

# **Management of Opioid Therapy for Chronic pain**

**May, 2010**



## FDA Warnings/Regulatory Alert Subsequent to CPG Completion

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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 15)
- Table 3 (Page 27)
- Table E1 (Page 62, 63)
- Table E2 (Page 67)
- Table E3 (Page 68)
- Table E4 (Page 69)

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

**Department of Veterans Affairs  
Department of Defense**

**GUIDELINE SUMMARY**

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

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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 PTSD, 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 Operations Iraqi and Enduring Freedom (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.

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 of the full guideline – 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.<br><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.<br><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.<br><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.<br><i>At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</i>  |
| I  | <i>The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention.</i><br><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 to the full guideline](#).

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 full guideline.

## Opioid Therapy Guideline Update Working Group

| VA  | DoD   |
|---|---|
| <b>Michael E. Clark, PhD</b>  | <b>Jeffrey Barr, Maj, USAF, MC (Co-Chair)</b>   |
| <b>Rollin M. Gallagher, MD, MPH (Co-Chair)</b>  | Thomas Brooks, LTC, AN, USA   |
| <b>Francine Goodman, Pharm. D</b>   | Allison J. Franklin, MAJ, MC, USA   |
| Susan J. Hagan, MSN   | Kevin T. Galloway, LTC, AN, USA   |
| Timothy Lee, MD   | Sushma Jani, MD   |
| Shannon Miller, MD  | James E. McCrary, Lt Col, USAF, MC  |
| <b>Jack M. Rosenberg, MD (Co-Chair)</b>   | Patrick A. Sherman, MAJ, MS, USA  |
| <b>Nancy L. Wiedemer, RN, CRNP</b>  | James J. Staudenmeier, COL, MC, USA   |
|   | Shana Trice, Pharm. D   |
| <b>Office of Quality and Performance, VHA</b><br><br>Carla Cassidy, RN, MSN, NP   | <b>Quality Management Division<br/>US Army Medical Command</b><br><br>Ernest Degenhardt, MSN, RN, ANP-FNP<br><br>Marjory Waterman, MN, RN |
| FACILITATOR<br><b>Oded Susskind, MPH</b>  |   |
| <b>Healthcare Quality Informatics</b><br><br>Martha D'Erasmus, MPH<br><br>Rosalie Fishman, RN, MSN, CPHQ<br><br>Joanne Marko, MS, SLP |   |

\* **Bolded** names are members of the CORE Editorial Panel.

Additional contributor contact information is available in [Appendix H to the full guideline](#)

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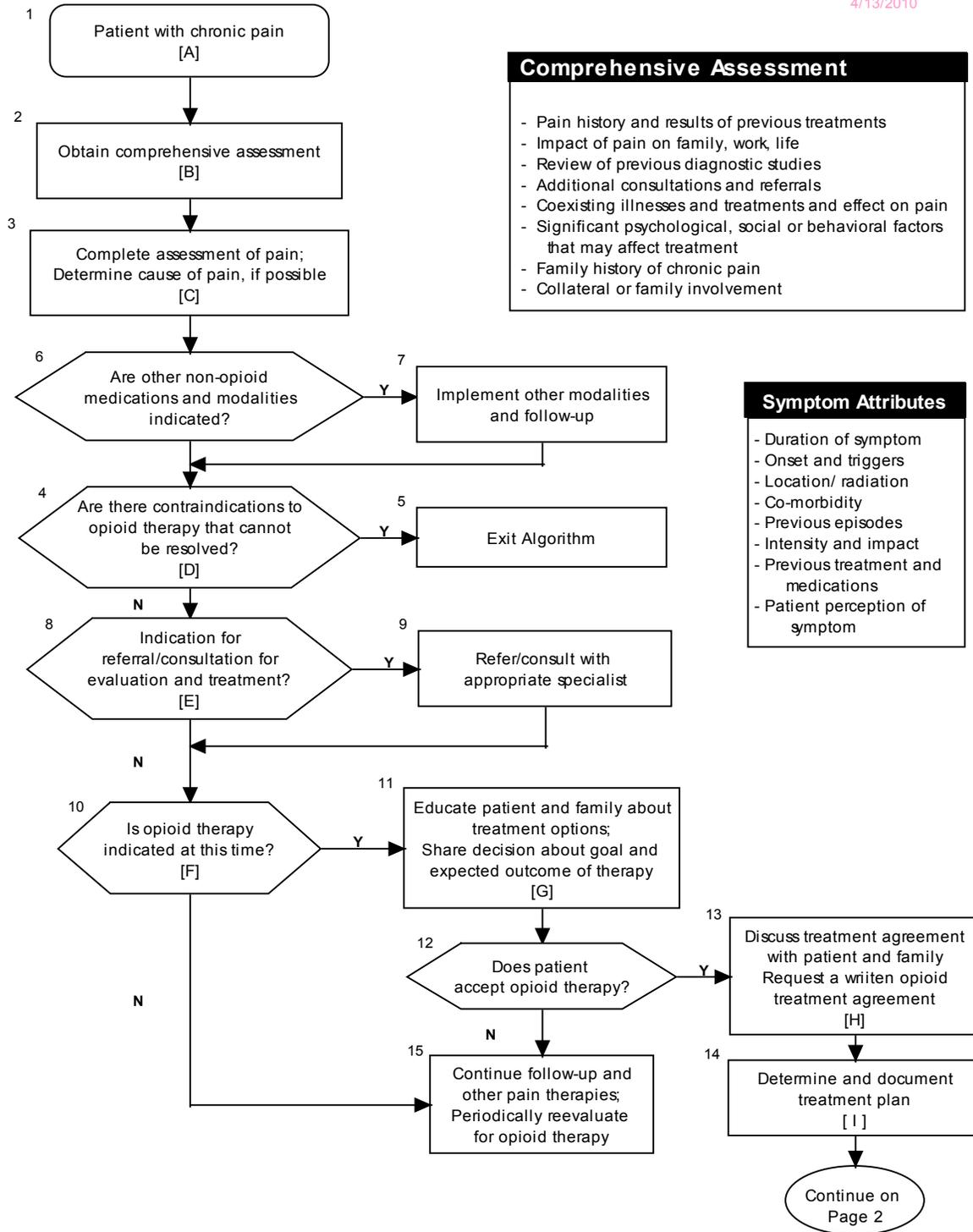
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Algorithms

