as demonstrated by the body of evidence. Thus, the grade (i.e., A, B, C, D or I) assigned to guideline recommendations reflect both variables; the Quality of the evidence and the potential clinical benefit that the intervention may provide to patients (see Table A4).

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, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality [QE]	
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 A-3: Net Effect of the Intervention [NE]	
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 at 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 A-4: Final Grade of Recommendation [SR]				
	<i>The net benefit of the intervention</i>			
<i>Quality of Evidence</i>	Substantial	Moderate	Small	Zero or Negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Strength of Recommendation Rating [SR]

A	A strong recommendation that the clinicians provide the intervention to eligible patients. <i>Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</i>
B	A recommendation that clinicians provide (the service) to eligible patients. <i>At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</i>
C	No recommendation for or against the routine provision of the Intervention is made. <i>At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. <i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. <i>Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</i>

Lack of Evidence – Consensus of Experts

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group.

This update of the OT Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, and academia, as well as guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in Appendix H.

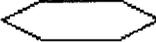
Algorithm Format

The clinical algorithm incorporates the information presented in the guideline in a format which maximally facilitates clinical decision-making. The use of the algorithmic format was chosen because of evidence showing that such a format improves data collection, diagnostic and therapeutic decision-making, and changes patterns of resource use.

The algorithmic format allows the provider 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 (Society for Medical Decision-Making Committee, 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. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

REFERENCES

- Agency for Health Care Policy and Research (AHCPR). Manual for conducting systematic review. August 1996. Prepared by Steven H. Woolf.
- Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force, Current methods of the U.S. Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001 Apr;20(3 Suppl):21-35. Available at; <http://www.ahrq.gov/clinic/ajpmsuppl/harris1.htm>
- Society for Medical Decision-Making Committee (SMDMC). Proposal for clinical algorithm standards, SMDMC on Standardization of Clinical Algorithms. *Med Decis Making* 1992 Apr-Jun; 12(2):149-54.
- United States Preventive Service Task Force (USPSTF). Guide to clinical preventive services. 2nd edition. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1996.
- Woolf SH. Practice guidelines, a new reality in medicine II; Methods of developing guidelines. *Arch Intern Med* 1992 May; 152(5):946-52.

Opioid Therapy – PICO Questions to guide literature search

Q #	Population	Intervention	Comparison	Outcome
1	Patient with chronic pain AND respiratory disorders	Use of OT	Alternative pain control	Increased harm, mortality
2	Patient with chronic pain	Use of OT	Alternative pain control	Increase risk for sleep disorders
3	Patient with chronic pain AND cardiac disease	Use of OT, methadone	Alternative pain control	Increase harm , mortality
4	Patient with chronic pain W or w/o Comorbidity of major mental illnesses	Use of OT	Alternative pain control	Increase risk for suicide attempt
5	Patient with chronic pain who are at high risk for suicide	Use of OT	Alternative pain control	Increase risk for suicide attempt
6	Patient on chronic pain with adverse effects: a. constipation b. Low testosterone /prolactin c. Immune system dysfunction d. Lower vitamin D e. Sedation/delirium f. Osteoporosis	Strategies for minimizing AE		Better outcome and control of AE
7	Patients with noncancer chronic pain on OT with acute exacerbation	Use of breakthrough medication	Patients with cancer chronic pain on OT with acute exacerbation	Better pain control and adverse effects
8	Patients on OT with acute exacerbation	Use of prophylactic dose of meds	Use of breakthrough medication dosage	Better pain control and adverse effects
12	Patient with Chronic pain and	OT	No OT	Improve outcome and decrease harm
13	Management of OT	Modified care model	Usual Primary care	Improve outcomes and minimize AE, aberrant behaviors

APPENDIX B: Urine Drug Test

Table B1: Length of Time Drugs of Abuse Can Be Detected in Urine

Drug	Time
Alcohol	7-12 h
Amphetamine	48 h
Methamphetamine	48 h
Barbiturate	
Short-acting (eg, pentobarbital)	24 h
Long-acting (eg, phenobarbital)	3 wk
Benzodiazepine	
Short-acting (eg, lorazepam)	3 d
Long-acting (eg, diazepam)	30 d
Cocaine metabolites	2-4 d
Marijuana	
Single use	3 d
Moderate use (4 times/wk)	5-7 d
Daily use	10-15 d
Long-term heavy smoker	>30 d
Opioids	
Codeine	48 h
Heroin (morphine)	48 h
Hydromorphone	2-4 d
Methadone	3 d
Morphine	48-72 h
Oxycodone	2-4 d
Propoxyphene	6-48 h
Phencyclidine	8 d

Sources:

- Moeller K, Lee K, Kissack J. Urine Drug Screening: Practical Guide for Clinicians. *Mayo Clin Proc* January 2008;83(1):66-76
- Inaba DS, Cohen WE. *Uppers, Downers, All Arounders: Physical and Mental Effects of Psychoactive Drugs*. 5th ed. Ashland, OR: CNS Publications, Inc; 2004.
- Woelfel JA. Drug abuse urine tests: false-positive results. *Pharmacist Lett/Prescribers Lett*. 2005;21(3):210-314.
- Council on Scientific Affairs. Scientific issues in drug testing. *JAMA*. 1987;257(22):3110-3114.
- Heit HA, Gourlay DL. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27(3):260-267.
- Rosse RB, Deutsch LH, Deutsch SI. Medical assessment and laboratory testing in psychiatry. In: Sadock BJ, Sadock VA, eds. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry*. Vol 1. 7th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2000;732-755.
- Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monit*. 2004;26(2):200-205.

APPENDIX C: Sample Opioid Pain Care Agreement

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 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 for the treatment of my chronic pain. Regular follow-up care is required and only my provider will prescribe these medications for my chronic pain 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 if requested to do so.
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 may not prescribe extra medication for me. I may 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, medications not prescribed for me (tranquilizers), and all illicit drugs.
9. I agree to periodic unscheduled drug screens.
10. I understand that I may become physically 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.
13. My providers may obtain information from State controlled substances databases and other prescription monitoring programs.

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.deaiversion.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.

REFERENCES:

DEA Briefs and Background, Drug Policy, Controlled Substances Act. (2002) Available at <http://www.usdoj.gov/dea/pubs/csa.html>.

DEA Drug Scheduling. (2002) Available at <http://www.usdoj.gov/dea/pubs/scheduling.html>.

Department of Justice, Drug Enforcement Administration, Diversion Control Program Website. Available at <http://www.deadiversion.usdoj.gov/>.

Department of Veterans Affairs, Veterans Health Administration. VHA Handbook 1108.1: Controlled Substances (Pharmacy Stock). May 16, 1997. Washington, DC. Available at <http://www.va.gov/publ/direc/health/handbook/1108-1.htm>

APPENDIX E:
Drug Tables

Table E 1: Use of Short-acting, Orally Administered Opioids in Adults

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 ¹	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 ²). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown.
Oxymorphone	10 to 20 mg q 4 to 6 h (may start at 5 mg to improve tolerabilit y)	Individually titrate as needed and tolerated	34 to 45 — 4	Elderly or debilitated – use with caution and start at low end of dosing range; levels are increased 40% in patients ≥ 65 yr old Hepatic dysfunction – <i>Mild</i> hepatic impairment: use cautiously, start at low end of dosing range, and titrate slowly. <i>Moderate and Severe</i> hepatic impairment: contraindicated. Renal dysfunction – bioavailability is increased 57%– 65% in moderate and severe impairment; start at lower doses and titrate slowly.	Must be taken on an empty stomach at least 1 hour before or 2 hours after a meal. Food has been shown to increase peak levels of oxymorphone immediate- release by 38%. Must NOT be taken concomitantly with alcohol. Alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% with extended-release oxymorphone.

Short-Acting Opioid [†]	Initial Oral Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (h)	Dosing in Special Populations	Other Considerations
Propoxyphene (alone or in combination with APAP)	HCl: 65 mg q 6 to 8 hours Napsylate: 100 mg q 6 to 8 hours	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/day APAP; 2000 mg/day 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; half-life of propoxyphene and noproxyphene 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 noproxyphene 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. Warning: Avoid propoxyphene in patients who are suicidal or addiction prone. Many propoxyphene-related fatalities involved patients with histories of emotional disturbances, suicidal ideation / attempts, and misuse of tranquilizers, alcohol, and other CNS-active drugs.
Tapentadol	50 mg q4–6 hours	Subsequent dose is 50, 75, or 100 mg q4–6h, adjusted to analgesia and tolerability. Second dose may be given 1 h after the first dose if necessary. Max recommended dose: 700 mg on first day, 600 mg on subsequent days.	— 60 4 to 6	Elderly – Consider starting at the lower end of recommended doses. Hepatic dysfunction – <i>Mild hepatic impairment:</i> No dosage adjustment. <i>Moderate hepatic impairment:</i> Start at 50 mg and give subsequent doses at least 8 h apart (max. 3 doses in 24 h). <i>Severe hepatic impairment:</i> Use is not recommended. Renal dysfunction – Not recommended in severe renal impairment. No dosage adjustment for mild or moderate renal impairment. Respiratory dysfunction – Use with caution because of respiratory depressant effects; consider non-mu-opioid agonist analgesics; use tapentadol only under careful medical supervision at lowest effective dose	If used in combination with other CNS depressants, consider dose reduction of one or both agents. Use caution in patients taking serotonergic agents or use alternative agent.

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 every morning	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 Dose carefully or use another agent in patients on serotonergic agents

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, Percocan and Zydone package inserts (2001)^{6,7,8}; Purdue, MSIR package insert (2001)⁹ and OxyIR package insert (2000)^{9,10}; Michalek (1998)¹¹; Davis and Homs (2001)¹²
APAP = Acetaminophen; ASA = Aspirin (acetylsalicylic acid); IBU = Ibuprofen; MAOI = Monoamine oxidase inhibitor

† Check local formulary for available formulations.
‡ CYP-2D6 Inhibiting Drugs: *Antihistamines* (amiodarone, propafenone, quinidine [strong inhibitor]; *analgesics* (methadone [weak inhibitor], propoxyphene); *anticholinergics* (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); *histamine₂ receptor antagonists* (cimetidine); *neuroleptics* (chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine); *protease inhibitors* (ritonavir), *quinine compounds* (hydroxychloroquine, quinine, quinidine), *selective serotonin reuptake inhibitors* (fluoxetine, fluvoxamine, paroxetine, sertraline), and *miscellaneous compounds* (clomipramine, ketoconazole, ticlopidine).

Table E 2: Use of Long-acting Opioids in Adults

Long-Acting Opioid †	Initial Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (h)	Dosing In Special Populations	Other Considerations
Fentanyl Transdermal System	<p>25 mcg/h transdermally. q 72 h</p> <p>CONTRAINDICATED in non-opioid-tolerant patients</p> <p>12 mcg/h dose has not been evaluated as an initial dose</p>	<p>Increments should be based on supplemental opioid doses, using a ratio of 12 mcg/h t.d. fentanyl for every 45 mg/24 h of supplemental oral morphine equivalent</p> <p>Make increments at least 3 d after initial dose then not more often than q 6 d thereafter as necessary</p>	<p>12 to 18 (h) 24 to 72 (h) 48 to 72</p>	<p>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 transdermal fentanyl is unknown; use reduced dose</p> <p>Hepatic / Renal dysfunction – Insufficient information; use with caution</p> <p>Patients with fever– increased body temperature may increase release of fentanyl from the transdermal system; monitor patients for opioid adverse effects and modify dosage as necessary</p>	<p>Consider t.d. fentanyl in patients with persistent, moderate to severe pain who cannot take oral long-acting morphine and methadone. T.d. fentanyl should ONLY be used in patients who are already receiving opioid therapy, are opioid-tolerant, and require a daily dose at least equivalent to fentanyl 25 mcg/h.</p> <p>Patients considered opioid-tolerant are those who have been taking, for a week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.</p> <p>Avoid application of external heat sources (e.g., heating pads, electric blankets, heat lamps, saunas, hot tubs, hot baths, sunbathing, or heated water beds) to the application site while the patch is worn as heat may increase release of fentanyl from the t.d. system; monitor for opioid adverse effects and adjust dosage as necessary.</p> <p>Use extreme caution and frequent monitoring in patients receiving t.d. fentanyl and any CYP 3A4 inhibitor. §</p> <p>The use of transdermal fentanyl entails special safety considerations. All prescribers of t.d. fentanyl should be thoroughly familiar with the product's prescribing information. Patients must receive a copy of the Medication Guide.</p>

