



POCKET GUIDE FOR CLINICIANS FOR MANAGEMENT OF CHRONIC PAIN

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TABLE OF CONTENTS

INTRODUCTION.....	03
TYPES AND MECHANISM OF PAIN.....	04
CHRONIC PAIN AND PSYCHIATRIC COMORBIDITY.....	11
ASSESSMENT OF PAIN.....	15
STEPPED CARE MODEL OF CARE.....	23
PHARMACOLOGICAL INTERVENTIONS.....	29
NONPHARMACOLOGICAL INTERVENTIONS.....	46
OPIOID AND SUBSTANCE USE DISORDERS.....	54
OPIOID SAFETY AND RISK ASSESSMENT.....	70
OPIOID EDUCATION AND NALOXONE DISTRIBUTION PROGRAM.....	87
REFERENCES AND RESOURCES.....	92

INTRODUCTION

The International Association of Study of Pain defines *pain* as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described by an individual in terms of such damage.

Pain is the most common physical symptom, affecting 100 million Americans, more than diabetes, heart disease and cancer combined. Clinicians in virtually any healthcare setting encounter individuals with pain. Pain is associated with a wide range of injury and disease. An estimated 20% of American adults report disruptive sleep due to pain or physical discomfort. Ineffective management of pain can result in increased outpatient visits, hospitalizations, length of hospital stay and readmissions. It poses a significant public health challenge with annual costs of \$560-\$635 billion, including incremental healthcare costs and lost productivity. Most importantly, it affects quality of life, placing emotional and financial burdens on individuals and their families.^{1, 2}

TYPES AND MECHANISMS OF PAIN

Pain can be classified based on pain physiology, type of tissue involved and time course

Physiology: Nociceptive, neuropathic and inflammatory

Tissue type: Somatic and visceral

Time course: Acute, chronic and acute on chronic

Nociceptive: Normal response to noxious insult or injury to body tissues such as skin, muscles, visceral organs, joints, tendons or bones, often described as deep and aching. Examples include:

- **Somatic:** Musculoskeletal (joint and myofascial pain), cutaneous; often well localized
- **Visceral:** Hollow organs and smooth muscle; usually referred

Neuropathic: Initiated or caused by a primary lesion or disease in the somatosensory nervous system, resulting in sensory abnormalities, such as

numbness, hypersensitivity (hyperalgesia or allodynia) and paresthesias, such as burning, tingling and electric shock like. Examples include:

- **Peripheral:** Diabetic neuropathy, postherpetic neuralgia, carpal tunnel syndrome
- **Central:** Spinal cord injury, phantom limb (postamputation), and post-stroke pain

Inflammatory: Pain caused by activation and sensitization of the nociceptive pain pathway by a variety of mediators released at a site of tissue inflammation

- Examples include appendicitis, rheumatoid arthritis, inflammatory bowel disease, and herpes zoster

However, *more than one mechanism may be present due to overlap of pathological processes* resulting in more than 1 type of pain for an individual. Additionally, some well-recognized pain disorders such as cancer pain, migraine, fibromyalgia, and others, are not easily classifiable.

Temporal Classification of Pain

Acute pain: Pain of less than 3 months' duration with distinct onset and an obvious cause; examples include acute pain secondary to trauma, burns and infarction.

Chronic pain: Generally, pain that persists beyond normal tissue healing time of

3 or more months, with inadequate response to treatment; it is often associated with prolonged physical, functional, and psychological impairment.

Acute on chronic pain: Acute pain superimposed on underlying chronic pain

Pathophysiology of Pain

Pain sensation is a normal response to injury or disease with a biologically important protective function. It involves several essential elements and peripheral and central physiological processes within the nociceptive system.⁵

- **Essential elements:** Nociceptors, peripheral nerve, dorsal horn of spinal cord, second-order neurons, ascending tracts and supraspinal projections
- **Physiological processes:** Transduction, transmission, pain modulation, perception, sensitization

Nociceptors: Unspecialized, free, lightly myelinated or unmyelinated nerve endings that convert (transduce) a variety of stimuli (mechanical, thermal, and chemical) into nerve impulses

Peripheral nerves: Contain 3 types of primary sensory afferents with varying responses

A-beta ($A\beta$): Thick, myelinated, respond maximally to light touch and/or moving stimuli

A-delta ($A\delta$): Small-diameter myelinated, respond to sharp prickly pain;
C-fiber: Thin, unmyelinated, respond to dull aching pain

Dorsal horn of the spinal cord: Receives input from the peripheral nerves and is the site of synaptic modulation and transmission

Ascending tracts: Spinothalamic tracts transmit nerve stimuli through the dorsal horn of the spinal cord to the thalamus

Transduction: Conversion of a noxious, mechanical, or chemical stimulus into an electrical stimulus (action potential)

Transmission

- **Peripheral:** Action potentials are conducted to the dorsal horn of the spinal cord through peripheral sensory afferent fibers.
- **Synaptic:** Peripheral nerves synapse with second-order neurons in dorsal horn.
- **Central:** Nerve impulses ascend to the thalamus and brain stem nuclei and are subsequently relayed to multiple areas of the brain.