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

4/13/2010



**Comprehensive Assessment**

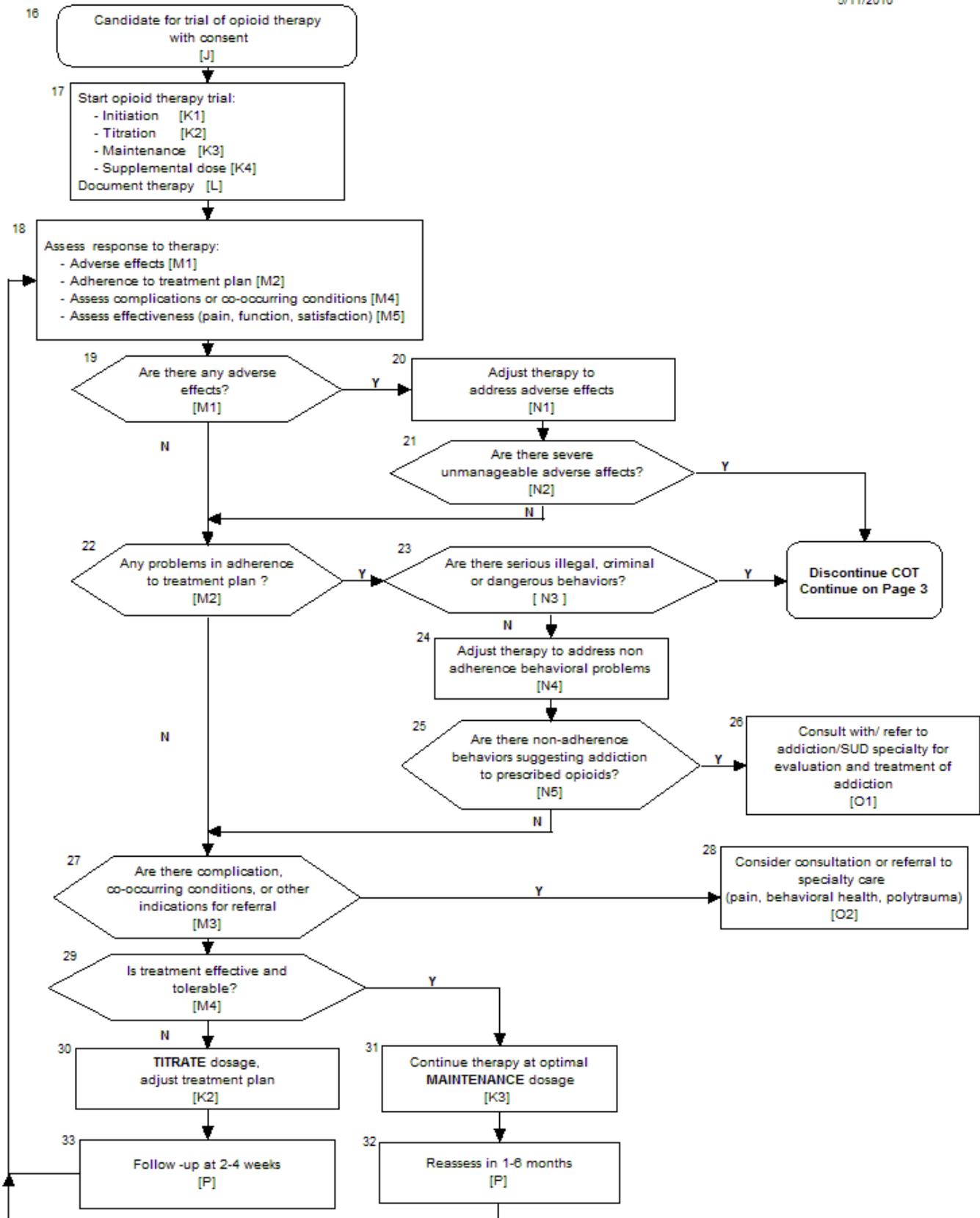
- Pain history and results of previous treatments
- Impact of pain on family, work, life
- Review of previous diagnostic studies
- Additional consultations and referrals
- Coexisting illnesses and treatments and effect on pain
- Significant psychological, social or behavioral factors that may affect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