Long-Acting Opioid †	Initial Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (H)	Dosing in Special Populations	Other Considerations
Methadone	<p>2.5 to 10 mg orally, q 8 to 12 h</p> <p>More frequent administration (q 6 h) may be necessary during initiation to maintain analgesia—use extreme caution to avoid overdosage due to long plasma half-life</p>	<p>Increments of 2.5 mg q 8 h may be made every 5 to 7 days</p> <p>START LOW AND GO SLOW</p>	<p>30 to 60 —</p> <p>4 to 12</p> <p>Analgesic duration increases with continued use and cumulative effects</p>	<p>Elderly or debilitated—reduce dosage; in elderly, clearance may be decreased</p> <p>Hepatic dysfunction – in patients with stable chronic liver disease or mild to moderate hepatic dysfunction, no dosage adjustments required</p> <p>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</p>	<p>Recommended first- or second-line long-acting agent, but prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone</p> <p>Plasma half-life (22 to 128 h short-term; 24 to 48 h at steady-state) may be longer than the analgesic duration</p> <p>Methadone has little cross-tolerance with other opioids; therefore, even patients with a high degree of opioid tolerance may be at risk for overdose when switched to methadone</p> <p>Monitor patients extra carefully during initiation, conversions to and from other opioids, and dose titration</p> <p>Delayed analgesia or toxicity may occur because of drug accumulation after repeated doses, e.g., on days 2 to 5; if patient has excessive sedation during this timeframe, consider temporarily holding dose(s), lowering the dose, and/or slowing the titration rate</p> <p>Once a stable analgesic dose is reached, the dosing interval may be extended to q 8 to 12 h or longer</p> <p>SHOULD NOT BE USED FOR AS-NEEDED (P.R.N.) SUPPLEMENTAL OPIOID THERAPY</p> <p>The only long-acting opioid available as an oral solution</p> <p>For dosing recommendations in patients previously exposed to opioids, see Methadone Dosing Recommendations for Treatment of Chronic Pain</p> <p>Urinary excretion decreases and elimination half-life increases when urinary pH exceeds 6</p> <p>May prolong QTc intervals on ECG; Risk-of torsades de pointes</p>

Long-Acting Opioid †	Initial Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (h)	Dosing in Special Populations	Other Considerations
Morphine Controlled Release (CR) / Sustained Release (SR) and Extended Release (ER)	15 mg q 8 to 12 h (CR / SR) to 30 mg q 24 h (ER)	Total daily increments of < 30 to 40 mg/d may be made q 2 d	30 to 60 30 to 60 Varies by product, overall range is 8 to 24	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 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 orally 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 ³). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown

Long-Acting Opioid †	Initial Dosage	Dosage Titration	Analgesic Onset (Min) Peak (Min) Duration (h)	Dosing in Special Populations	Other Considerations
Oxycodone Extended Release	5 mg orally every 12 h	May increase by 5 to 10 mg every 12 h every 3-7 days	— 1 (fasted state) —	Elderly (≥ 65 years old) and debilitated: Levels are about 40% higher in elderly vs. younger subjects. Use caution, starting at the low end of dosing range and titrating slowly. Renal dysfunction: Bioavailability is increased by 57% in moderate impairment and by 65% in severe impairment. In patients with creatinine clearance (CrCl) rate less than 50 mL/min, oxycodone should be started with the lowest dose and titrated slowly Hepatic dysfunction: Contraindicated in patients with moderate or severe hepatic impairment (bioavailability is substantially increased). Use caution in patients with mild hepatic impairment, starting with lowest dose and titrating slowly.	Must be taken on an empty stomach at least 1 hour before or 2 hours after a meal. Food has been shown to increase peak levels of oxycodone ER by 50%. Must NOT be taken concomitantly with alcohol. Alcohol (240 ml of 4% to 40% ethanol) can cause highly variable effects on peak drug levels, ranging from a decrease of 50% to an increase of 270% with ER oxycodone.
Tramadol ER	100 mg once daily If converting from tramadol IR, start at 24-h dosage equivalent rounded down to closest 100-mg increment	Increase by 100 mg every 5 days based on analgesia and tolerability. Max dose: 300 mg/day	— 12 h 24 h	Elderly > 65 years: use caution, usually starting at low end of dosing range; use even greater caution in patients > 75 years. Hepatic dysfunction: Should not be used in severe hepatic impairment (Child-Pugh Class C) Renal dysfunction: Should not be used if CrCl less than 30 ml/min.	Must be swallowed whole and must not be chewed, crushed, or split.

P.O. = Per Os (orally); t.d. = Transdermally

† Check local formulary for available formulations.

‡ CYP-2D6 Inhibiting Drugs: Antiarrhythmics (amiodarone, propafenone, quinidine [strong inhibitor], propoxyphene); antihistamines (diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro]); histamine2 receptor antagonists (cimetidine); neuroleptics (chlorpromazine, haloperidol, methothimeprazine, perphenazine, thioridazine); protease inhibitors (ritonavir), quinone compounds (hydroxychloroquine, quinacrine, quinine); selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline), and miscellaneous compounds (clomipramine, ketoconazole, ticlopidine).

§ CYP-3A4 Inhibiting Drugs: Ritonavir, ketoconazole, itraconazole, troleanomycin, clarithromycin, nefinavir, nefazodone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil

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



Table E 3: OPIOID Formulations

Generic name	ORAL				Transmucosal	Buccal	Rectal	Transdermal
	IR	12h (SR/CR)	24h (ER)	OS				
Codeine/APAP, ASA	x			x				
Codeine	x							
Fentanyl								x
Fentanyl citrate					x			
Hydrocodone /APAP	x			x				
Hydromorphone	x			x			x	
Methadone	x			x				
Morphine	x	x	x	x			x	
Oxycodone	x	x		x				
Oxycodone / APAP, ASA, IBU	x			x				
Oxymorphone	x	x						
Propoxyphene	x							
Propoxyphene / APAP	x							
Tramadol	x		x					
Tramadol / APAP	x							

IR = immediate release; SR = sustained release; CR = controlled release; ER = extended release; OS = oral solution

Table E 4: Black Box Warnings, Contraindications, and Other Considerations (also see drug interactions table)

Medication	Black Box Warnings, Contraindications, and Other Considerations
Codeine	<p>Contraindications</p> <ul style="list-style-type: none"> • Respiratory depression • Acute or severe bronchial asthma or hypercarbia • Paralytic ileus • Hypersensitivity to codeine or any component <p>Other Considerations</p> <ul style="list-style-type: none"> • Caution postoperatively and in: <ul style="list-style-type: none"> ○ Elderly or debilitated patients ○ Patients with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression ○ Chronic obstructive pulmonary disease or cor pulmonale ○ Severe hepatic or renal dysfunction ○ Hypothyroidism or Addison's disease ○ Prostatic hypertrophy or urethral stricture ○ CNS depression, acute alcoholism, or delirium tremens ○ Pancreatic/biliary tract disease • May induce or aggravate seizures. • Ultra-rapid CYP 2D6 metabolizers may convert codeine into morphine more rapidly and completely than others, resulting in higher than expected serum morphine levels and possible overdose symptoms. Prevalence estimated at 0.5 to 1% in Chinese and Japanese, 0.5% to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. • May cause elevated plasma amylase and lipase due to spasm of sphincter of Oddi

Medication	Black Box Warnings, Contraindications, and Other Considerations
Fentanyl transdermal	<p data-bbox="280 352 305 541">Black Box Warnings</p> <ul style="list-style-type: none"> <li data-bbox="321 352 345 730">• High content of fentanyl in the patches may be a particular target for abuse and diversion. <li data-bbox="362 352 459 730">• Indicated for management of persistent, moderate to severe chronic pain that requires continuous, around-the-clock opioid administration for an extended period of time, and cannot be managed by other means. Use only in patients who are already receiving opioid therapy, have demonstrated opioid tolerance, and require a total daily dose at least equivalent to fentanyl transdermal system 25 mcg/hour. Use in non-opioid tolerant patients may lead to fatal respiratory depression. <li data-bbox="475 352 524 730">• Peak fentanyl levels between 24 and 72 hours; serious or life-threatening hypoventilation may occur, even in opioid-tolerant patients, during the initial application period. <li data-bbox="540 352 581 730">• Overestimating dose when converting patients from another opioid medication can result in fatal overdose with the first dose. Patients thought to have had a serious adverse event, including overdose, require monitoring and treatment for at least 24 hours. <li data-bbox="597 352 621 730">• Administer to children only if opioid tolerant and 2 years of age or older. <li data-bbox="638 352 678 730">• Concomitant use with CYP 3A4 inhibitors may increase plasma concentrations, increase or prolong adverse drug effects, and cause potentially fatal respiratory depression. <li data-bbox="695 352 719 730">• Using damaged or cut fentanyl transdermal patches can lead to rapid release of fentanyl and absorption of a potentially fatal dose. <li data-bbox="735 352 784 730">• Potential for temperature-dependent increases in fentanyl release, resulting in possible overdose and death. Avoid exposing application site and surrounding area to direct heat sources; monitor patients with fever or increased core body temperature. <p data-bbox="800 352 824 541">Contraindications</p> <ul style="list-style-type: none"> <li data-bbox="841 352 865 541">• Patients who are not opioid tolerant <li data-bbox="881 352 906 541">• Management of acute pain or for short-term treatment <li data-bbox="922 352 946 541">• Management of post-op pain, mild pain, or intermittent pain <li data-bbox="963 352 1003 541">• Significant respiratory depression (especially in unmonitored settings) <li data-bbox="1019 352 1044 541">• Acute or severe bronchial asthma <li data-bbox="1060 352 1084 541">• Known or suspected paralytic ileus <li data-bbox="1101 352 1125 541">• Hypersensitivity to fentanyl or any component <p data-bbox="1141 352 1166 541">Other Considerations</p> <ul style="list-style-type: none"> <li data-bbox="1182 352 1222 730">• Should not be used in patients particularly susceptible to intracranial effects of CO₂ retention (increased intracranial pressure, impaired consciousness, coma) <li data-bbox="1239 352 1263 541">• Caution in: <ul style="list-style-type: none"> <li data-bbox="1279 352 1304 541">○ Elderly, cachectic, or debilitated patients <li data-bbox="1320 352 1360 730">○ Significant chronic obstructive pulmonary disease or cor pulmonale; substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression <li data-bbox="1377 352 1401 541">○ Impaired renal or hepatic function <li data-bbox="1417 352 1442 541">○ Head injury, brain tumors <li data-bbox="1458 352 1482 541">○ Bradyarrhythmias <li data-bbox="1498 352 1523 730">○ Biliary tract disease, including acute pancreatitis.

Medication	Black Box Warnings, Contraindications, and Other Considerations
Fentanyl transmucosal lozenges	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • Abuse liability similar to other opioid analgesics. • Indicated only for management of breakthrough cancer pain in patients with malignancies already receiving and tolerant to opioid therapy for underlying persistent cancer pain • Must not be used in opioid non-tolerant patients • Intended for use only by oncologists and pain specialists knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. • Contains medicine in an amount that can be fatal to a child. Keep out of reach of children and discard opened units properly. • Concomitant use with strong and moderate CYP 3A4 inhibitors may increase plasma concentrations and cause potentially fatal respiratory depression. <p>Contraindications</p> <ul style="list-style-type: none"> • Opioid non-tolerant patients <p>Management of acute or postoperative pain</p> <ul style="list-style-type: none"> • Hypersensitivity to fentanyl or any component <p>Other Considerations</p> <ul style="list-style-type: none"> • Titrate cautiously in patients with chronic obstructive pulmonary disease or medical conditions predisposing to hypoventilation • Extreme caution in patients susceptible to intracranial effects of CO₂ retention • Caution in patients with head injury, bradyarrhythmias, renal or hepatic dysfunction • See product information for titration schedule; once successful dose found, limit consumption to four or fewer units per day • Fentanyl transmucosal lozenges and buccal tablets are NOT interchangeable.