Pain perception: This is a process by which a noxious event is recognized as pain, with multiple components.

- **Sensory discriminative component:** Somatosensory and insular cortex allows identification of type, intensity and location of the noxious event.

- **Affective-emotional component:** Limbic system defines the response, and the prefrontal cortex moderates the associated behavior.

Modulation of pain perception

- **Peripheral:** Synaptic transmission is inhibited by activation of A β fibers by light touch.
- **Descending:** Projections from the brain stem nuclei to the dorsal horn result in modulation of nociception.

Inhibition occurs through release of neurotransmitters, such as serotonin, norepinephrine, and opioids.

Facilitation can occur because of fear and anxiety.

Sensitization: This involves decreased threshold for activation of primary afferent nociceptors and stimulus intensification due to intense, repeated, or prolonged exposure to damaged or inflamed tissues. Low pH, prostaglandins, leukotrienes, and other inflammatory mediators such as bradykinin play a significant role in sensitization. Sensitization occurs at the level of the peripheral nerve terminal (peripheral sensitization) as well as at the level of the dorsal horn of the spinal cord (central sensitization). Examples include:

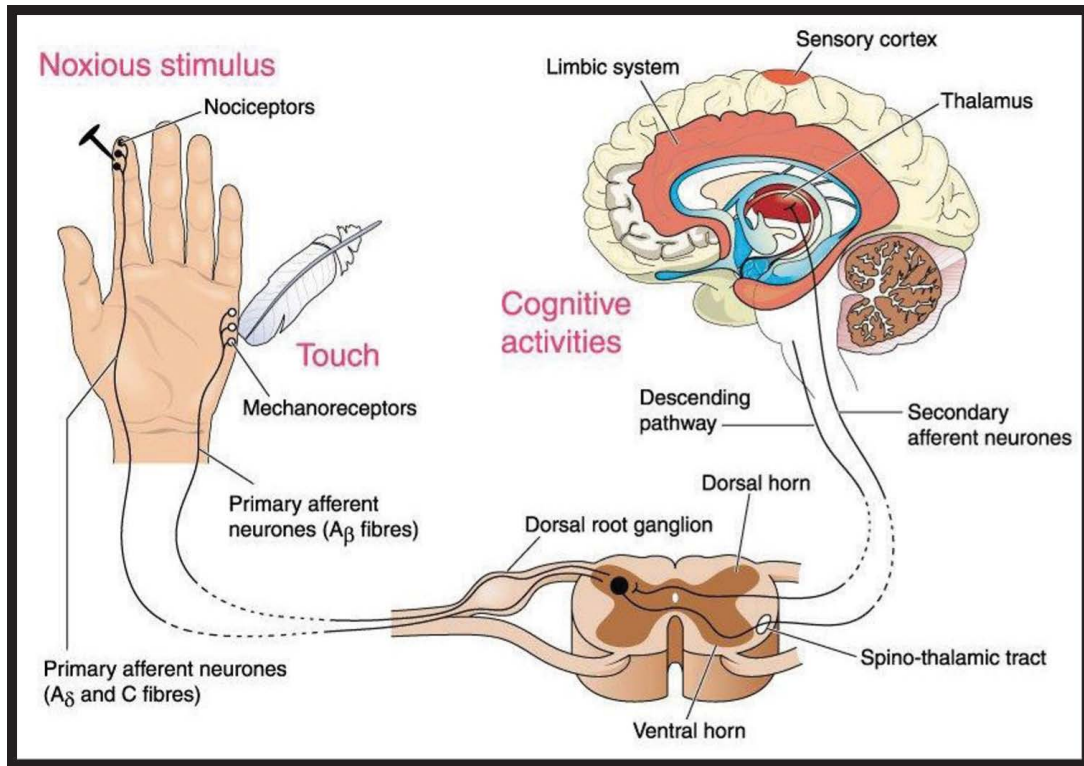
- **Allodynia:** Following injury, normally innocuous stimuli can produce pain and soreness.
- **Hyperalgesia:** This involves a mild, noxious stimulus that results in intense pain.