**Symptom Attributes**

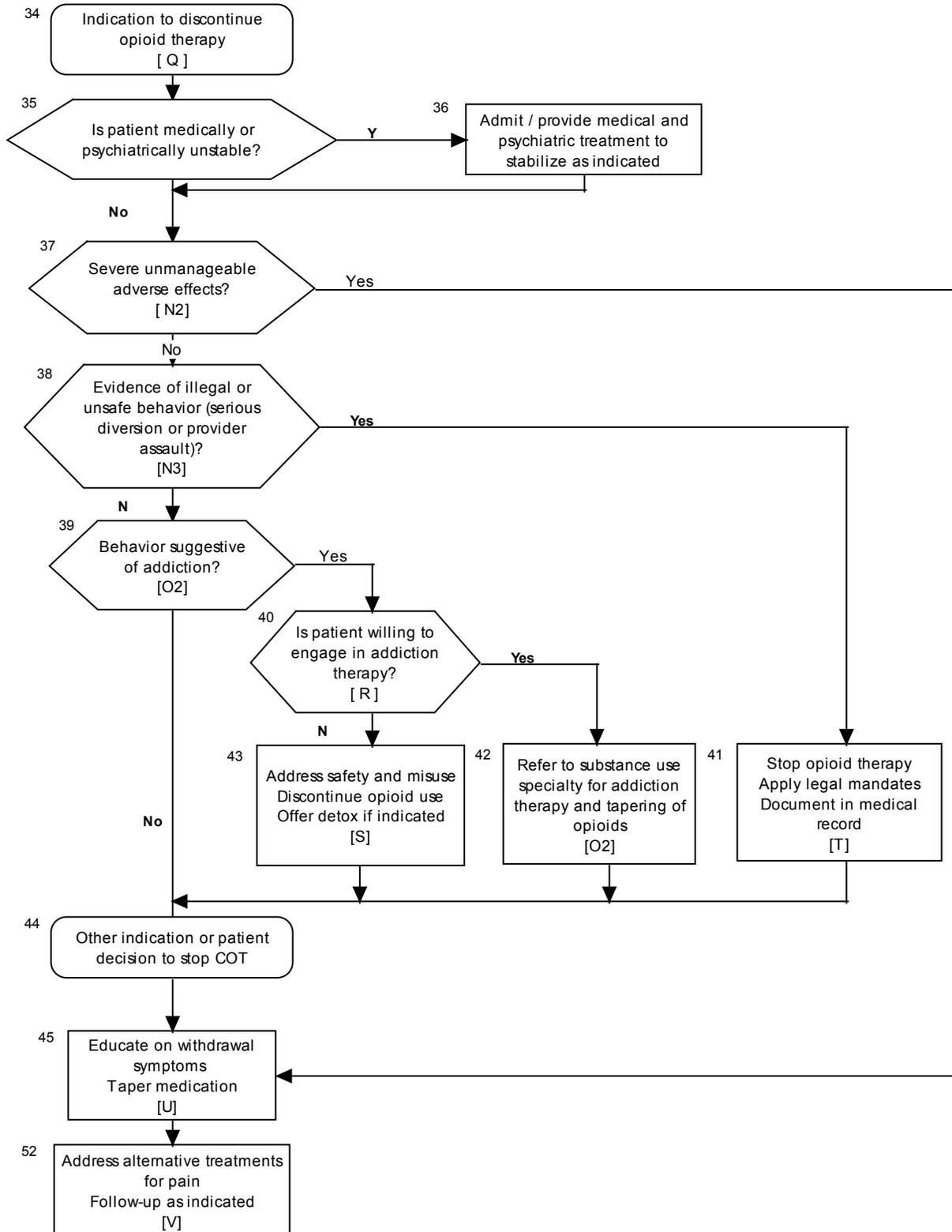
- Duration of symptom
- Onset and triggers
- Location/ radiation
- Co-morbidity
- Previous episodes
- Intensity and impact
- Previous treatment and medications
- Patient perception of symptom

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

5/11/2010



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



## Annotations

### Definitions

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#### 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 (ASAM, 1997)

#### Pseudoaddiction

Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may “clock watch,” and may otherwise seem 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

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### A. Patient with Chronic Pain

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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

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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.

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<sup>a</sup>**

| Phenanthrenes   | Diphenylheptanes            | Phenylpiperidine | Other                    |                        |
|---|-----------------------------|------------------|--------------------------|------------------------|
| Codeine<br>Hydrocodone<br>Hydromorphone<br>Morphine<br>Oxycodone<br>Oxymorphone | Methadone<br>Propoxyphene ✗ | Fentanyl         | Tramadol ✗<br>Tapentadol | <b>See FDA Warning</b> |

<sup>a</sup> for contraindication regarding specific medications (See Appendix E)

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

### OBJECTIVE

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.