Medication	
Fentanyl buccal tablets	<p>Black Box Warnings, Contraindications, and Other Considerations</p> <p>Black Box Warnings</p> <ul style="list-style-type: none"> • Abuse liability similar to other opioid analgesics. • Indicated only for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to around-the-clock opioid therapy for underlying persistent cancer pain. Intended to be used only by healthcare professionals knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain. Not indicated for use in opioid non-tolerant patients including those with only as needed (PRN) prior exposure. • Deaths have occurred as a result of improper patient selection and/or improper dosing. • Because of differences in the extent of absorption, substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose. When prescribing, do NOT convert patients on a mcg per mcg basis from fentanyl transmucosal lozenges to fentanyl buccal tablets. When dispensing, do not substitute fentanyl buccal tablets for fentanyl transmucosal lozenges. • If the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY one additional dose using the same strength and must wait at least 4 hours before taking another dose. • Contains medicine in an amount that can be fatal to a child. Keep out of reach of children. • Use with strong and moderate CYP450 3A4 inhibitors may result in potentially fatal respiratory depression. <p>Contraindications</p> <ul style="list-style-type: none"> • Opioid non-tolerant patients. • Management of acute or postoperative pain including headache/migraine • Hypersensitivity to fentanyl or any component <p>Other Considerations</p> <ul style="list-style-type: none"> • Caution in renal or hepatic dysfunction, patients with chronic obstructive pulmonary disease or medical conditions predisposing to respiratory depression, and patients with bradyarrhythmias. • Extreme caution in patients susceptible to intracranial effects of CO2 retention (increased intracranial pressure or impaired consciousness); caution in patients with head injury. <p>Contraindications</p> <ul style="list-style-type: none"> • Hypersensitivity to hydrocodone or acetaminophen <p>Other Considerations</p> <ul style="list-style-type: none"> • Caution postoperatively and in: <ul style="list-style-type: none"> ○ Elderly or debilitated patients ○ Pulmonary disease ○ Head injury, other intracranial lesions, or increased intracranial pressure ○ Severe hepatic or renal impairment ○ Addison's disease ○ Prostatic hypertrophy, or urethral stricture ○ Acute abdominal conditions • Dosing limited due to acetaminophen content.
Hydrocodone/AP	

Medication	Black Box Warnings, Contraindications, and Other Considerations
<p>Hydromorphone</p>	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • Injectable hydromorphone available in 1-, 2-, 4- and 10-mg/mL concentration; high-potency 10 mg/mL concentration ONLY for use in opioid-tolerant patients. • High potential for abuse and risk of respiratory depression <p>Contraindications</p> <ul style="list-style-type: none"> • Patients with respiratory depression in absence of resuscitative equipment • Status asthmaticus • Hypersensitivity to hydromorphone • Obstetrical analgesia <p>Other Considerations</p> <ul style="list-style-type: none"> • Use with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. • Caution in patients with: <ul style="list-style-type: none"> ◦ Elderly or debilitated patients and those with severe impairment of hepatic, pulmonary or renal function ◦ Head injury, other intracranial lesions, or increased intracranial pressure ◦ Circulatory shock ◦ Myxedema, hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease) ◦ Toxic psychoses, acute alcoholism, delirium tremens, CNS depression or coma ◦ Prostatic hypertrophy or urethral stricture ◦ Gall bladder disease ◦ Biliary tract disease ◦ Kyphoscoliosis ◦ Following gastrointestinal surgery ◦ Acute abdominal conditions • Contains sodium metabisulfite (potential for allergic-type reactions including anaphylactic symptoms and asthmatic episodes in susceptible individuals)

Medication	Black Box Warnings, Contraindications, and Other Considerations
Methadone	<p data-bbox="277 1396 302 1591">Black Box Warnings</p> <ul style="list-style-type: none"> <li data-bbox="321 346 402 1591">• Deaths reported during initiation of methadone for opioid dependence; some cases appear related to too-rapid titration without appreciation for accumulation of methadone over time. Understanding methadone pharmacokinetics and vigilance during initiation and titration is critical. Strongly caution patients against self-medicating with CNS depressants during initiation of methadone. <li data-bbox="407 346 456 1591">• Peak respiratory effects typically occur later and persist longer than peak analgesic effects, particularly in the early dosing period; can contribute to iatrogenic overdose. <li data-bbox="461 346 526 1591">• Methadone inhibits cardiac potassium channels and prolongs the QTc interval. QTc interval prolongation and serious arrhythmia (torsades de pointes) observed; more common in patients being treated for pain with large, multiple daily doses. <li data-bbox="531 863 555 1591">• Federal law governs distribution and use for treatment of opioid addiction. <li data-bbox="560 974 584 1591">• Methadone dispersible tablets are for oral administration only. <p data-bbox="589 1423 613 1591">Contraindications</p> <ul style="list-style-type: none"> <li data-bbox="633 1087 657 1591">• Hypersensitivity to methadone or any component <li data-bbox="662 346 727 1591">• Any situation where opioids are contraindicated, such as patients with respiratory depression (in absence of resuscitative equipment or in unmonitored situations) and patients with acute bronchial asthma or hypercarbia <li data-bbox="732 1220 756 1591">• Known or suspected paralytic ileus <p data-bbox="761 1396 786 1591">Other Considerations</p> <ul style="list-style-type: none"> <li data-bbox="805 346 854 1591">• Incomplete cross-tolerance with other opioids makes dosing during conversion from other opioids to methadone complex; a high degree of "opioid tolerance" does not eliminate possibility of methadone overdose. <li data-bbox="859 346 924 1591">• Extreme caution in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and central nervous system (CNS) depression or coma. <li data-bbox="928 1438 953 1591">• Caution in: <ul style="list-style-type: none"> <li data-bbox="972 359 997 1535">○ Elderly and debilitated patients, severe hepatic or renal dysfunction, and patients known to be sensitive to CNS depressants <li data-bbox="1002 422 1026 1535">○ Comorbid conditions or concomitant medications which may predispose to dysrhythmia or reduced ventilatory drive <li data-bbox="1031 1157 1055 1535">○ Patients predisposed to hypotension <li data-bbox="1060 1142 1084 1535">○ Hypothyroidism or Addison's disease <li data-bbox="1089 1108 1114 1535">○ Prostatic hypertrophy or urethral stricture <li data-bbox="1118 827 1143 1535">○ Head injury, other intracranial lesions, or increased intracranial pressure <li data-bbox="1148 1226 1172 1535">○ Acute abdominal conditions <li data-bbox="1177 346 1242 1591">• Methadone shown to inhibit cardiac potassium channels and prolong QTc interval. <ul style="list-style-type: none"> <li data-bbox="1180 346 1245 1535">○ Use with particular caution in patients already at risk for development of prolonged QTc interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia). <li data-bbox="1250 436 1282 1535">○ Careful monitoring in patients with a history of cardiac conduction abnormalities, on medications affecting cardiac conduction, and other situations suggesting an increased risk of dysrhythmia.

Medication	Black Box Warnings, Contraindications, and Other Considerations
Morphine	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • 8-12 hour extended release tablets <ul style="list-style-type: none"> ○ Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time ○ Swallow whole; taking broken, chewed, dissolved, or crushed tablets leads to rapid release and absorption of a potentially fatal dose. ○ <i>MS Contin (brand name)</i> – 100 mg and 200 mg tablets for use in opioid-tolerant patients only • 24-hour extended release capsules <ul style="list-style-type: none"> ○ Indicated for once daily administration for relief of moderate to severe pain requiring around-the-clock opioid therapy for an extended period of time ○ Swallow whole or sprinkle on applesauce; do not chew, crush, or dissolve due to risk of rapid release and absorption of a potentially fatal dose. ○ <i>Avizta (brand name)</i> – Patients must not consume alcoholic beverages or medications containing alcohol; may result in rapid release and absorption of a potentially fatal dose of morphine. ○ <i>Kadian (brand name)</i> – 100 mg and 200 mg capsules for use in opioid-tolerant patients only. <p>Contraindications</p> <ul style="list-style-type: none"> • Known hypersensitivity to morphine, morphine salts, or any component • Respiratory depression in the absence of resuscitative equipment • Acute or severe bronchial asthma or hypercarbia • Known or suspected paralytic ileus <p>Other Considerations</p> <ul style="list-style-type: none"> • Extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression • Caution in: <ul style="list-style-type: none"> ○ Elderly or debilitated patients and those with severe renal or hepatic impairment ○ Circulatory shock ○ Hypothyroidism or Addison's disease ○ Prostatic hypertrophy or urethral stricture ○ CNS depression, toxic psychosis, acute alcoholism, or delirium tremens ○ Head injury, intracranial lesions, or a preexisting increase in intracranial pressure ○ Acute abdominal conditions ○ Biliary tract disease, including acute pancreatitis • Like all opioids, may induce or aggravate seizures. • <i>Avizta brand of 24-hour extended release capsules</i> – limit to a maximum dose of 1600 mg per day due to fumaric acid content; higher doses may result in serious renal toxicity.

Medication	Black Box Warnings, Contraindications, and Other Considerations
<p>Oxycodone</p>	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • (12-hour controlled release tablets) <ul style="list-style-type: none"> ◦ Abuse liability similar to morphine. ◦ Indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time; not intended for use as an as-needed analgesic. ◦ 80 and 160 mg tablets for use in opioid-tolerant patients only ◦ Swallow whole; rapid release if broken, chewed, or crushed may lead to absorption of a potentially fatal dose. <p>Contraindications</p> <ul style="list-style-type: none"> • Known hypersensitivity to oxycodone • Any situation where opioids are contraindicated, such as patients with significant respiratory depression (in absence of resuscitative equipment or unmonitored situations) and patients with acute bronchial asthma or hypercarbia • Known or suspected paralytic ileus <p>Other Considerations</p> <ul style="list-style-type: none"> • Caution in <ul style="list-style-type: none"> ◦ Debilitated patients or severe impairment of hepatic, pulmonary or renal function ◦ Kyphoscoliosis associated with respiratory depression ◦ Adrenocortical insufficiency (e.g., Addison's disease), myxedema or hypothyroidism ◦ Circulatory shock ◦ Prostatic hypertrophy or urethral stricture; and toxic psychosis. ◦ Acute alcoholism, delirium tremens, CNS depression, coma ◦ Acute abdominal conditions ◦ Patients with biliary tract disease, including acute pancreatitis ◦ Patients predisposed to hypotension (e.g., due to depleted blood volume or medications that compromise vasomotor tone) • Like all opioids, may induce or aggravate seizures.

Medication	Black Box Warnings, Contraindications, and Other Considerations
Oxycodone	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • 12-hour extended release tablets <ul style="list-style-type: none"> ○ Abuse liability similar to other opioid analgesics ○ Indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time; NOT intended for use as an as needed analgesic. ○ Swallow whole; taking broken, chewed, dissolved, or crushed tablets may lead to rapid release and absorption of a potentially fatal dose of oxycodone. ○ Patients must not consume alcoholic beverages or medications containing alcohol; may result in increased plasma levels and a potentially fatal overdose of oxycodone. <p>Contraindications</p> <ul style="list-style-type: none"> • Hypersensitivity to oxycodone, any component, or morphine analogs such as codeine • Respiratory depression (except in monitored settings and in the presence of resuscitative equipment) • Acute or severe bronchial asthma or hypercarbia • Known or suspected paralytic ileus • Patients with moderate and severe hepatic impairment. <p>Other Considerations</p> <ul style="list-style-type: none"> • Extreme caution in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. • Caution in: <ul style="list-style-type: none"> ○ Elderly and debilitated patients, severe impairment of pulmonary or renal function, and patients known to be sensitive to CNS depressants ○ Kyphoscoliosis associated with respiratory depression ○ Patients with mild hepatic impairment (contraindicated for patients with moderate or severe hepatic impairment) ○ Patients predisposed to hypotension due to depleted blood volume or other drugs that compromise vasomotor tone ○ Circulatory shock ○ Adrenocortical insufficiency (e.g., Addison's disease), myxedema or hypothyroidism ○ Prostatic hypertrophy or urethral stricture ○ Acute alcoholism, delirium tremens, CNS depression or coma, toxic psychosis ○ Acute abdominal conditions • Like all opioids, may induce or aggravate seizures.