Other central mechanisms:

- **Referred pain and organ convergence:** Activation of the spinal neurons that receive input from both the viscera (organs) as well as skin result in referred pain to the area of skin.

Sympathetically Maintained Pain: Complex Regional Pain Syndrome (CRPS)

This involves development of spontaneous pain in the region of nerve injury, which may be of a burning quality. This pain may spontaneously manifest after a delay of hours to days or weeks and may be accompanied by swelling of the extremities, periarticular bone loss, and arthritic changes in the distal joints. CRPS can be produced by a variety of injuries, including fractures of bones, soft-tissue trauma, myocardial infarction, and stroke; CRPS can be rapidly relieved by blocking the sympathetic nervous system. CRPS type I (also known as reflex sympathetic dystrophy) appears without obvious nerve injury, and CRPS type II (also known as posttraumatic neuralgia or, if severe, causalgia) occurs after an identifiable nerve injury.



CHRONIC PAIN AND PSYCHIATRIC COMORBIDITY

Chronic pain and psychiatric disorders have bidirectional relationships. Both are common in the general population, mediated by shared common neural mechanisms, and are treated by some shared pharmacological and behavioral interventions. Further, chronic pain is associated with increased risk of suicide and substance use.

Depression: The estimated current, or 12-month, prevalence of depressive symptoms is more than 20% in individuals with arthritis, migraines and pelvic pain. Depression prevalence increases to more than 50% in individuals with fibromyalgia, temporomandibular joint pain, chronic back pain, and abdominal pain. The prevalence of major depressive disorders, dysthymia and bipolar disorders ranges from 2%-61%, 1%-9%, and 1%-21%, respectively, across all chronic pain groups⁶.

Individuals with chronic neck or low back pain are up to 2.5 times more likely to experience an episode of depression at 6- and 12-months' follow-up. Conversely, pain-free individuals with depression are up to 4 times more likely to develop neck or low back pain than individuals without depression. Some studies also suggest a dose-response relationship between intensity of pain and severity of depression. Functional imaging studies in individuals

with fibromyalgia and/or abdominal and low back pain suggest alterations in brain regions responsible for processing emotional stimuli, such as the anterior cingulate cortex and the prefrontal cortex.⁶

Anxiety: As with depression, a bidirectional relationship exists between chronic pain and anxiety, particularly in individuals with migraines. Individuals with migraines are 2 to 3 times more likely to be diagnosed with Generalized Anxiety Disorder, Panic Disorder, agoraphobia and Posttraumatic Stress Disorder (PTSD), while individuals with anxiety disorders are twice as likely to develop migraine headaches than individuals without anxiety disorders. Functional imaging studies suggest activation of overlapping brain regions (thalamus, anterior cingulate cortex and prefrontal cortex) by both chronic pain and anxiety.⁶

Substance use: Individuals with chronic pain are also at risk for other substance use disorders (SUD), with the highest prevalence rates for individuals with fibromyalgia, chronic spinal pain, and arthritis.⁶ Like depression and anxiety, chronic pain and substance use disorders have a bidirectional relationship, with estimated prevalence of chronic pain of 27% to 87% in individuals with SUD. Individuals with SUD are 1.5 times more likely to develop chronic pain, and individuals with chronic pain are 2 to 3 times more likely to develop SUD. Across all pain groups, the prevalence of alcohol use disorders ranges from 2% to 22%, and the combined prevalence of drug abuse, drug dependence, or any SUD (Opioid Use Disorder [OUD] not specified) ranges from 1% to 25%. From a neurobiological perspective, the medial prefrontal cortex is involved in processing pain and the development of SUD is a key component in the reward pathway.⁶

The true incidence of OUD in individuals with chronic pain receiving opioids in the United States is unknown. Review of the literature indicates the estimated incidence to be as high as 26%, with a sharp increase in prevalence since 1990s. According to the Research Abuse, Diversion and Addiction Related Surveillance System, prescription drug abuse is heavily localized in rural, suburban, and small urban areas. Hydrocodone and immediate-release Oxycodone are the most widely abused drugs. Some risk factors for development of OUD with chronic opioid therapy include young age, multiple pain complaints, history of mood disorder and psychosocial stressors, history of opioid abuse, illicit drug abuse including cannabis and a prior history of substance use treatment.⁷

Suicide: Chronic pain is associated with increased suicide risk with a rate of 45 to 81 per 100,000 person years. Suicidal ideation is reported by 28 to 48% of individuals with chronic pain.⁶ The pain-related risk factors include pain intensity, pain-related psychological factors, comorbid mental health conditions and analgesic medication use⁶.