## 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

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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.

## 2. DETERMINATION OF THE APPROPRIATENESS OF OPIOID THERAPY

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### D. Are There Contraindications to Opioid Therapy that Cannot be Resolved?

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#### 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](#)).

## 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*

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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

## 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](#)

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

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

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

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### OBJECTIVE

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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

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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

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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

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

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### OBJECTIVE

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

### BACKGROUND

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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

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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.

## I. Determine and Document Treatment Plan

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### *OBJECTIVE*

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Identify and describe key elements of the opioid treatment plan.

### *BACKGROUND*

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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*

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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.

### **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.

### 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](#)).

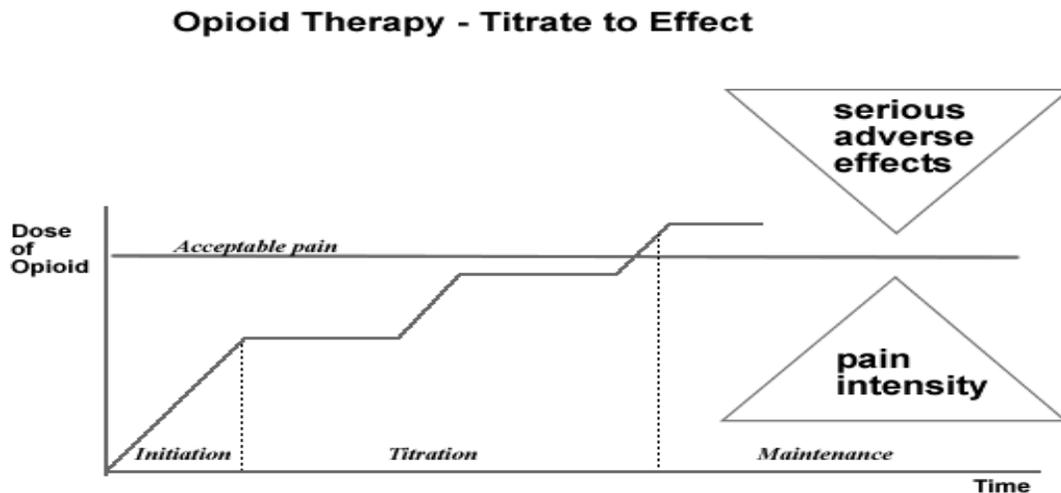


Figure 1 Opioid Therapy Titrate to Effect

## K1. Initiation Phase

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### OBJECTIVE

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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

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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

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#### **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.

**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* <sup>†</sup>             | ◆ <sup>e</sup> | ×                   | ◆ and ↓           | ×              |               |          | ◆ and ↓                | Less effective             |
| Fentanyl transdermal             | +                     | +                 | C <sup>††</sup>             | UC (c)         | ◆ and ↓             |                   | ◆              |               |          |                        |                            |
| Hydrocodone                      |                       |                   | C <sup>††</sup>             | PC             |                     |                   | ◆              |               |          |                        | ? less effective           |
| Hydromorphone                    | + (OS, RS)            | + (RS)            | B <sup>††</sup>             | PC             | ◆ and ↓             |                   | ◆(RBD)         |               |          |                        |                            |
| Methadone (e)                    | + (OS)                |                   | B <sup>††</sup>             | PC             | ◆ and ↓             |                   | ◆              | ◆             |          |                        |                            |
| Morphine                         | + (OS, RS)            | + (RS)            | C <sup>††</sup>             | PC             |                     | ↓ or ×            | ◆ or ×(RBD)    |               |          | ◆ and ↓                |                            |
| Morphine SR/CR (8-12h); ER (24h) |                       |                   |                             |                |                     |                   |                |               |          |                        |                            |
| Oxycodone                        | + (OS)                |                   | B <sup>††</sup>             | PC             |                     | ◆ and ↓           | ×(ND)          |               |          |                        | ? less effective           |
| Oxycodone CR (12h)               |                       |                   |                             |                |                     |                   |                |               |          |                        |                            |
| Oxymorphone                      |                       |                   | B <sup>††</sup>             | PC             | ×                   | ◆ and ↓           | ◆(RBD)         |               |          |                        |                            |
| Oxymorphone ER (12h)             |                       |                   |                             |                |                     |                   |                |               |          |                        |                            |
| Propoxyphene                     |                       |                   | C <sup>††</sup>             | PC             | ×                   | ×                 | ×              |               | ◆        | ×                      |                            |
| Tapentadol                       |                       |                   | C <sup>†</sup>              | ×(f)           | ◆                   | ↓ or ×            | ×(ND)          |               | ◆        |                        |                            |
| Tramadol                         |                       |                   | C <sup>†</sup>              | PC             | ◆ and ↓             | ◆ and ↓           | ×(RBD)         |               | ×        | ◆ and ↓                | ? less effective           |
| Tramadol ER (24h)                |                       |                   |                             |                |                     |                   |                |               |          |                        |                            |

✗

✗

See FDA Warning

- (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 of the full guideline for 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 3<sup>rd</sup> 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

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## K2. Titration Phase

### OBJECTIVE:

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<br>Worsening or progression of pain condition<br>Exacerbation of a different chronic medical condition<br>A new acute medical condition<br>Concurrent mental health condition (e.g. depression, anxiety, PTSD, SUD)<br>Concurrent stressor<br>Development of opioid tolerance<br>Opioid induced hyperalgesia<br>Drug interaction | Improvement of the underlying medical condition<br>Improvement in the patients' biopsychosocial status secondary to an interdisciplinary approach to pain management |

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 E](#))
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, 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 (Appendix E: [Table E4](#))
  - 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 E4 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-2](#), and [Appendix F of the Full Guideline for 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 E4](#), for equianalgesic doses and conversion methods.