Medication	Black Box Warnings, Contraindications, and Other Considerations
<p>Propoxyphene Propoxyphene/APAP</p>	<p>Black Box Warnings</p> <ul style="list-style-type: none"> • Do not prescribe for patients who are suicidal or addiction prone. Prescribe with caution for patients taking tranquilizers or antidepressants and those who use alcohol in excess. • Do not exceed recommended dose (600 mg propoxyphene/day); limit alcohol intake. • Propoxyphene products in excessive doses, alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdose are not uncommon. • Prescribe with caution for patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. • Many propoxyphene-related fatalities involved patients with histories of emotional disturbances, suicidal ideation / attempts, and misuse of tranquilizers, alcohol, and other CNS-active drugs. <p>Contraindications</p> <ul style="list-style-type: none"> • Hypersensitivity to propoxyphene (or acetaminophen in combination products) <p>Other Considerations</p> <ul style="list-style-type: none"> • Caution in patients with hepatic or renal impairment • Take acetaminophen content of combination product into account; do not use concomitantly with other acetaminophen-containing products.
<p>Tapentadol</p>	<p>Contraindications</p> <ul style="list-style-type: none"> • Impaired pulmonary function (significant respiratory depression, acute or severe bronchial asthma, hypercapnia in unmonitored settings or absence of resuscitative equipment) • Known or suspected paralytic ileus • Use within 14 days of monoamine oxidase inhibitors (MAOIs) <p>Other Considerations</p> <ul style="list-style-type: none"> • Increased risk of respiratory depression in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction • Not recommended in patients with severe renal or hepatic impairment. • Caution in: <ul style="list-style-type: none"> ◦ Conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma. ◦ Moderate hepatic impairment ◦ Head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure ◦ History of seizure or a condition that increases seizure risk ◦ Biliary tract disease, including pancreatitis. • Inhibits reuptake of serotonin and norepinephrine; potentially life-threatening serotonin syndrome could result with concomitant use of other serotonergic agents and drugs that impair metabolism of serotonin (e.g., MAOIs).

Medication	Black Box Warnings, Contraindications, and Other Considerations
Tramadol Tramadol/ APAP	<p>Contraindications</p> <ul style="list-style-type: none"> • Hypersensitivity to tramadol (or acetaminophen in combination products), any component, or opioids • Any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs; may worsen central nervous system and respiratory depression in these patients. <p>Other Considerations</p> <ul style="list-style-type: none"> • Seizures reported within the recommended dosage range; increased risk above recommended dosage range and in patient with seizure disorder, history of seizures, in conditions with increased risk of seizures, or with other drugs that increase seizure risk. Observe maximum dose limits. • Serious anaphylactoid reactions reported, often following first dose. Other allergic reactions reported. Patients with a history of anaphylactoid reaction to codeine and other opioids may be at increased risk. • Inhibits reuptake of serotonin and norepinephrine; concomitant use with MAOIs or selective serotonin reuptake inhibitors (SSRIs) may increase risk of seizures, serotonin syndrome. • Caution in patients with increased intracranial pressure or head injury • Cautious dosing in patients with a creatinine clearance < 30mL/min, patients with cirrhosis, and elderly patients • Should not be taken with alcohol-containing beverages • Use naloxone with caution in overdose; may precipitate seizures. • Take acetaminophen content of combination product into account. • Tramadol/APAP not recommended in patients with liver disease

Source: Prescribing Information

Table E 5: Opioid Drug Interactions

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management:
<i>Opioids</i>			
Antipsychotics Opioids	Opioids Antipsychotics	Increase	Increased sedation, variable effects on respiratory depression; enhanced cardiovascular effects (antimuscarinic & alpha-blockade)
Anticholinergics	Opioids	Increase	Urinary retention and/or constipation (potentially severe; may lead to paralytic ileus)
Barbiturates Opioids	Opioids Barbiturates	Increase	Additive CNS and respiratory effects
Benzodiazepines Opioids	Opioids Benzodiazepines	Increase	Additive CNS effects
CNS depressants Opioids	Opioids CNS depressants	Increase	Enhanced respiratory, CNS, and cardiovascular effects; reduce dose of one or both agents
Cimetidine	Opioids	Increase	Enhanced effect
MAO inhibitors Opioids	Opioids MAO inhibitors	Increase	All opioids relatively contraindicated in patients who have received MAOIs within 14 days, due to risk of hypertensive coma; hypertension reported; remember long half-life of MAOIs; reactions may occur several weeks after MAOI discontinued
Opioid agonist/ antagonists or partial agonists	Opioids	Decrease	Do not administer opioid agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, butorphanol) or partial agonists (e.g., buprenorphine) to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic; may precipitate withdrawal symptoms
Phenothiazines	Opioids	Increase	Increased analgesia, toxicity; reduce dose
Serotonergic agents	Opioids	Increase	Potential for serotonin syndrome
Opioids	Skeletal muscle relaxants	Increase	May enhance neuromuscular blockade and increase respiratory depression
<i>Codeine</i>			

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management:
CYP 2D6 inhibitors	Codeine	Decrease	
Quinidine	Codeine	Decrease	Decreases analgesic effect; alternative opioid may be necessary
Fentanyl			
Amiodarone	Fentanyl	Increase	Profound bradycardia, sinus arrest, hypotension
CYP 3A4 inhibitors	Fentanyl	Increase	Fentanyl metabolized primarily by CYP 3A4; CYP 3A4 inhibitors may increase fentanyl plasma concentration; carefully monitor over an extended period of time; adjust fentanyl dose as needed
CYP 3A4 inducers	Fentanyl	Decrease	May increase fentanyl clearance
Benzo diazepines (diazepam)	Fentanyl	Increase	May produce cardiovascular depression with high doses of fentanyl
Droperidol	Fentanyl	Increase	May depress pulmonary arterial pressure, resulting in hypotension
Erythromycin	Fentanyl	Increase	May inhibit metabolism and increase effect; monitor for prolonged or recurrent respiratory depression and sedation; lower dose or consider alternative opioid
Nitrous oxide	Fentanyl	Increase	May cause cardiovascular depression with high-dose fentanyl
Protease inhibitors – e.g., ritonavir, saquinavir, nelfinavir	Fentanyl	Increase	May increase plasma concentrations, toxicity
Hydromorphone			
CYP 2D6 inhibitors	Hydromorphone	Decrease	
Methadone			
Azole antifungals (CYP 3A4 inhibitors)	Methadone	Increase	
Barbiturates	Methadone	Decrease	May decrease methadone effects and/or trigger withdrawal symptoms; higher methadone dose may be required
Benzodiazepines	Methadone	Increase	Co-administration of methadone with benzodiazepines may substantially increase the potential of a fatal outcome due to potentiation of respiratory depressant effects.

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management:
Erythromycin	Methadone	Increase	May inhibit metabolism and increase effect; monitor for respiratory depression, sedation; consider lower dose or alternative opioid
Grapefruit juice	Methadone	Increase	
Fluvoxamine	Methadone	Increase	May inhibit methadone metabolism; use with caution
Nucleoside reverse transcriptase inhibitors (NRTIs) Methadone	Methadone NRTIs	Increase Decrease / Increase	Coadministration with abacavir may increase methadone clearance, increasing effect; may require dose adjustment. Coadministration may decrease levels of didanosine, stavudine, but may increase levels of zidovudine; monitor zidovudine closely, may require dose adjustment
Nonnucleoside reverse transcriptase inhibitors (NNRTIs) – e.g., nevirapine, efavirenz	Methadone	Decrease	May reduce methadone effect and/or trigger withdrawal symptoms; anticipate adjusting methadone dose and monitoring symptoms when NNRTI started or discontinued
Phenytoin	Methadone	Decrease	May decrease effect, possibly due to increased hepatic metabolism
Protease inhibitors – e.g., ritonavir, saquinavir, nelfinavir	Methadone	Decrease	May decrease effect of methadone
Rifamycins – e.g., rifampin	Methadone	Decrease	May increase metabolism, resulting in reduced effect and symptoms of withdrawal; may require higher dose
Urinary acidifiers	Methadone	Increase	Increase renal clearance of methadone
Methadone	Desipramine	Increase	May increase desipramine blood levels
<i>Morphine</i>			
Lidocaine Morphine	Morphine Lidocaine	Increase	Respiratory depression and loss of consciousness may occur
MAOIs Morphine	Morphine MAOIs	Increase	Severe and unpredictable potentiation; reactions may include agitation, seizures, diaphoresis, fever, possibly progressing to coma, apnea, death; opioids not recommended within 14 days of MAOIs. Reactions may occur several weeks after discontinuing MAOIs.
Neostigmine	Morphine	Increase	Increases intensity and duration of analgesic effect

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management:
Reserpine	Morphine	Decrease	Decreases analgesic effect
Rifamycins – e.g., rifampin	Morphine	Decrease	May decrease analgesic effect of morphine; alternative may be necessary
Tricyclic antidepressants (e.g., amitriptyline, clomipramine, nortriptyline)	Morphine	Increase	Potential for increased CNS, respiratory depression; monitor
Morphine	Diuretics	Decrease	May reduce efficacy by inducing release of antidiuretic hormone
Morphine	Warfarin	Increase	May increase anticoagulation; monitor
Oxycodone			
CYP 2D6 inhibitors	Oxycodone	Increase	Oxycodone metabolized in part by CYP 2D6 to oxycodone; unknown clinical significance
Propofol	Oxycodone	Increase	Increased risk of bradycardia
Voriconazole	Oxycodone	Increase	Inhibits CYP 3A4, increasing exposure to oxycodone; lower doses may be needed
Propoxyphene			
Cigarette smoking	Propoxyphene	Decrease	May induce hepatic enzymes, decrease effect
Protease inhibitors – e.g., ritonavir, saquinavir, nelfinavir	Propoxyphene	Increase	Contraindicated
Propoxyphene	Carbamazepine	Increase	May inhibit carbamazepine metabolism, increase serum concentrations, toxicity
Propoxyphene	Warfarin	Increase	May increase anticoagulation; monitor
<i>Tapentadol – note: tapentadol primarily metabolized by Phase 2 glucuronidation; does not appear to inhibit or induce CYP P450 enzymes; clinically relevant drug interactions mediated by these systems unlikely; pharmacokinetics not affected by increased gastric pH (omeprazole) or GI motility (metoclopramide); low protein binding.</i>			
Serotonergic antidepressants	Tapentadol	Increase	Potential for additive serotonergic effects; increased risk for serotonin syndrome
Tapentadol	Serotonergic antidepressants		

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management:
<i>Tramadol – note: extensively metabolized by multiple pathways, including CYP 2D6 and 3A4; formation of active metabolite M1 dependent on CYP 2D6</i>			
Carbamazepine	Tramadol	Decrease	Increases tramadol metabolism; seizure risk associated with tramadol, not recommended
CYP 3A4 inhibitors	Tramadol	Decrease	May decrease tramadol clearance
CYP 3A4 inducers	Tramadol	Increase	May increase tramadol clearance
CYP 2D6 inhibitors	Tramadol	Increase	Quinidine results in increased concentrations of tramadol and reduced concentrations of M1; other CYP 2D6 inhibitors (e.g., fluoxetine, paroxetine, amitriptyline) may inhibit metabolism; no clinically significant changes with cimetidine
Serotonergic antidepressants Tramadol	Tramadol Serotonergic antidepressants	Increase	Potential for additive serotonergic effects; increased risk for seizures, serotonin syndrome. Use caution. If possible, avoid this combination.
Tramadol	Digoxin	Increase	Rare reports of digoxin toxicity
Tramadol	Other drugs that increase seizure risk		
Tramadol	Warfarin	Increase	Rare reports of altered warfarin effect, including elevated prothrombin time; monitor
CYP 2D6 inhibitors - <i>Analgesics</i> - methadone [weak inhibitor], propoxyphene <i>Antihistamines</i> - diphenhydramine, chlorpheniramine [in vitro], brompheniramine [in vitro], triprolidine [in vitro] <i>Histamine₂ receptor antagonists</i> - cimetidine <i>Neuroleptics</i> - chlorpromazine, haloperidol, methotrimeprazine, perphenazine, thioridazine <i>Protease inhibitors</i> - ritonavir <i>Quinine compounds</i> - hydroxychloroquine, quinaquine, quinine <i>Selective serotonin reuptake inhibitors</i> - fluoxetine, fluvoxamine, paroxetine, sertraline <i>Miscellaneous compounds</i> - clomipramine, ketoconazole, ticlopidine	<i>Antiarrhythmics</i> - amiodarone, propafenone, quinidine [strong inhibitor]		
CYP 3A4 inhibitors - <i>Azole antifungals</i> [e.g., ketoconazole, fluconazole, voriconazole, itraconazole] <i>Protease inhibitors</i> [e.g., ritonavir] Grapefruit, grapefruit juice	<i>Macrolide antibiotics</i> [e.g., clarithromycin]		