Sexual abuse: Victims of sexual abuse are 2.5 to 3.5 times more likely to develop fibromyalgia and chronic musculoskeletal and pelvic pain complaints.⁶

Personality characteristics and disorders: Individuals with chronic pain who experience higher levels of negative emotions such as fear, worry, frustration, anger and jealousy have increased reactivity to pain, increased disability, poor quality of life, poor coping strategies, and greater pain-related anxiety and suffering⁶.

Cigarette smoking: Prevalence of smoking in individuals with chronic pain has increased over the years to 28.4% in 2010. Those who smoke and experience chronic pain report greater pain severity, being more likely to use opioids, and using higher doses of opioids⁶.



ASSESSMENT OF PAIN

COMPARATIVE PAIN SCALE CHART (Pain Assessment Tool)										
										
0 Pain Free	1 Very Mild	2 Discomforting	3 Tolerable	4 Distressing	5 Very Distressing	6 Intense	7 Very Intense	8 Utterly Horrible	9 Excruciating Unbearable	10 Unimaginable Unspeakable
No Pain	Minor Pain			Moderate Pain			Severe Pain			
Feeling perfectly normal	Nagging, annoying, but doesn't interfere with most daily living activities. Patient able to adapt to pain psychologically and with medication or devices such as cushions.			Interferes significantly with daily living activities. Requires lifestyle changes but patient remains independent. Patient unable to adapt pain.			Disabling; unable to perform daily living activities. Unable to engage in normal activities. Patient is disabled and unable to function independently.			

Effective management of pain starts with accurate, timely assessment. It is an ongoing process that often relies on the use of screening and assessment tools to quantify the location, severity and duration of the subjective pain experience.

- Some helpful tips for an effective approach include:
- Accept an individual’s self-reported pain as accurate.
 - Allow individuals to describe their pain, in their own words, as much as possible.

- Use active listening with observation of behavior and body language.
- Involve the family to gain a complete understanding of the person's pain symptoms, especially when the individual is not able to provide a complete history, e.g., an elderly person with cognitive impairment.

Every individual who presents with pain requires a basic evaluation within the primary care setting. People who do not respond to initial interventions (see Step 1 of Stepped Care Model) may need a comprehensive assessment in multidisciplinary and/or specialized settings.

P-Provokes and Palliates:

- What causes, aggravates and relieves pain?
- Positions/situations that increase or relieve pain?

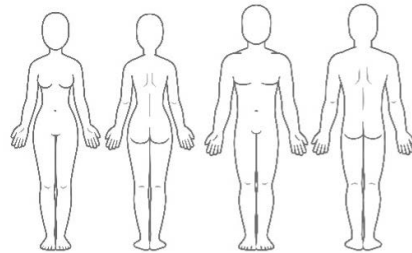
Q-Quality: Sharp/dull/stabbing/burning/crushing (helps differentiate the type or cause of pain-see Types of Pain section)

R-Region and radiation: Can use picture of front and back of human body. Pain can be primary to the location or secondary (referred pain)

S- Severity: Use pain scales

- Numerical rating scale
- Visual Analogue Scale
- Wong-Baker Pain Faces Rating Scale (PFS)

T-Time: Start time, continuous/intermittent, duration (acute vs. chronic), emergent or not?



Key elements of the basic evaluation include:

1. Characteristics of pain: PQRST approach
2. Past medical history
3. Detailed physical examination

Characteristics of pain: PQRST approach

Past medical history:

1. History of pain and diagnosis
2. Past interventions for pain management including medications, surgical interventions, injections, physical therapy, devices, alternative medicine and behavioral interventions
3. Past medical and surgical history, including allergies, trauma and active medical comorbidities, especially including hypertension, diabetes, stroke, heart disease, sleep apnea, pulmonary problems, etc.

Physical examination:

1. Systemic signs, e.g., fever, weight loss, fatigue
2. Detailed neurological examination

3. Evaluation of the extremities
4. Review of specific radiographic and imaging studies

Key elements of a comprehensive evaluation include psychiatric and psychological assessment, in addition to the basic evaluation.