**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.

## 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 1/6<sup>th</sup> 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.

**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.

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## 4. ASSESSMENT OF PATIENT STATUS AND RESPONSE TO THERAPY

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### M1. Assess for Adverse Effects

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#### *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.

### M2. Assess Adherence

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#### *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 that 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

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<br>- History of legal problems<br>- Positive UDT | - Family history of drug abuse<br>- History of childhood sexual abuse<br>- History of DUIs or drug convictions<br>- Lost or stolen prescriptions<br>- Obtaining opioids from alternate sources<br>- High SOAPP or SOAPP-R scores | - Male sex<br>- History of an anxiety disorder<br>- History of prescribed drug misuse<br>- Race (nonwhite)<br>- Education<br>- History of MVAs<br>- History of schizophrenia |

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

### 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.

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

#### *OBJECTIVE*

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

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

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### OBJECTIVE

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 (NRS) (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](http://www1.va.gov/pain_management/docs/Outcomes.doc) ]

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## 5. ADJUSTMENT OF THERAPY

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### N1. Address Adverse Effects

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#### *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*

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##### ***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  |  |  |
| <b>Medical comorbidities that can lead to osteoporosis:</b>  |  |  |
| <ul style="list-style-type: none"> <li>• AIDS/HIV</li> <li>• Ankylosing spondylitis</li> <li>• Blood and bone marrow disorders</li> <li>• Breast cancer</li> <li>• Cushing's syndrome</li> <li>• Eating disorders</li> <li>• Emphysema</li> <li>• Female athlete triad</li> <li>• Gastrectomy</li> <li>• Gastrointestinal bypass procedures</li> <li>• Hyperparathyroidism</li> <li>• Hyperthyroidism</li> </ul> | <ul style="list-style-type: none"> <li>• Idiopathic scoliosis</li> <li>• Inflammatory bowel disease</li> <li>• Diabetes mellitus</li> <li>• Kidney disease</li> <li>• Lupus</li> <li>• Lymphoma and leukemia</li> <li>• Malabsorption syndromes (e.g., celiac disease, Crohn's disease)</li> <li>• Multiple myeloma</li> <li>• Multiple sclerosis</li> <li>• Organ transplants</li> <li>• Parkinson's disease</li> </ul> | <ul style="list-style-type: none"> <li>• Poor diet</li> <li>• Post-polio syndrome</li> <li>• Premature menopause</li> <li>• Prostate cancer</li> <li>• Rheumatoid arthritis</li> <li>• Severe liver disease (including biliary cirrhosis)</li> <li>• Spinal cord injuries</li> <li>• Stroke (CVA)</li> <li>• Thalassemia</li> <li>• Thyrotoxicosis</li> <li>• Weight loss</li> </ul> |
| <b>Certain drugs that can lead to osteoporosis:</b>  |  |  |
| <ul style="list-style-type: none"> <li>• Aluminum-containing antacids</li> <li>• Antiepileptic drugs, such as phenytoin, phenobarbital, carbamazepine, and possibly non-enzyme-inducing agents</li> <li>• Aromatase inhibitors, such as anastrozole, exemestane and letrozole</li> <li>• Cancer chemotherapeutic drugs</li> <li>• Cyclosporine A</li> </ul>  | <ul style="list-style-type: none"> <li>• Glucocorticoids, such as cortisone and prednisone</li> <li>• Gonadotropin releasing hormone (GnRH) such as leuprolide and goserelin</li> <li>• Heparin</li> <li>• Lithium</li> <li>• Medroxyprogesterone acetate for contraception</li> <li>• Methotrexate</li> </ul>   | <ul style="list-style-type: none"> <li>• Proton pump inhibitors (PPIs)</li> <li>• Selective serotonin reuptake inhibitors (SSRIs)</li> <li>• Tacrolimus</li> <li>• Tamoxifen (premenopausal use)</li> <li>• Thiazolidenediones (pioglitazone and rosiglitazone)</li> <li>• Thyroid hormones in excess</li> </ul>   |

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## N2 Severe Unmanageable Adverse Effects

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

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

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### 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**

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

### RECOMMENDATIONS

1. Address safety issues immediately and apply legal mandates as appropriate.

2. Dangerous or illegal behaviors may require immediate cessation of the opioid therapy with consideration of appropriate treatment of potential withdrawal symptoms.
3. Document and refer to behavior health specialty those patients demonstrating behaviors suggestive of suicide.
4. 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.
5. 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.

## **N4. Minor Non-adherence or Medication Misuse**

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### *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.