Precipitant	Object	Effect	Clinical Signs / Symptoms and Management
CYP 3A4 inducers (e.g., rifampin, carbamazepine, phenytoin)			
Drugs that increase seizure risk: e.g., SSRIs, TCAs, other tricyclics (cyclobenzaprine, promethazine, etc.), other opioids, MAOIs, antipsychotics			
CNS depressants (e.g., barbiturates, tranquilizers, alcohol, phenothiazines, tranquilizers, sedative-hypnotics, ethanol)			
Serotonergic agents - sibutramine MAOIs triptans	serotonergic antidepressants (SSRIs, nefazodone, venlafaxine, duloxetine, tricyclics [TCAs])		

Source: Facts & Comparisons Online

Table E 6: Equianalgesic and conversion doses 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 12 mcg/h fentanyl transdermally for every 45 mg of oral morphine or equivalent (see Table E7, <i>Initial Fentanyl Transdermal Dosage</i>)
Hydrocodone	30	50% to 67% of estimated oral equianalgesic dose
Hydromorphone	7.5	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 <i>Methadone Dosing Recommendations for Treatment of Chronic Pain</i> 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
Oxymorphone	10	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
Tapentadol	No data (50 to 100 [‡])	50 to 100 mg q 4 to 6 h
Tramadol	No data (100 to 150 [‡])	25 mg every morning

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-naïve patients. Doses of tapentadol and tramadol should NOT be considered equianalgesic to the doses of pure agonists. Equianalgesic doses have not been established for conversions between either tapentadol or tramadol and pure opioid 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 E 7: Initial Fentanyl Transdermal Dosage (only for converting another opioid to fentanyl)

Oral 24-hour morphine (mg/d)	Fentanyl transdermal (mcg/h)
60–134	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: Janssen Prescribing Information on Duragesic (Fentanyl Transdermal System) (2008)

Table E7b. Converting from Fentanyl Transdermal System to Other Opioids

There are no FDA-approved dosing instructions on how to convert patients from fentanyl to other opioids. After discontinuing the fentanyl patch, titrate the new opioid according to the patient's level of pain relief and tolerability.

Do not use this table to convert from fentanyl transdermal system to other opioid analgesics because these conversion dosage recommendations are conservative. Use of table E7 for conversion from fentanyl to other opioids can overestimate the dose of the new agent and may result in overdose of the new agent.

Take into consideration that serum fentanyl concentrations decline gradually after removal of the patch, decreasing about 50% in approximately 17 (range 13-22) hours.

Use conservative conversion doses and provide the patient with supplemental short-acting opioids to be taken as needed.

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 analgesic action may be 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 F 1: Points to Consider About Equianalgesic Conversion Ratios

A number of equianalgesic dosing tables underestimate the potency of methadone. [†]	[†] Management of Cancer Pain, Clinical Practice Guidelines, AHCP (1994) ³⁵ ; Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada (1984) ³⁶ ; Twycross (1990) ³⁷ ; Levy (1985) ³⁸
Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids.	[‡] 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}
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). [§]	[§] Bruera (1999) ⁴⁰
There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients. [§]	Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain. ¹
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.	

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 F 2: 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, <i>start low and go slow</i> .
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 F 3: 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 and decrease previous opioid dose by 1/3rd every 5 d (Complete conversion period = 15 days)												
<p>* Calculation of MET dose based on oral morphine-equivalent [MOR-E] doses:</p> <table border="0"> <tr> <td>Methadone [MET]</td> <td>2 mg</td> <td>Examples:</td> </tr> <tr> <td>Morphine [MOR]</td> <td>30 mg</td> <td>250 mg/d MOR = $250 \times 2 / 30 = 17$ mg/d MET ~ 5 mg q 8 h</td> </tr> <tr> <td>Hydromorphone [HMO]</td> <td>8 mg</td> <td>60 mg/d HMO = $60 \times 2 / 8 = 15$ mg/d MET = 5 mg q 8 h</td> </tr> <tr> <td>Oxycodone [OXY]</td> <td>15 mg</td> <td>120 mg/d OXY = $120 \times 2 / 15 = 16$ mg/d MET ~ 5 mg q 8 h</td> </tr> </table> <p>600 mg/d MOR = $600 \times 2 / 30 = 40$ mg/d MET First dose: 1/3rd of 40 mg/d = 13 mg/d ~ 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</p>				Methadone [MET]	2 mg	Examples:	Morphine [MOR]	30 mg	250 mg/d MOR = $250 \times 2 / 30 = 17$ mg/d MET ~ 5 mg q 8 h	Hydromorphone [HMO]	8 mg	60 mg/d HMO = $60 \times 2 / 8 = 15$ mg/d MET = 5 mg q 8 h	Oxycodone [OXY]	15 mg	120 mg/d OXY = $120 \times 2 / 15 = 16$ mg/d MET ~ 5 mg q 8 h
Methadone [MET]	2 mg	Examples:													
Morphine [MOR]	30 mg	250 mg/d MOR = $250 \times 2 / 30 = 17$ mg/d MET ~ 5 mg q 8 h													
Hydromorphone [HMO]	8 mg	60 mg/d HMO = $60 \times 2 / 8 = 15$ mg/d MET = 5 mg q 8 h													
Oxycodone [OXY]	15 mg	120 mg/d OXY = $120 \times 2 / 15 = 16$ mg/d MET ~ 5 mg q 8 h													
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														
<p>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</p>															
<ol style="list-style-type: none"> 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 Titrate MET day by day according to patient's symptoms and the number of rescue doses administered 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 hours 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.

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.

- 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.
- 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

References

1. Foley KM, Houde RW. Methadone in cancer pain management: individualize dose and titrate to effect. *J Clin Oncol* 1998;16:3213-5.
2. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol* 1998;16:3216-21.
3. Lawlor PG, Turner KS, Hanson J, Bruera ED. Dose ratio between morphine and methadone in patients with cancer pain: a retrospective study. *Cancer* 1998;82:1167-73.
4. Bruera E, Pereira J, Watanabe S, Belzile M, Kuehn N, Hanson J. Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer* 1996;78:852-7.
5. Ayonrinde OT, Bridge DT. The rediscovery of methadone for cancer pain management. *Med J Aust* 2000;173:536-40.
6. Morley JS, Makin MK. Comments on Ripamonti et al., *Pain*, 70 (1997) 109-115. *Pain* 1997;73:114-5.
7. Hanks GW, Conno F, Cherny N et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84:587-93.
8. Symonds P. Methadone and the elderly (letter). *Br Med J* 1977;1:512.
9. Bruera E, Watanabe S, Fainsinger RL, Spachynski K, Suarez-Almazor M, Inturrisi C. Custom-made capsules and suppositories of methadone for patients on high-dose opioids for cancer pain. *Pain* 1995;62:141-6.
10. Ettinger DS, Vitale PJ, Trump DL. Important clinical pharmacologic considerations in the use of methadone in cancer patients. *Cancer Treat Rep* 1979;63:457-9.
11. Mercadante S, Casuccio A, Fulfaro F et al. Switching from morphine to methadone to improve analgesia and tolerability in cancer patients: a prospective study. *J Clin Oncol* 2001;19:2898-904.
12. Gagnon B, Bruera E. Differences in the ratios of morphine to methadone in patients with neuropathic pain versus non-neuropathic pain. *J Pain Symptom Manage* 1999;18:120-5.
13. Mercadante S, Casuccio A, Calderone L. Rapid switching from morphine to methadone in cancer patients with poor response to morphine. *J Clin Oncol* 1999;17:3307-12.
14. Hagen NA, Wasylenko E. Methadone: outpatient titration and monitoring strategies in cancer patients. *J Pain Symptom Manage* 1999;18:369-75.

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://vawww.sites.lm.va.gov/pain/opioids/> or reference 51.

15. Krames E. The Bruera/Neumann article reviewed. Discussion of Bruera E, Neumann CM. Role of methadone in the management of pain in cancer patients. *Oncology* 1999;13:1275-1282. *Oncology* 1999;13:1288-1289.
16. Ripamonti C, Zecca E, Bruera E. An update on the clinical use of methadone for cancer pain. *Pain* 1997;70:109-15.
17. Garrido MJ, Troconiz IF. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. *J Pharmacol Toxicol Methods* 1999;42:61-6.
18. Wolff K, Rostami-Hodjegan A, Shires S et al. The pharmacokinetics of methadone in healthy subjects and opiate users. *Br J Clin Pharmacol* 1997;44:325-34.
19. Olsen GD, Wendel HA, Livermore JD, Leger RM, Lynn RK, Gerber N. Clinical effects and pharmacokinetics of racemic methadone and its optical isomers. *Clin Pharmacol Ther* 1977;21:147-57.
20. Verebely K, Volavka J, Mule S, Resnick R. Methadone in man: pharmacokinetic and excretion studies in acute and chronic treatment. *Clin Pharmacol Ther* 1975;18:180-90.
21. Inturrisi CE, Verebely K. Disposition of methadone in man after a single oral dose. *Clin Pharmacol Ther* 1972;13:923-30.
22. Wolff K, Rostami-Hodjegan A, Hay AW, Raistrick D, Tucker G. Population-based pharmacokinetic approach for methadone monitoring of opiate addicts: potential clinical utility. *Addiction* 2000;95:1771-83.
23. de Vos JW, Geerlings PJ, van den Brink W, Ufkes JG, van Wilgenburg H. Pharmacokinetics of methadone and its primary metabolite in 20 opiate addicts. *Eur J Clin Pharmacol* 1995;48:361-6.
24. Wolff K, Hay AW, Raistrick D, Calvert R. Steady-state pharmacokinetics of methadone in opioid addicts. *Eur J Clin Pharmacol* 1993;44:189-94.
25. Nilsson MI, Gronbladh L, Widerlov E, Anggard E. Pharmacokinetics of methadone in methadone maintenance treatment: characterization of therapeutic failures. *Eur J Clin Pharmacol* 1983;25:497-501.
26. Anggard E, Nilsson MI, Holmstrand J, Gunne LM. Pharmacokinetics of methadone during maintenance therapy: pulse labeling with deuterated methadone in the steady state. *Eur J Clin Pharmacol* 1979;16:53-7.
27. Nilsson MI, Anggard E, Holmstrand J, Gunne LM. Pharmacokinetics of methadone during maintenance treatment: adaptive changes during the induction phase. *Eur J Clin Pharmacol* 1982;22:343-9.
28. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM. Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. *Clin Pharmacol Ther* 1987;41:392-401.
29. Gourlay GK, Cherry DA, Cousins MJ. A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. *Pain* 1986;25:297-312.
30. Plummer JL, Gourlay GK, Cherry DA, Cousins MJ. Estimation of methadone clearance: application in the management of cancer pain. *Pain* 1988;33:313-22.
31. Denson DD, Concilus RR, Warden G, Raj PP. Pharmacokinetics of continuous intravenous infusion of methadone in the early post-burn period. *J Clin Pharmacol* 1990;30:70-5.
32. Grochow L, Sheidler V, Grossman S, Green L, Enterline J. Does intravenous methadone provide longer lasting analgesia than intravenous morphine? A randomized, double-blind study. *Pain* 1989;38:151-7.
33. Hanson J, Ginman C, Hartvig P, et al. Clinical evaluation of oral methadone in treatment of cancer pain. *Acta Anaesthesiol Scand* 1982;74:124-127.
34. Sawe J, Hansen J, Ginman C et al. Patient-controlled dose regimen of methadone for chronic cancer pain. *Br Med J (Clin Res Ed)* 1981;282:771-3.
35. AHCPR. Management of Cancer Pain, Clinical Practice Guidelines. Rockville, MD: Agency for Health Care Policy and Research; U.S. Department of Health and Human Services; 1994. AHCPR Pub. No. 94-0592.