Psychiatric assessment:

1. Past psychiatric history:
 - Anxiety, depression, somatoform disorders, PTSD, attention-deficit hyperactivity disorder and other diagnosed or suspected disorders.
 - Substance use and abuse, including alcohol, illicit drugs, tobacco, caffeine
 - Suicide attempts
2. Developmental history, including history of childhood neglect, trauma, or abuse
3. Social history:
 - Social supports
 - Family dynamics affecting pain, such as overprotective family member who is also a “pain patient,” serious conflicts in partnership or family

- Work involvement and attitudes, such as conviction that work damages the body, limited support in job, dissatisfaction with job
 - Coping mechanisms, including current and prior coping strategies
4. Opioid risk assessment, including prescription use pattern

Psychological assessment:

Common assessment tools often used for psychological assessment of pain include:

1. **McGill Pain Questionnaire^{8, 9}**: Widely used, relatively brief, assesses location, degree, and a variety of emotional modifiers
2. **West Haven-Yale Multidimensional Pain Inventory¹⁰**: Gives comprehensive evaluation of interference and disability, longer time
3. **Pain Outcomes Questionnaire¹¹**: Standardized with Veterans Health Administration (VHA) patient samples; designed for use as repeated assessment measure; has intake, discharge, and follow-up versions; measures different pain impacts across domains, including: activities of daily living, pain-related fears, mobility problems, negative affect, vitality and pain severity

The Minnesota Multiphasic Personality Inventory, Second Edition^{12, 13} Minnesota Multiphasic Personality Inventory, Restructured Form¹⁴: These well-known

and widely used personality inventories, although not pain-assessment tools specifically, can give a basic understanding of the individual's personality and how the person generally views the world and can also provide meaningful information about perceptions of pain and physical functioning.

Key elements of psychological assessment include:

1. **Location, type, chronicity:** Consider possibility of over- or underreporting of symptoms
2. **Degree:** Current, least, worst and average pain
3. **Impact of pain:** Emphasis on functioning, quality of life and pain behaviors.
 - Level of Interference: Work-related productivity, finances, activities of daily living and participation in life activities, leisure activities, family relationships
 - Disability
 - Mood
 - Language used to describe pain
4. **Cognitive factors affecting pain:**
 - "Exercise/strain is harmful"
 - Pain must disappear completely before activity is resumed

- Catastrophizing
- Conviction that pain is uncontrollable
- Fixed ideas on development of treatment plan

5. Emotional factors affecting pain:

- Extreme fear of pain and impairment
- Depressive reactions
- Increased awareness of physical symptoms
- Helplessness/resignation

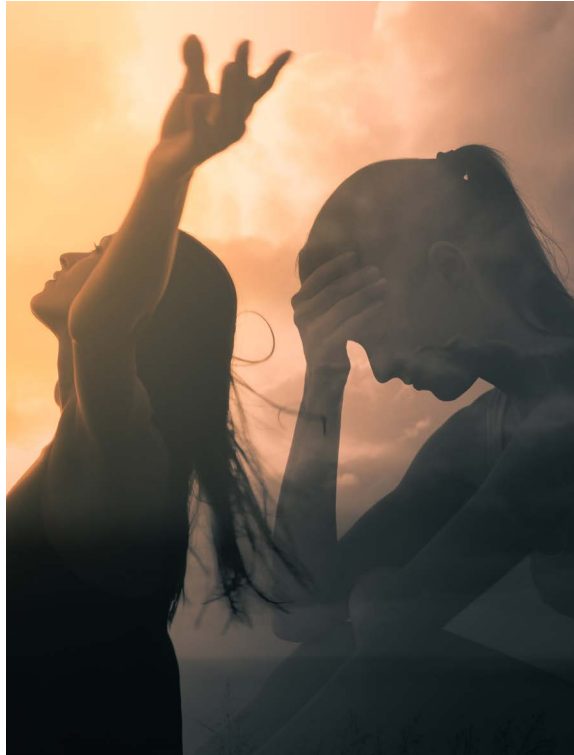
6. Behavioral factors affecting pain:

- Distinctly cautious behavior
- Withdrawal from normal daily activities
- Distinctly preventive behavior
- Extreme pain behavior
- Disturbance of sleep
- Abuse of medication

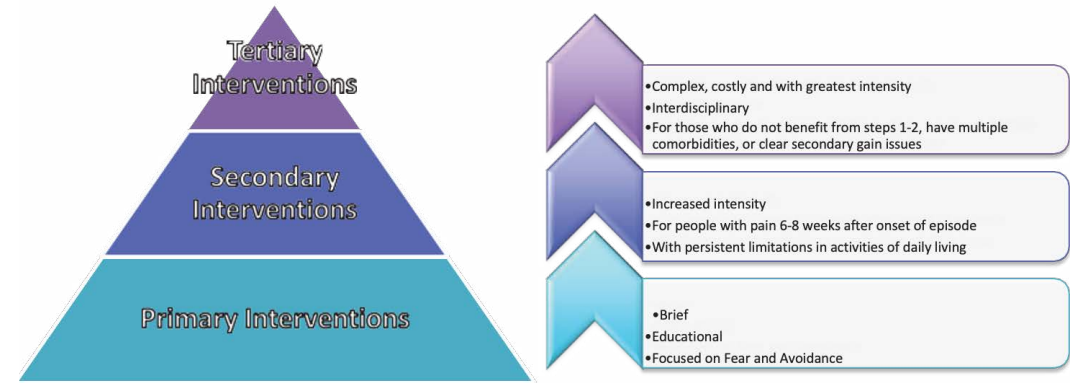


7. Diagnosis-related factors:

- Multiple diagnoses
- Impairment supported by physician
- Fear of serious medical illness
- Dissatisfaction with prior treatment
- Exclusive emphasis on somatic interventions
- High healthcare utilization