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

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### *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.

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## 6. CONSULTATION/REFERRAL

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### 01. Consultation or Referral to SUD/Addiction Specialty for Evaluation and Treatment of Non-Adherence Behaviors, or Misuse Suggestive of Addiction to Prescribed Medication, Including Addiction

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#### BACKGROUND

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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

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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 a 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> |

## 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)

## 7. FOLLOW-UP

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### P. Follow-up at Appropriate Intervals

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#### *OBJECTIVE*

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Evaluate pain as a guide to further intervention.

#### *BACKGROUND*

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

#### *RECOMMENDATIONS*

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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.

## 8. DISCONTINUE OPIOID THERAPY

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### Q. Indication to Discontinue OT

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#### BACKGROUND

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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

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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](#))

#### ***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

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### BACKGROUND

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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

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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.

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

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### BACKGROUND

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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

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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

## **T. Discontinue Opioid Therapy; Taper Medication**

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### *OBJECTIVE*

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

### *BACKGROUND*

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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*

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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**

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### *OBJECTIVE*

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

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## 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.

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## 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.va.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.va.gov/Files/OpioidGdline.pdf>)

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## V. Follow-up as Indicated

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### OBJECTIVE

Provide appropriate long-term surveillance.

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### 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*

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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

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### W. OT in Patient with History of Substance Use

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#### RECOMMENDATIONS

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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]

#### ***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.

### X. OT and Risk for Sleep Apnea

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#### BACKGROUND

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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

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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]

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## APPENDICES

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Appendices A, D, F, H and I can be found in the full Guideline at: <http://www.healthquality.va.gov>

## 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:**

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## APPENDIX C: Sample Opioid Pain Care Agreement

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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 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)<br>Peak (Min)<br>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)<br>Ceiling effect occurs at doses > 60 mg/dose   | 15 to 30<br>30 to 60<br>4 to 6                      | Elderly or debilitated– Use with caution<br>Hepatic dysfunction – conversion to active metabolite (morphine) may be reduced in patients with cirrhosis; avoid use in patients with liver disease<br>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<br>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<br>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<br>30 to 60<br>4 to 8                      | Elderly or debilitated – Use with caution; start at low end of dosing range<br>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<br>30 to 60<br>4 to 6                      | Elderly or debilitated – Use with caution, starting at low end of dosing range.<br>Hepatic / Renal dysfunction – Use with caution.   |   |

| Short-Acting Opioid †                                | Initial Oral Dosage  | Dosage Titration   | Analgesic Onset (Min)<br>Peak (Min)<br>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<br>60 to 90<br>2 to 6                      | Elderly or debilitated – give with extreme caution; use lower dose<br>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<br>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<br>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<br>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<br>30 to 60<br>3 to 6                      | Elderly or debilitated– reduce dosage<br>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 <sup>‡</sup> ). 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 tolerability) | Individually titrate as needed and tolerated   | 34 to 45<br>—<br>4                                  | Elderly or debilitated – use with caution and start at low end of dosing range; levels are increased 40% in patients ≥ 65 yr old<br>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.<br>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%.<br>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. |

✗  
See FDA  
Warning

| Short-Acting Opioid †                            | Initial Oral Dosage   | Dosage Titration  | Analgesic Onset (Min)<br>Peak (Min)<br>Duration (H) | Dosing In Special Populations   | Other Considerations  |
|--|---|---|---|---|---|
| Propoxyphene (alone or in combination with APAP) | HCl: 65 mg q 6 to 8 hours<br>Napsylate: 100 mg q 6 to 8 hours | Increase dose as needed and tolerated<br>Maximum daily dose is 390 mg/d for HCl salt and 600 mg/d for napsylate salt<br>(Maximum daily dose of APAP: 4000 mg/day APAP; 2000 mg/day APAP in chronic alcoholics)                  | 15 to 60<br>120 to 180<br>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<br>Elderly or debilitated – Use is not recommended in elderly <sup>1</sup> ; half-life of propoxyphene and norpropoxyphene may be markedly prolonged (36 and 53 h, respectively) in elderly patients. <sup>2</sup> Use with caution in debilitated patients.<br>Hepatic disease – Increased bioavailability of propoxyphene; reports of hepatotoxicity; avoid use in patients with liver disease<br>Renal dysfunction – Propoxyphene and norpropoxyphene accumulate in renal insufficiency; may result in respiratory or CNS depression, neurotoxicity, or cardiotoxicity; avoid use | Seizures and cardiac arrhythmias may occur with the use of high doses or with renal failure<br>Equianalgesic doses for propoxyphene salts: 65 mg HCl ≅ 100 mg napsylate.<br>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 q4–6hours   | Subsequent dose is 50, 75, or 100 mg q4–6h, adjusted to analgesia and tolerability.<br>Second dose may be given 1 h after the first dose if necessary.<br>Max recommended dose: 700 mg on first day, 600 mg on subsequent days. | —<br>60<br>4 to 6                                   | Elderly – Consider starting at the lower end of recommended doses.<br>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.<br>Renal dysfunction – Not recommended in severe renal impairment. No dosage adjustment for mild or moderate renal impairment.<br>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.<br>Use caution in patients taking serotonergic agents or use alternative agent.   |