36. Health & Welfare Canada. Cancer pain: a monograph on the management of cancer pain. Ottawa, Canada: Health & Welfare Canada, Minister of Supply and Services; 1984. H42-2/5.
37. Twycross R, Lack S. Pain relief. In: Twycross R, Lack S, eds. Therapeutics in terminal cancer, 2nd edition. Edinburgh: Churchill Livingstone; 1990;2:11-39.
38. Levy MH. Pain management in advanced cancer. *Semin Oncol* 1985;12:394-410.
39. Ripamonti C, De Conno F, Groff L et al. Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: comparison of two clinical experiences. *Ann Oncol* 1998;9:79-83.
40. Bruera E, Neumann CM. Role of methadone in the management of pain in cancer patients. *Oncology (Huntingt)* 1999;13:1275-82; discussion 1285-8, 1291.
41. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. *Support Care Cancer* 2001;9:73-83.
42. Jellin JM, Gregory P, Batz F, Hitchens K, et al. Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database, 3rd ed. Stockton, CA: Therapeutic Research Faculty; 2000.
43. Brown LS, Sawyer RC, Li R, Cobb MN, Colborn DC, Narang PK. Lack of a pharmacologic interaction between rifabutin and methadone in HIV-infected former injecting drug users. *Drug Alcohol Depend* 1996;43:71-7.
44. CPSO Task Force on CNMP. Evidence-based recommendations for medical management of chronic non-malignant pain: College of Physicians and Surgeons of Ontario (CPSO); Nov 2000.
45. De Conno F, Groff L, Brunelli C, Zecca E, Ventafridda V, Ripamonti C. Clinical experience with oral methadone administration in the treatment of pain in 196 advanced cancer patients. *J Clin Oncol* 1996;14:2836-42.
46. Friedman LL. Using Methadone. Lecture presented at: American Academy of Hospice and Palliative Medicine, 13th Annual Assembly; 22 June 2001; Phoenix, AZ.
47. Morley J, Makin M. The use of methadone in cancer pain poorly responsive to other opioids. *Pain Rev* 1998;5:51-58.
48. Gardner-Nix JS. Oral methadone for managing chronic nonmalignant pain. *J Pain Symptom Manage* 1996;11:321-8.
49. Novick DM, Kreek MJ, Fanizza AM, Yancovitz SR, Gelb AM, Stenger RJ. Methadone disposition in patients with chronic liver disease. *Clin Pharmacol Ther* 1981;30:353-62.
50. Kreek MJ, Schechter AJ, Gutjahr CL, Hecht M. Methadone use in patients with chronic renal disease. *Drug Alcohol Depend* 1980;5:197-205.
51. Portenoy RK. Pain specialists and addiction medicine specialists unite to address critical issues. American Pain Society Web site. APS bulletin (online). 1999;9(2). Available at: <http://www.ampainsoc.org/pub/bulletin/mar99/president.htm>. Accessed 5 October 2001.

APPENDIX G: Acronym List

ADRB	Aberrant Drug Related Behavior
APS	American Pain Society
ASAM	American Society of Addiction Medicine
BID	Bis In Die (Latin: twice a day)
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CNCP	Chronic Non Cancer Pain
OT	Opioid Therapy
CPAP	Continuous Positive Airway Pressure
CPG	Clinical Practice Guideline
CR	Controlled-Release
CSA	Central Sleep Apnea
DC	Discontinue
DEA	Drug Enforcement Administration
DHEAS	Dehydroepiandrosterone Sulfate
DoD	Department of Defense
DSM-IV	Diagnostic and Statistical Manual – Version IV
DUI	Driving Under the Influence (drugs or alcohol)
EMG	Electromyography
ER	Emergency Room
GI	Gastrointestinal
IASP	International Association for the Study of Pain
LBP	Low Back Pain
LE	Level of Evidence
MAOI	Monoamine Oxidase Inhibitors
MSE	Mental Status Examination
mTBI	Mild Traumatic Brain Injury
MVA	Motor Vehicle Accident
N & V	Nausea and Vomiting
NRS	Numerical Rating Scale
NSAID	Non-Steroid Anti-Inflammatory Drug
OIH	Opioid-induced hyperalgesia
OAT	Opioid agonist therapy
OPCA	Opioid Pain Care Agreement
ORT	Opioid Risk Tool
OSA	Obstructive Sleep Apnea
OT	Opioid Therapy
PA	Pills Anonymous
PHN	Postherpetic Neuralgia
PO	Per Os (Latin: by mouth, orally)
PRN	Pro Re Nata (Latin: as needed)
PTSD	Post Traumatic Stress Disorder
QE	Quality of the Evidence
RCT	Randomized Controlled Trial
RS	Rectal Suppository
SA	Substance Abuse
SAD	Seasonal Affective Disorder
SOAPP	Screening and Opioid Assessment of Patients with Pain
SR	Strength of Recommendation
SUD	Substance Use Disorder
TBI	Traumatic brain Injury

TDS	Transdermal System
TENS	Transcutaneous Electrical Nerve Stimulation
TID	Ter In Die (Latin: three times a day)
TJC	The Joint Commission (formerly JCAHO)
UDS	Urine Drug Screen
UDT	Urine Drug Test
VA	Veterans Administration
WG	Working Group

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**VA/DoD Clinical Practice Guideline
Management of Opioid Therapy for Chronic Pain**

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APPENDIX I: Bibliography

- Akbik H, Butler SF, Budman SH, Fernandez K, Katz NP, Jamison RN. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage* 2006;32:287-93.
- Alattar MA, Scharf SM. Opioid-associated central sleep apnea: a case series. *Sleep Breath* 2009 May;13(2) 201-6.
- Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006 Jan;144:127-34.
- Allan L, Hays H, Jensen NH de Waroux BL, Bolt M, Donald R, Kalso E. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001;322(7295):1154-8.
- Angst MS, Clark DJ. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 2006; 104:570-87.
- APS 2004 - Public policy statement on the rights and responsibilities of healthcare professionals in the use of opioids for the treatment of pain. A consensus document from American Pain Society, American Academy of Pain Medicine and the American Society of Addiction Medicine. Available at: <http://www.ampainsoc.org/advocacy/pdf/rights.pdf>
- Atluri S, Sudarshan G. Evaluation of abnormal urine drug screens among patients with chronic non-malignant pain treated with opioids. *Pain Physician* 2003 Oct;6(4):407-9.
- Atluri SL, Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. *Pain physician* 2004;7:333-8.
- Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000 Feb;84(2-3):203-11.
- Bednar NM, Harrigan EP, Ruskin JN. Rosades de pointes associated with non antiarrhythmic drugs and observations on gender and QTc. *Am J Cardiol* 2002 Jun1;89(11)1316-9.
- Benyamin R, Trescot A, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R. Opioid complications and side effects. 2008 Mar;11(2 Suppl):S105-20.
- Braden JB, Sullivan MD. Suicidal thoughts and behavior among adults with self-reported pain conditions in the national comorbidity survey replication. *J Pain* 2008;9(12):1106-15.
- Breitfeld C, Eikermann M, Kienbaum P, Peters J. Opioid "holiday" following antagonist supported detoxification during general anesthesia improves opioid agonist response in a cancer patient with opioid addiction. *Anesthesiology* 2003 Feb;98(2):571-3.
- Breivik EK, Skoglund LA. Comparison of present pain intensity assessments on horizontally and vertically oriented visual analogue scales. *Methods Find Exp Clin Pharmacol* 1998;20(8):719-24.
- Breivik H. Opioids in cancer and chronic non-cancer pain therapy-indications and controversies. *Acta Anaesthesiol Scand* 2001;45 (9):1059-66.
- Brown RL, Fleming MF, Patterson JJ. Chronic opioid analgesic therapy for chronic low back pain. *J Am Board Fam Pract* 1996 May-Jun;9(3):191-204.
- Burchman SL, Pagel PS. Implementation of a formal treatment agreement for outpatient management of chronic nonmalignant pain with opioid analgesics. *J Pain Symptom Manage* 1995;10(7):556-63.

- Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain* 2004 Nov;112:65-75.
- Butler SF, Budman SH, Fernandez KC, Fanciullo GJ, Jamison RN. Cross-Validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *J Addict Med* 2009 Jun 1;3(2):66-73.
- Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, Jamison RN. Development and validation the Current Opioid Misuse Measure. *Pain* 2007;130:144-56.
- Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain* 2008 Apr;9(4):360-72.
- Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, Shi M, Lacouture PG. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol* 1999 Apr;26(4):862-9.
- Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yuan W, Eliot L, Babul N, Lynch PM. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002;23(4):278-91.
- Caldwell JR, Rapoport RJ, Davis JC, Offenberg HL, Marker HW, Roth SH, Yian W, Eliot L, Babul N, Lynch PM. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002;23(4):278-91.
- Canadian Pain Society. 2002 – See Jovey et al., 2003
- Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Aust N Z J Public Health*. 2002 Aug;26(4):358-62.
- Caraco Y, Sheller J, Wood AJ. Impact of ethnic origin and quinidine coadministration on codeine's disposition and pharmacodynamic effects. *J Pharmacol Exp Ther* 1999;290(1):413-22.
- Cherny N, Ripamonti C, Pereira J. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001;19(9):2542-54.
- Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009 Feb;10(2):147-59.
- Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik ST, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* Feb 2009;10(2):113-30.
- Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain* 2009 Feb;10(2):131-46.
- Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain* 2008 Jul-Aug;24(6):479-96.
- Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *J Pain* 2006 Jan;7(1):43-8.
- Clark MR, Stoller KB, Brooner RK. Assessment and management of chronic pain in individuals seeking treatment for opioid dependence disorder. *Can J Psychiatry* 2008;53:496-508.

- Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330(9):592-6.
- Cleeland CS, Shacham S, Dahl JL, Orrison W. CSF beta-endorphin and the severity of pain. *Neurology* 1984;34(3):378-80.
- Cleeland CS, Syrjala KL. How to assess cancer pain. In: DC Turk; R Melzack, editors. *Handbook of Pain Assessment*. New York: The Guilford Press; 1992. p. 362-87.
- Cohen RI, Chopra P, Upshur C. Guide to conservative, medical, and procedural therapies. *Geriatrics* 2001 Nov; 56(11):38-42.
- Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR. Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. *Anesth Analg* 1992;75(5):747-52.
- Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA, Chavez J, Ashley J, Lebo D, McCracken M, Portenoy RK. Breakthrough cancer pain: A randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). *Pain* 2001 Mar;91(1-2):123-30.
- Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and "problematic" substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage* 1998 Dec;16(6):355-63.
- Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD. Introduction of a self-report version of the Prescription Drug Use Questionnaire and relationship to medication agreement noncompliance. *J Pain Symptom Manage* 2008 Oct;36(4):383-95.
- CPSO 2000 - Task Force on CNMP. Evidence-based recommendations for medical management of chronic non-malignant pain: College of Physicians and Surgeons of Ontario (CPSO); Nov 2000. Available at: <http://www.ihs.gov/NonMedicalPrograms/NC4/Documents/EBMchronicpainguidelines2000.pdf>
- Crider AB, Glaros AG. A meta-analysis of EMG biofeedback treatment of temporomandibular disorders. *J Orofac Pain* 1999 Winter;13(1):29-37.
- Crombez G, Vlaeyen JW, Heuts PH, Lysens R. Pain-related fear is more disabling than pain itself: evidence on the role of pain-related fear in chronic back pain disability. *Pain* 1999;80(1-2):329-39.
- Cruciani RA. Methadone: to ECG or not to ECG...That is still the question. *J Pain Symptom Manage* 2008 Nov;36(5):545-52.
- Currie SR, Hodgins DC, Crabtree A, Jacobi J, Armstrong S. Outcome from integrated pain management treatment for recovering substance abusers. *J Pain* 2003;4:91-100.
- Daniell HW, Lentz R, Mazer N. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. *J Pain* 2006 Mar;7(3):200-10.
- Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. *J Pain* 2006 Dec;7(12):901-7.
- Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain* 2002 Oct;3(5):377-84.
- Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain* 2008 Jan;9(1):28-36.
- Daniell, Harry MD, Lentz R, Mazer N: Open-Label Pilot Study of Testosterone Patch Therapy in Men With Opioid-Induced Androgen Deficiency. *J Pain* 2006 Mar;7(3):200-10.
- Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging* 2003;20:23-57.
- De Conno F, Caraceni A, Gamba A, Mariani L, Abbattista A, Brunelli C, La Mura A, Ventafridda V. Pain measurement in cancer patients: a comparison of six methods. *Pain*. 1994 May;57(2):161-6.