STEPPED CARE MODEL OF CARE



Research has demonstrated that activity avoidance is a primary process in the conversion of acute pain into a chronic condition, especially with back pain. Most people with acute pain will return to functioning without much intervention, but a small percentage will develop significant disability-related interference and may become high users of medical services.

Von Korff and Moore¹⁵ proposed the Stepped-Care Model for pain to stratify resource utilization for management of back pain. This model used a 3-tiered approach to maximize benefit for the individual and promote return to the highest level of functioning achievable. At the base of this system are educational strategies designed to challenge fears associated with reinjury or symptom exacerbation that were perpetuated through inactivity and activity avoidance. This model suggests that Step One interventions should be available to everyone through self-care educational materials distributed in Primary Care with a goal of addressing specific worries associated with the pain condition. Gatchel¹⁶ expanded upon this by emphasizing the role of biopsychosocial concerns that may influence a treatment course and recommended assessment of these issues to determine the degree of treatment. Those who have minimal psychosocial factors associated with their pain level are generally less complex and require less medical service. When there is a higher degree of impairment, the individual will likely require more intensive treatment. The VHA has adopted the Stepped-Care model on a national level and now mandates a variety of actions and programs to expand its implementation.¹⁷

Diagram of Stepped Care Model

The model provides guidance regarding treatment implementation considering the medical complexity of the individual being treated and, more broadly, the interaction between the treatment and the person being treated. Otis,

Macdonald, and Dobscha¹⁸ and the VHA¹⁷ suggest treatments for Step One patients should be done within Primary Care with input from consultative services for diagnostic or treatment purposes.

Step One

Step One is often characterized as care for individuals who are experiencing new and acute pain. They present for a Primary Care appointment or as a “walk- in” with a complaint of new pain. These individuals require a basic medical evaluation (see Assessment of Pain) to assess the cause of the pain and to make specific treatment recommendations and address any specific concerns, particularly if they are related to fear and activity avoidance (see Medical Evaluation for Pain description). Basic educational materials about specific conditions and recommendations should be sufficient to help most individuals return to functioning.

With respect to chronic pain at the Step One level, these are individuals who continue to have persistent pain, generally related to a chronic medical condition, who maintain functioning with minimal pain interference and no disability. They generally function well on a steady regimen of physical activity and basic medical support. These people understand that the pain is likely to persist, and they find that pain is not an overwhelming or particularly distressing event. They use medication appropriately, and there is no active abuse of other substances.

Consultation: Consultative services from medical pain experts may be beneficial in Step One cases to clarify the diagnostic impression and make suggestions about the basic treatment for the underlying condition. Psychological consultation may be useful for determining specific psychosocial factors, which may impact treatment, and for addressing pain-related fears that persist despite assurances by medical providers about the nature of the condition. These interventions may be delivered in an individual or group format. Frequently, they involve clinicians who are co-located or integrated into Primary Care.

Interventions:

Medical: Management within primary care setting

Psychological

Step Two

Step Two is characterized as care for individuals who continue to have activity limitations at 6 to 8 weeks¹⁵ for acute conditions. Step Two is pertinent to care for those who have persistent limitations and associated psychological distress, usually in the form of depression, persistent anxiety, low self-esteem, and significant fear-avoidance for chronic conditions. These people have moderate-to-high levels of pain-related interference, which may lead to disability. Additionally, individuals with chronic pain conditions with comorbid psychological or psychiatric conditions such as PTSD or substance use (which

may or may not be directly related to the pain condition), have an innate higher level of need for their condition and could be classified as Step Two patients.

Referral: A basic medical evaluation with a diagnostic impression of the pain condition and noninvasive strategies are generally ineffective with persistent activity avoidance. A comprehensive pain evaluation with a thorough medical evaluation and an in-depth psychological evaluation should be done. Evaluation and treatment are most effective if done by a multidisciplinary or interdisciplinary team of pain specialists.