| Short-Acting Opioid †   | Initial Oral Dosage | Dosage Titration   | Analgesic Onset (Min)<br>Peak (Min)<br>Duration (H) | Dosing In Special Populations   | Other Considerations  |
|---|---------------------|--|---|---|---|
|  See FDA Warning<br>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)<br><br>Subsequent increments of 50 mg/d may be made every 3 d to 200 mg/d (50 mg q 6 h)<br><br>After titration, may give 50 to 100 mg q 4 to 6 h<br><br>Maximum daily dose: 400 mg/d<br>(Maximum 4000 mg/d APAP; 2000 mg/d APAP in chronic alcoholics) | < 60<br>~120 to 240<br>3 to 6                       | Elderly or debilitated: In elderly patients >75 y: give < 300 mg/d in divided doses. Use with caution in debilitated patients.<br><br>Hepatic dysfunction – Decrease dosage to 50 mg q 12 h in patients with cirrhosis<br><br>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<br><br>Dose carefully or use another agent in patients on serotonergic agents |

Sources: Ortho-McNeil, Tylenol with codeine package insert (2000)<sup>5</sup>; Ortho-McNeil, Ultram package insert (2001)<sup>4</sup>; Drug Facts and Comparisons (2002)<sup>6</sup>; Endo, Percocet, Percodan and Zydone package inserts (2001)<sup>6,7,8</sup>; Purdue, MSIR package insert (2001)<sup>9</sup> and OxyIR package insert (2000)<sup>9,10</sup>; Michalets (1998)<sup>11</sup>; Davis and Homs (2001)<sup>12</sup>  
 APAP = Acetaminophen; ASA = Aspirin (acetylsalicylic acid); IBU = Ibuprofen; MAOI = Monoamine oxidase inhibitor

† Check local formulary for available formulations.

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

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

| Long-Acting Opioid †        | Initial Dosage   | Dosage Titration   | Analgesic Onset (Min)<br>Peak (Min)<br>Duration (H) | Dosing In Special Populations   | Other Considerations   |
|-----------------------------|--|--|---|---|--|
| Fentanyl Transdermal System | 25 mcg/h transdermally. q 72 h<br><br>CONTRAINDICATED in non-opioid-tolerant patients<br>12 mcg/h dose has not been evaluated as an initial dose | 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<br>Make increments at least 3 d after initial dose then not more often than q 6 d thereafter as necessary | 12 to 18 (h)<br>24 to 72 (h)<br>48 to 72            | Elderly or debilitated – Avoid initiation at doses > 25 mcg/h unless patient is already taking > 135 mg oral morphine or equivalent. In elderly patients, clearance of i.v. fentanyl may be greatly decreased; relevance to transdermal fentanyl is unknown; use reduced dose<br>Hepatic / Renal dysfunction – Insufficient information; use with caution<br>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 | 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,<br>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.<br>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.<br>Use extreme caution and frequent monitoring in patients receiving t.d. fentanyl and any CYP 3A4 inhibitor. §<br>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. |

| Long-Acting Opioid † | Initial Dosage  | Dosage Titration   | Analgesic Onset (Min)<br>Peak (Min)<br>Duration (H)  | Dosing In Special Populations  | Other Considerations  |
|----------------------|---|--|--|--|---|
| Methadone            | 2.5 to 10 mg orally.<br>q 8 to 12 h<br>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 | Increments of 2.5 mg q 8 h may be made every 5 to 7 days<br><b>START LOW AND GO SLOW</b> | 30 to 60<br>—<br>4 to 12<br>Analgesic duration increases with continued use and cumulative effects | Elderly or debilitated—reduce dosage; in elderly, clearance may be decreased<br>Hepatic dysfunction – in patients with stable chronic liver disease or mild to moderate hepatic dysfunction, no dosage adjustments required<br>Renal dysfunction – methadone and its metabolites do not accumulate in patients with renal failure; however, dosage reduction by up to 50% is recommended in end-stage renal failure or dialysis patients | Recommended first- or second-line long-acting agent, but prescribers of methadone should be thoroughly familiar with its complex pharmacokinetic and pharmacodynamic properties or consult a clinician with experience in dosing methadone<br>Plasma half-life (22 to 128 h short-term; 24 to 48 h at steady-state) may be longer than the analgesic duration<br>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<br>Monitor patients extra carefully during initiation, conversions to and from other opioids, and dose titration<br>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<br>Once a stable analgesic dose is reached, the dosing interval may be extended to q 8 to 12 h or longer<br><b>SHOULD NOT BE USED FOR AS-NEEDED (P.R.N.) SUPPLEMENTAL OPIOID THERAPY</b><br>The only long-acting opioid available as an oral solution<br>For dosing recommendations in patients previously exposed to opioids, see Methadone Dosing Recommendations for Treatment of Chronic Pain<br>Urinary excretion decreases and elimination half-life increases when urinary pH exceeds 6<br>May prolong QTc intervals on ECG; Risk-of torsades de pointes |