- Definitions 2001 – Definitions related to the use of opioids for the treatment of pain. A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. Available at <http://www.painmed.org/pdf/definition.pdf>
- Dobscha SK, Corson K, Flores JA, Tansill EC, Gerrity MS. Veterans affairs primary care clinicians' attitudes toward chronic pain and correlates of opioid prescribing rates. *Pain Med* 2008;Jul-Aug;9(5):564-71.
- Dunbar SA, Katz NP. Chronic opioid therapy for nonmalignant pain in patients with a history of substance abuse: report of 20 cases. *J Pain Symptom Manage* 1996;11(3):163-71.
- Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007;129:355-62.
- Eisenberg E, McNicol ED, Carr DB. Efficacy of mu-opioid agonists in the treatment of evoked neuropathic pain: systematic review of randomized controlled trials. *Eur J Pain* 2006 Nov;10(8):667-76.
- Ersek M, Cherrier MM, Overman SS, Irving GA. The cognitive effects of opioids. *Pain Manag Nurs* 2004;5:75-93.
- Fagan MJ, Chen JT, Diaz JA, Reinert SE, Stein MD. Do internal medicine residents find pain medication agreements useful? *Clin J Pain* 2008 Jan;24(1):35-8.
- Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain* 2000 Dec 1;88(3):287-94.
- Fishbain DA, Cole B, Lewis J, Rosomoff HL, Rosomoff RS. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med* 2008 May-Jun;9(4):444-59.
- Fishbain DA. Approaches to treatment decisions for psychiatric comorbidity in the management of the chronic pain patient. *Med Clin North Am* 1999 May;83(3):737-60, vii.
- Fishman SM, Bandman TB, Edwards A, Borsook D. The opioid contract in the management of chronic pain. *J Pain Symptom Manage* 1999 Jul;18(1):27-37.
- Fishman SM, Wilsey B, Yang J, Reisfield GM, Bandman TB, Borsook D. Adherence monitoring and drug surveillance in chronic opioid therapy. *J Pain Symptom Manage* 2000 Oct;20(4):293-307.
- Fleming MF, Davis J, Passik SD. Reported lifetime aberrant drug-taking behaviors are predictive of current substance use and mental health problems in primary care patients. *Pain Med* 2008 Nov;9(8):1098-106.
- Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. *Pain* 1992;49(2):221-30.
- Fortin JD, Bailey GM, Vilensky JA. Does opioid use for pain management warrant routine bone mass density screening in men? *Pain Physician* 2008 Jul-Aug;11(4):539-41.
- Friedman DP. Perspectives on the medical use of drugs of abuse. *J Pain Symptom Manage* 1990 Feb;5(1 Suppl):S2-5.
- Frost H, Lamb SE, Klaber Moffett JA, Fairbank JC, Moser JS. A fitness programme for patients with chronic low back pain: 2-year follow-up of a randomised controlled trial. *Pain* 1998 Apr;75(2-3):273-9.
- Furlan AD, Sandoval JA, Mallis-Gagnon A, Tunks E. Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects. *CMAJ* 2006 May 23;174(11):1589-94.
- Gallagher RM. Treatment planning in pain medicine. Integrating medical, physical, and behavioral therapies. *Med Clin North Am*. 1999 May;83(3):823-49, viii.
- Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R. Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997;87(5):1075-81.
- Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *NEngl J Med* 2005 Mar 31;352(13):1324-34.

- Glidewell RN. Acetazolamide as an adjunct to CPAP treatment: a case of complex sleep apnea in a patient on long acting opioid therapy. *J Clin Sleep Med* 2009;5:63-4.
- Goldberg K, Simel D, Oddone E. Effect of an opioid management system on opioid prescribing and unscheduled visits in a large primary care clinic. *JCOM* 2005 Dec;12(12):621-28.
- Gomez-Batiste X, Madrid F, Moreno F, Gracia A, Trelis J, Nabal M, Alcalde R, Planas J, Camell H. Breakthrough Cancer Pain: Prevalence and Characteristics in Patients in Catalonia, Spain. *J Pain Symptom Manage* 2002;24(1):45-52.
- Goodwin JL, Kraemer JJ, Bajwa ZH. The use of Opioids in the treatment of Osteoarthritis: when, why, and how? *Curr Rheumatol Rep* 2009 Feb;11(1):5-14.
- Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol* 1998 Nov 1;148(9):887-92.
- Guzmán J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: systematic review. *BMJ* 2001 Jun 23;322(7301):1511-6.
- Hagen NA, Biondo P, Stiles C. Assessment and Management of Breakthrough Pain in Cancer Patients: Current Approaches and Emerging Research. *Curr Pain Headache Rep* 2008 Aug;12:241-8.
- Hakansson AF, Schlyter F, Berglund M. Factors associated with history of non-fatal overdose among opioid users in the Swedish criminal justice system. *Drug Alcohol Depend* 2008 Apr 94;(1-3):48-55.
- Hale ME, Fleischmann R, Salzman R, Wild J, Iwan T, Swanton RE, Kaiko RF, Lacouture PG. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain* 1999;15(3):179-83.
- Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA* 2008 Dec 10;300(22):2613-20.
- Hancock CM, Burrow MA. OxyContin use and abuse. *Clin J Oncol Nurs* 2002;6(2):109-10.
- Harati Y, Gooch C, Swenson M, Edelman SV, Greene D, Raskin P, Donofrio P, Cornblath D, Olson WH, Kamin M. Maintenance of the long-term effectiveness of tramadol in treatment of the pain of diabetic neuropathy. *J Diabetes Complications* 2000 Mar-Apr;14(2):65-70.
- Harden RN. Chronic opioid therapy: another reappraisal. *APS Bulletin* 2002 Jan/Feb; 12(1). Available at: <http://www.ampainsoc.org/pub/bulletin/jan02/poli1.htm>
- Hariharan J, Lamb GC, Neuner JM. Long-term opioid contract use for chronic pain management in primary care practice. A five year experience. *J Gen Intern Med* 2007 Apr;22(4):485-90.
- Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain* 2009 Mar;10(3):316-22.
- Heidrich DE. Controlled-release oxycodone hydrochloride (OxyContin). *Clin Nurse Spec* 2001;15(5):207-9.
- Herr K., Chronic pain in the older patient: management strategies. 2. *J Gerontol Nurs* 2002 Feb;28(2):28-
- Holmes CP, Gatchel RJ, Adams LL, Stowell AW, Hatten A, Noe C, Lou L. An opioid screening instrument: long-term evaluation of the utility of the Pain Medication Questionnaire. *Pain Pract* 2006 Jun;6(2):74-88.
- Huse E, Larbig W, Flor H, Birbaumer N. The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 2001;90(1-2):47-55.
- IASP, 1994 - IASP Pain Definition Terminology. Available at: http://www.iasp-pain.org/AM/Template.cfm?Section=Pain_Definitions&Template=/CM/HTMLDisplay.cfm&ContentID=1728

- Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. *Gen Hosp Psychiatry* 2008 Nov-Dec;30(6):521-7.
- Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, Shilliday BB, DeWalt DA, Pignone MP. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res* 2006 Apr 4;6:46.
- Jackman RP, Purvis JM, Mallett BS. Chronic nonmalignant pain in primary care. *Am Fam Physician* 2008 Nov 15;78(10):1155-62.
- Jacobson L, Mariano AJ, Chabal C, Chancy EF, Mar C. What is adequate and appropriate pain treatment? *JAMA* 1996 May;275(17):1310-1.
- Jacox A, Carr DB, Payne R. New clinical-practice guidelines for the management of pain in patients with cancer. *N Engl J Med* 1994;330(9):651-5.
- Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine* 1998 Dec1;23(23):2591-600.
- Javaheri S, Malik A, Smith J, Chung E. Adaptive pressure support servoventilation: a novel treatment for sleep apnea associated with use of opioids. *J Clin Sleep Med* 2008 Aug 15;4(4):305-10.
- Jensen MP, Strom SE, Turner JA, Romano JM. Validity of the Sickness Impact Profile Roland scale as a measure of dysfunction in chronic pain patients. *Pain* 1992 Aug;50(2):157-62.
- Jensen MP, Turner JA, Romano JM. Changes in beliefs, catastrophizing, and coping are associated with improvement in multidisciplinary pain treatment. *J Consult Clin Psychol* 2001;69(4):655-62.
- Jensen MP, Turner JA, Romano JM. Chronic pain coping measures: individual vs. composite scores. *Pain* 1992 Dec;51(3):273-80.
- Jensen MP, Turner LR, Turner JA, Romano JM. The use of multiple-item scales for pain intensity measurement in chronic pain patients. *Pain* 1996 Sep;67(1):355-40.
- Joranson DE, Cleeland CS, Weissman DE, Gilson AM. Opioids for chronic cancer and non-cancer pain: a survey of state medical board members; 1992. Available at: <http://www.painpolicy.wisc.edu/publicat/92jmldo.htm>
- Joranson DE, Gilson AM, Dahl JL, Haddox JD. Pain management, controlled substances, and state medical board policy: a decade of change. *J Pain Symptom Manage* 2002 Feb;23(2):138-47.
- Jovey RD, Ennis J, Gardner-Nix J, Goldman B, Hays H, Lynch M, Moulin D; Canadian Pain Society. Use of opioid analgesics for the treatment of chronic noncancer pain--a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manag*. 2003 Spring;8 Suppl A:3A-28A.
- Katz N, Mazer N. The impact of opioids on the endocrine system. *Clin J Pain* 2009 Feb;25(2):170-5.
- Kim TW, Alford DP, Malabanan A, Holick MF, Samet JH. Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend* 2006 Dec 1;85(3):258-62.
- Kinjo M, Setoguchi S, Schneeweiss S, Solomon DH. Bone mineral density in subjects using central nervous system-active medications. *Am J Med* 2005 Dec;118(12):1414.
- Kirkpatrick A, Derasari M, Kalra M, Miller R, Beede AM. Clinical outcomes using a protocol-contract for opioid use in patients with advanced reflex sympathetic dystrophy. *Anesthesiology* 1994 Sep;81:A1039.
- Knight EL, Avorn J. Quality indicators for appropriate medication use in vulnerable elders. *Ann Intern Med* 2001;135 (8 Pt 2):703-10.
- Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC. QTc interval screening in methadone treatment. *Ann Intern Med* 2009;150:387-95.

- Kuukkanen T, Mälkiä E. Effects of a three-month active rehabilitation program on psychomotor performance of lower limbs in subjects with low back pain: a controlled study with a nine-month follow-up. *Percept Mot Skills* 1998 Dec;87(3 Pt 1):739-53.
- Large RG, Schug SA. Opioids for chronic pain of non-malignant origin--caring or crippling. *Health Care Anal* 1995 Feb;3(1):5-11.
- Laval G, Sang B, Mallaret M, Villard ML. New Level III opioids of the World Health Organization. *Rev Med Interne* 2002 Jan;23 (1):55-70.
- Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc* 1999;47(1):40-50.
- Leung A, Wallace MS, Ridgeway B, Yaksh TL. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain* 2001;91(1-2):177-87.
- Magni GS, Rigatti-Luchini S, Fracca F, Merskey H. Suicidality in chronic abdominal pain: an analysis of the Hispanic Health and Nutrition Examination Survey (HHANES). *Pain* 1998 May;76(1-2):137-44.
- Malone MD, Strube MJ, Scogin FR. Meta-analysis of non-medical treatments for chronic pain. *Pain* 1988; 34(3):231-44.
- Management of Substance Use Disorder in the Primary Care Setting. Washington, DC: VA/DoD Evidence-Based Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs, and Health Affairs, Department of Defense, September 2009. Office of Quality and Performance. Available at: <http://www.healthquality.va.gov/>
- Manchikanti L, Manchukonda R, Pampati V, Damron KS, Brandon DE, Cash KA, McManus CD. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician* 2006 Apr;9(2):123-9.
- Markman JD. Not so fast: The reformulation of fentanyl and breakthrough chronic non-cancer pain. *Pain* 2008 Jun;136(3):227-9.
- Mattick RP, Hall W. Are detoxification programmes effective? *Lancet* 1996 Jan 13;347(8994):97-100.
- McCaffery M, Pasero C. Assessment: underlying complexities, misconceptions, and practical tools. In: M McCaffery; C Pasero, editors. *Pain: Clinical Manual*. 2nd ed. CV Mosby Company. St. Louis: MO; 1999. p. 35-75, 291-2.
- McCaffery M, Pasero CL. Talking with patients and families about addiction. *Am J Nurs* 1998;98(3):18-21.
- McCarberg, B. The Treatment of Breakthrough Pain. *Pain Med* 2007 Jan-Feb;8(S1):S8-S13.
- McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. *BMJ* 2009 Jun 16;338:b2225.
- McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, Lau J, Carr D; American Pain Society. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003 Jun;4(5):231-56.
- Meghani S, Wiedemer N, Becker W, Gracely E, Gallagher RM. Predictors of resolution of aberrant drug behavior in chronic pain patients treated in a structured opioid risk management program. *Pain Med* 2009 Jul-Aug;10(5):858-65.
- Miaskowski C. Patient education about cancer pain management: how much time is enough? *Pain* 2008 Mar;135(1-2):1-2.
- Michna E, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, Palombi D, Jamison RN. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manage* 2004;28:250-8.