Interventions:

Medical

Psychological: Once the level of the physical limitations has been evaluated medically and substantiated

Step Three

Step Three (often referred to as Functional Restoration) is characterized by focus on severe pain-related interference and disability. Individuals are frequently physically de-conditioned, and pain is clearly affected by low-to-minimal levels of activity and marked fear and pain avoidance. Negative psychosocial factors associated with the experience of pain include pain-related catastrophizing, attention-seeking behaviors (i.e., playing the sick role), and feigning symptoms for either financial or psychological reasons. It is important

to consult a mental health clinician regarding the possibility of integrating covert measures of feigning to inform your comprehensive assessment and treatment plans.

There are often significant psychological or psychiatric comorbidities with moderate-to-severe depression and anxiety with the potential for suicidality or suicidal behaviors. Additionally, there may be significant substance use and a heavy reliance on opioid medication, which is used to treat not only the physical discomfort but also psychological distress. This may not be evident until opioid medication is tapered, but this phenomenon is frequently marked by requests for increasing dosages of opioid-based medication, opioid misuse or abuse, and significantly aggressive behaviors. If you begin tapering an individual from an opioid medication and observe increasing agitation and misuse/abuse of the medications, this may be indicative of the individual's warranting a higher level of care (i.e., intensive outpatient, residential, or inpatient care).

(Opioid diversion is not indicative of a pain condition but is rather an indication of aberrant behavior, as the person is engaging in illegal activity for financial gain).

Referral: Individuals who are at this stage of their pain experience will need extensive medical and psychological evaluations and intensive and interdisciplinary treatment. They need careful monitoring for adherence and significant support to overcome both physical and psychological barriers. Treatment is usually conducted in a day treatment or residential program.

PHARMACOLOGICAL INTERVENTIONS

The [VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain](#)¹⁹ recommends against initiation of long-term opioid therapy for chronic pain. In all cases non-opioid and non-pharmacologic alternatives for pain management should be part of the treatment plan, and attempts should be made to taper the person off buprenorphine. Providers should be prepared, however, to provide long-term treatment with buprenorphine in individuals with persistent opioid dependence or OUD who are unable to taper off.

Studies have shown that several pharmacological agents (Opioid and no-opioid) are effective for chronic pain management, most regimens ranging from 2 weeks to 6 months.



Table 1. Commonly used pharmacological agents.

Analgesic Medication	Mechanism of action	Examples	Type of Pain
Nonopioids	Inhibit activity of cyclooxygenase- 1 (COX-1) and/or cyclooxygenase- 2 (COX-2) thus decreasing the production of prostaglandins	Aspirin, ibuprofen, naproxen, etodolac, meloxicam, piroxicam, and acetaminophen	Nociceptive pain
CGRP Antagonists	Mediate trigeminovascular pain transmission and neurogenic inflammation	Erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant, atogepant	Migraine (third line)
Opioids	Act by binding to μ -opioid receptors in the brain	Morphine, codeine, hydrocodone	

Analgesic Medication	Mechanism of action	Examples	Type of Pain
Adjuvants			
Antidepressants	Block reuptake of serotonin and norepinephrine	Amitriptyline, nortriptyline, venlafaxine, duloxetine	Neuropathic pain Fibromyalgia
Anticonvulsants	Modulation of Ion channels	topiramate, valproic acid carbamazepine, gabapentin, pregabalin,	Migraine Neuropathic pain Fibromyalgia
Muscle Relaxants	Direct action on CNS CNS and other unknown mechanism	Baclofen, tizanidine, Methocarbamol, cyclobenzaprine,	Fibromyalgia Muscle spasms Tension headache
Topical Agents	Block generation and transmission of nerve signals to the brain through peripheral actions	Capsaicin (substance P), lidocaine (Na ⁺ channel), diclofenac (NSAID), and menthol-methyl salicylate (local anesthetic- weak kappa opioid agonist)	Nociceptive (inflammatory) and Neuropathic pain
Beta-Blockers			Migraine

Choosing an appropriate medication for management of pain depends on several factors, such as diagnosis, intensity and duration of pain, medical and psychiatric comorbidities; treatment setting; past medication trials; drug interactions; side-effect profile; and treatment adherence and cost. It starts with setting realistic goals for treatment that focus on decreasing the pain with least added side-effects and improving an individual’s functioning and quality of life while minimizing the risk of addiction. At the initiation of medication management, consideration should also be given to when and how to discontinue opioid therapy if benefits do not outweigh risks.

Pharmacology of Nonopioid Analgesics

Cox inhibitors are the most widely used analgesics across the world. They inhibit central and peripheral hyperalgesia. Continuous blockade of production of prostacyclin (PGI2, Vasoprotective), however, increases cardiovascular risk, such as myocardial infarction and stroke.

Table 2. Pharmacology of opioid analgesics.