| Long-Acting Opioid †  | Initial Dosage   | Dosage Titration  | Analgesic Onset (Min)<br>Peak (Min)<br>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)<br><br>to<br>30 mg q 24 h (ER) | Total daily increments of < 30 to 40 mg/d may be made q 2 d   | 30 to 60<br>30 to 60<br>Varies by product; overall range is 8 to 24 | Elderly or debilitated – use with caution and at lower dose<br><br>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<br><br>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<br><br>M6G, an active metabolite, may accumulate in renal impairment and contribute to toxic effects<br><br>M3G, a metabolite without analgesic activity, may accumulate in renal impairment. This metabolite has been implicated in morphine-induced neurotoxicity, hyperalgesia, and allodynia.<br><br>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<br><br>Thereafter, the total daily dose may be increased by 25% to 50% of the current dose every 1 or 2 d | 30 to 60<br>90 to 180<br>8 to 12                                    | Elderly or debilitated patients – reduce initial dosage to 1/3 to 1/2 of the usual dose<br><br>Hepatic dysfunction – Reduce initial dose to 1/3 to 1/2 of the usual dose and use with caution<br><br>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<br><br>Controlled-release tablets should be swallowed whole, not broken, chewed, or crushed<br><br>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 <sup>‡</sup> ). Impact of decreased formation of oxymorphone on analgesic efficacy of oxycodone is unknown  |

| Long-Acting Opioid †         | Initial Dosage  | Dosage Titration   | Analgesic Onset (Min)<br>Peak (Min)<br>Duration (H) | Dosing In Special Populations  | Other Considerations   |
|------------------------------|---|--|---|--|--|
| Oxymorphone Extended Release | 5 mg orally every 12 h  | May increase by 5 to 10 mg every 12 h every 3–7 days   | —<br>1 (fasted state)<br>—                          | 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.<br>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, oxymorphone should be started with the lowest dose and titrated slowly<br>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 oxymorphone ER by 50%.<br>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 oxymorphone. |
| Tramadol ER                  | 100 mg once daily<br>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.<br>Max dose: 300 mg/day | —<br>12 h<br>24 h                                   | Elderly > 65 years: use caution, usually starting at low end of dosing range; use even greater caution in patients > 75 years.<br>Hepatic dysfunction: Should not be used in severe hepatic impairment (Child-Pugh Class C)<br>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.   |

 See FDA Warning

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

† Check local formulary for available formulations.

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

§ CYP-3A4 Inhibiting Drugs: Ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, 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 | LOZENGE      | TAB    | SUPP   | PATCH       |
| Codeine/APAP, ASA          | x    |             |          | x  |              |        |        |             |
| Codeine                    | x    |             |          |    |              |        |        |             |
| Fentanyl                   |      |             |          |    |              |        |        | x           |
| Fentanyl citrate           |      |             |          |    | x            | 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

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See FDA  
Warning

**Table E 4: Equianalgesic and conversion doses for patients previously receiving other opioids**

| Opioid Agent  | Estimated Oral Equianalgesic Dose (Mg)* | Initial Conversion Dose (Not Equianalgesic) <sup>†</sup>  |
|---------------|---|---|
| Codeine       | 180 to 200 <sup>‡</sup>                 | 30 mg q 4 to 6 h  |
| Fentanyl      | —<br>(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 E5, <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<br>2 to 4 chronic              | Methadone-to-morphine dosage proportion (%) is dependent on morphine-equivalent dose of previous opioid<br>For gradual conversion to methadone:<br><b>Oral morphine</b> <b>Methadone</b><br>< 200 mg/d        5 mg q 8 h<br>200 to 500 mg/d    ~7% of oral morphine-equivalent dose, given in divided doses q 8 h<br>> 500 mg/d        See <i>Methadone Dosing Recommendations for Treatment of Chronic Pain</i><br>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 <sup>§</sup>                   | 50% to 67% of estimated oral equianalgesic dose   |
| Oxymorphone   | 10                                      | 50% to 67% of estimated oral equianalgesic dose   |
| Propoxyphene  | 100 to 130 <sup>‡</sup>                 | HCl: 65 mg q 6 to 8 h<br>Napsylate: 100 mg q 6 to 8 h   |
| Tapentadol    | No data<br>(50 to 100 <sup>‡</sup> )    | 50 to 100 mg q 4 to 6 h   |
| Tramadol      | No data<br>(100 to 150 <sup>‡</sup> )   | 25 mg every morning   |

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

<sup>†</sup> 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 E5.

<sup>‡</sup> 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.

<sup>§</sup> Exceeds recommended initial dose (oxycodone 5 mg)



See FDA  
Warning

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**Opioid Conversion Instructions**

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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 fentanyl, see conversion doses in Table E5).
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.
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**Table E 5: 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)

### 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 E5 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 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                                |
| CNCP   | Chronic Non Cancer Pain                               |
| COPD   | Chronic Obstructive Pulmonary Disease                 |
| 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  | Screeener and Opioid Assessment of Patients with Pain |
| SR     | Strength of Recommendation                            |
| SUD    | Substance Use Disorder                                |
| TBI    | Traumatic brain Injury                                |

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|      |   |
|------|---|
| 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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