- Michna E, Jamison RN, Pham L-D, Ross EL, Janfaza D, Nedeljkovic SS, Narang S, Palombi D, Wasan AD. Urine toxicology screening among chronic pain patients on opioid therapy: Frequency and predictability of abnormal findings. *Clin J Pain* 2007 Feb;23:173-9.
- Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid dependent patient, *Anesthesiology* 2004 Jul;101(1):212-27.
- Moffett JK, Torgerson D, Bell-Syer S, Jackson D, Llewlyn-Phillips H, Farrin A, Barber J. Randomised controlled trial of exercise for low back pain: clinical outcomes, costs, and preferences. *BMJ* 1999 Jul 31;319(7205):279-83.
- Mogri M, Desai H, Webster L, Grant BJ, Mador MJ. Hypoxemia in patients on chronic opiate therapy with and without sleep apnea. *Sleep Breath* 2009 Mar;13(1):49-57
- Mogri M, Khan M, Grant B, Mador J. Central sleep apnea induced by acute ingestion of opioids. *Chest* 2008 Jun;133(6):1484-8.
- Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther* 2001;23:1429-45.
- NSDUH 2008 - National Survey on Drug Use and Health 2008. A study conducted for Substance Abuse and Mental Health Services Administration (SAMSHA). Available at: <http://www.oas.samhsa.gov/NSDUH/2K8NSDUH/tabs/toc.htm>
- Ogon M, Krismer M, Sollner W, Kantner-Rumplmair W, Lampe A. Chronic low back pain measurement with visual analogue scales in different settings. *Pain* 1996 Mar;64(3):425-8.
- Palce JA, Cohen FL. Validity of a verbally administered numeric rating scale to measure cancer pain intensity. *Cancer Nurs* 1997;20(2):88-93.
- Palangio M, Damask MJ, Morris E, Doyle RT Jr, Jiang JG, Landau CJ, de Padova A. Combination hydrocodone and ibuprofen versus combination codeine and acetaminophen for the treatment of chronic pain. *Clin Ther* 2000 Jul;22(7):879-92.
- Palangio M, Northfelt DW, Portenoy RK, Brookoff D, Doyle RT Jr, Dornseif BE, Damask MC. Dose conversion and titration with a novel, once-daily, OROS osmotic technology, extended-release hydromorphone formulation in the treatment of chronic malignant or nonmalignant pain. *J Pain Symptom Manage* 2002 May;23(5):355-68.
- Palm S, Lehzen S, Mignat C, Steinmann J, Leimenstoll G, Maier C. Does prolonged oral treatment with sustained-release morphine tablets influence immune function? *Anesth Analg* 1998;86:166-72.
- Palos GR. Opioids and cancer survivors: issues in side-effect management. *Oncol Nurs Forum* 2008 Nov;35 Suppl:13-9.
- Panchal S, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 2007;61(7):1181-7.
- Pappagallo M, Heinberg LJ. Ethical issues in the management of chronic nonmalignant pain. *Semin Neurol* 1997;17(3):203-11.
- Pappagallo M. Aggressive pharmacologic treatment of pain. *Rheum Dis Clin North Am* 1999 Feb; 25(1):193-213.
- Passik SD, Weinreb HJ. Managing chronic nonmalignant pain: overcoming obstacles to the use of opioids. *Adv Ther* 2000;17(2):70-83.
- Paul SM, Zelman DC, Smith M, Miasowski C. Categorizing the severity of cancer pain: further exploration of the establishment of cutpoints. *Pain* 2005 Jan;113(1-2):37-44.

- Peat S, Sweet P, Miah Y, Barklamb M, Larsen U. Assessment of analgesia in human chronic pain. Randomized double-blind crossover study of once daily repro-dose morphine versus MST continus. *Eur J Clin Pharmacol* 1999;55(8):577-81.
- Pełoso PM, Bellamy N, Bensen W, Thomson GT, Harsanyi Z, Babul N, Darke AC. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000 Mar;27(3):764-71.
- Petrone D, Kamin M, Olson W. Slowing the titration rate of tramadol HCl reduces the incidence of discontinuation due to nausea and/or vomiting: a double-blind randomized trial. *J Clin Pharm Ther* 1999;24(2):115-23.
- Pitkänen MT, Numminen MK, Tuominen MK, Rosenberg PH. Comparison of metoclopramide and ondansetron for the prevention of nausea and vomiting after intrathecal morphine. *Eur J Anaesthesiol.* 1997 Mar;14(2):172-7.
- Portenoy RK, Messina J, Xie F, Peppin J. Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study. *Curr Med Res Opin* 2007;23(1):223-33.
- Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: a chart review. *Anesth Analg* 2000;90(4):933-7.
- Ram KC, Eisenberg E, Haddad M, Pud D. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain - new perspective of opioid-induced hyperalgesia. *Pain* 2008 Oct 15;139(2):431-8.
- Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. *Clin J Pain* 2008 Mar-Apr;24(3):204-10.
- Rauk R, Ma T, Kerwin R, Ahdieh H. Titration with oxymorphone extended release to achieve effective long-term pain relief and improve tolerability in opioid-naive patients with moderate to severe pain. *Pain Med* 2008 Oct;9(7):777-85.
- Roth SH, Fleischmann RM, Burch FX, Dietz F, Bockow B, Rapoport RJ, Rutstein J, Lacouture PG. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med* 2000;160(6):853-60.
- Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. *Pharmacotherapy* 1999;19 (1):88-93.
- Salzman RT, Roberts MS, Wild J, Fabian C, reder RF, Goldenheim PD. Can a controlled-release oral dose form of oxycodone be used as readily as an immediate-release form for the purpose of titrating to stable pain control? *J Pain Symptom Manage* 1999;18(4):271-9.
- Schieffer BM, Pham Q, Labus J, Baria A, Van Vort W, Davis P, Davis F, Naliboff BD. Pain medication beliefs and medication misuse in chronic pain. *J Pain* 2005 Sep;6(9):620-9.
- Schuckman H, Hazelett S, Powell C, Steer S. A validation of self-reported substance use with biochemical testing among patients presenting to the emergency department seeking treatment for backache, headache, and toothache. *Subst Use Misuse* 2008;43(5):589-95.
- Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995 May;61(2):277-84.
- Shorr RI, Griffin MR, Daugherty JR, Ray WA. Opioid analgesics and the risk of hip fracture in the elderly: codeine and propoxyphene. *J Gerontol* 1992 Jul;47(4):M111-5.
- Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2007;29(4):588-601.

- Sindrup SH, Andersen G, Madsen C, Smith T, Brosen K, Jensen TS. Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial. *Pain* 1999a;83(1):85-90.
- Sindrup SH, Madsen C, Brosen K, Jensen TS. The effect of tramadol in painful polyneuropathy in relation to serum drug and metabolite levels. *Clin Pharmacol Ther* 1999b;66(6):636-41.
- Smith M T, Edwards RR, Robinson RC, Dworkin RH. Suicidal ideation, plans, and attempts in chronic pain patients: factors associated with increased risk. *Pain* 2004 Sep;111(1-2):201-8.
- Stetter F, Kupper S. Autogenic training: a meta-analysis of clinical outcome studies. *Appl Psychophysiol Biofeedback* 2002 Mar;27(1):45-98.
- Syrjala KL. Integrating medical and psychological treatments for cancer pain. In: CR Chapman; KM Foley, editors. *Current and emerging issues in cancer pain: research and practice*. New York: Raven Press, Ltd; 1993. p. 393-409.
- APS 1997 - The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain* 1997;13(1):6-8.
- Theodoulou ML, Harriss L, Hawton K, Bass C. Pain and deliberate self-harm: an important association. *J Psychosom Res* 2005 Apr;58(4):317-20.
- Thompson R, Kane V, Cook JM, Greenstein R, Walker P, Woody G. Suicidal ideation in veterans receiving treatment for opiate dependence. *J Psychoactive Drugs* 2006 Jun;38(2):149-56.
- Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients. A retrospective study. *Acta Anaesthesiol Scand* 1999;43(9):918-23.
- Turk DC, Swanson KS, Gatchel RJ. Predicting opioid misuse by chronic pain patients: a systematic review and literature synthesis. *Clin J Pain* 2008 Jul-Aug;24(6):497-508.
- Turk DC. A diathesis-stress model of chronic pain and disability following traumatic injury. *Pain Res Manag* 2002 Spring;7(1):9-19.
- Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J pain Symptom Manage* 1996 Nov;12(5):273-82. Or
- U.S. Department of Health and Human Services. Food and Drug Administration. E14:Clinical evaluation of QT/QTc Interval prolongation and proarrhythmic potential for non-arrhythmic drugs. CDER, Rockville MD. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129357.pdf>
- United States Government Accountability Office. GAO methadone-associated overdose deaths: factors contributing to increased deaths and efforts to prevent them;2009 Mar. Report No.: GAO-09-341. Available at: www.gao.gov
- Vlaeyen JW, Crombez G. Fear of movement/(re)injury, avoidance and pain disability in chronic low back pain patients. *Man Ther* 1999 Nov;4(4):187-95.
- Vlaeyen JW, de Jong J, Geilen M, Heuts PH, Breukelen G. Graded exposure in vivo in the treatment of pain-related fear: a replicated single-case experimental design in four patients with chronic low back pain. *Behav Res Ther* 2001 Feb;39(2):151-66.
- Walker JM, Farney RJ. Are opioids associated with sleep apnea? A review of the evidence. *Curr Pain Headache Rep* 2009;13:120-6.
- Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, Kronborg I. Central sleep apnea in stable methadone maintenance treatment patients. *Chest* 2005 Sep;128(3):1348-56.
- Wang D, Teichtahl H, Goodman C, Drummer O, Grunstein RR, Kronborg I. Subjective daytime sleepiness and daytime function in patients on stable methadone maintenance treatment: possible mechanisms. *J Clin Sleep Med* 2008 Dec 15;4(6):557-62.

- Wang JJ, Ho ST, Hu OY. Comparison of intravenous nalbuphine infusion versus saline as an adjuvant for epidural morphine. *Reg Anesth* 1996;21(3):214-8.
- Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain* 2007 May;23(4):307-15.
- Wasan A D, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain* 2007 May;23(4):307-15.
- Wasan AD, Butler SF, Budman SH, Fernandez K, Weiss RD, Greenfield SF, Jamison RN. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? *Clin J Pain* 2009 Mar-Apr;25(3):193-8.
- Wasan AD, Michna E, Janfaza D, Greenfield S, Teter CJ, Jamison RN. Interpreting urine drug tests: prevalence of morphine metabolism to hydromorphone in chronic pain patients treated with morphine. *Pain Med* 2007 Oct;9(7):918-23.
- Watson CP. The treatment of neuropathic pain: antidepressants and opioids. *Clin J Pain* 2000;16(2 Suppl):S49-55.
- Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. *Pain Med* 2008 May-Jun;9(4):425-32.
- Wiedemer NL, Harden PS, Arndt IO, Gallagher RM. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med* 2007;8(7):573-84.
- Wilsey BL, Fishman SM, Tsodikov A, Ogden C, Symreng I, Ernst A. Psychological comorbidities predicting prescription opioid abuse among patients in chronic pain presenting to the emergency department. *Pain Med* 2008 Nov;9(8):1107-17.
- Zacny JP. Morphine responses in humans: a retrospective analysis of sex differences. *Drug Alcohol Depend* 2001;63(1):23-8.
- Zelman DC, Hoffman DL, Seifeldin R, Dukes E. Development of a metric for a day of manageable pain control: derivation of pain severity cutpoints for low back pain and osteoarthritis. *Pain* 2003;106(1-2):35-42.