Drug	Dose mg	Adverse effects	Drug interactions	Contraindications (Absolute and relative)
<i>Nonselective, Acidic Drugs (NSAIDs)</i>				
Aspirin	50-1000 (max dose of 6 g) Not in use	Inhibits platelet aggregation for days, aspirin- induced asthma, ulceration and bleeds	Vitamin K antagonists	Allergic reaction, active ulceration or GI bleeds; hemorrhagic states, pregnancy and all contradictions listed below
Diclofenac Ibuprofen Indomethacin Ketoprofen Ketorolac Naproxen Meloxicam	25-75 200-800 50-150 25-100 250-500 7.5-15	Allergic reactions, dyspepsia, GI ulcerations, hypertension, water retention, vertigo, tinnitus	ACE inhibitors, glucocorticoids, diuretics, SSRIs, lithium ibuprofen: reduces low-dose aspirin's cardioprotection	Asthma, acute rhinitis, nasal polyps, angioedema, urticaria or other allergic reactions after taking ASA or NSAIDs; active peptic ulceration or GI bleeds; inflammatory bowel disease; established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease; renal failure

Drug	Dose mg	Adverse effects	Drug interactions	Contraindications (Absolute and relative)
Selective Cox-2 Inhibitors				
Acetaminophen	325mg-3 g	Liver damage	Not prominent	Liver damage, alcohol abuse
Celecoxib	100 to 200 mg	Allergic reactions (sulfonamide)	Affects metabolism of SSRIs and beta- blockers by blocking CYP2D6	Severe atherosclerosis, Renal failure
Etoricoxib	60: OA 90: RA 120: gout	Water retention, increased blood pressure	Decreased estrogen metabolism	Severe atherosclerosis, renal failure, poorly controlled blood pressure, cardiac failure

Pharmacology of CGRP Antagonists

A newer class of medication, CGRP antagonists, has been approved for migraine prevention in adults who are unresponsive to first- and second-line agents. They inhibit vasodilation and neurogenic inflammation by blocking the release of CGRP at all locations within the migraine pathway, thus acting as a migraine-preventive agent. CGRP monoclonal antibodies (mAbs) are large-molecule CGRP receptor or ligand antagonists that are given by injection. On the other hand, gepants are small-molecule CGRP receptor antagonists administered orally. *Gepants work to block CGRP from receptors to initiate the pain-signal process.*



Table 3. Pharmacology of CGRP Antagonists.

Drug	Dose	Adverse Effects	Drug Interactions	Contraindications
Erenumab	Initial: 70 mg once a month; 140mg S/C injection once monthly	HTN, constipation, hypersensitivity	Efgartigimod Alfa: May diminish the therapeutic effect	Hypersensitivity
Fremanezumab	225 mg once monthly or 675 mg (given as three consecutive injections of 225 mg each) every three months s/c	Injection site reaction	Efgartigimod Alfa: May diminish the therapeutic effect	Immunogenicity: Anti-fremanezumab antibodies and neutralizing antibodies may develop.
Galcanezumab	loading dose of 240 mg, given as 2 consecutive doses of 120 mg each, followed by monthly doses of 120 mg S/C	Injection-site reaction	Efgartigimod Alfa: May diminish the therapeutic effect	Hypersensitivity; Anti-galcanezumab antibodies and neutralizing antibodies may develop
Eptinezumab	100 mg given as an IV infusion over approximately 30 minutes every 3 months	upper respiratory tract infections, hypersensitivity, and fatigue	CYP3A4 Inducers (Strong): May decrease the serum concentration	

Drug	Dose	Adverse Effects	Drug Interactions	Contraindications
Rimegepant	75 mg every other day PO	Abd pain, skin rash Dyspnea	CYP3A4 Inducers (Strong): May decrease the serum concentration CYP3A4 Inhibitors (Strong): May increase the serum concentration	Hepatic and renal impairment and hypersensitivity
Atogepant	10 mg, 30 mg, or 60 mg once daily	constipation, nausea, and upper respiratory tract infections.	CYP3A4 Inducers (Strong): May decrease the serum concentration CYP3A4 Inhibitors (Strong): May increase the serum concentration	Hepatic and renal impairment

Table 4. Pharmacology of anticonvulsants and other non-opioid analgesics.

Drug	Dose	Adverse Effects	Drug Interactions	Contraindications
Selective Cox-2 Inhibitors				
Carbamazepine	200 - 500 mg PO BID (Trigeminal neuralgia)	Diplopia, ataxia, Stevens -Johnson syndrome, SIADH	Avoid grapefruit juice 2 D6 inducer, increased metabolism of contraceptives	Liver damage, alcohol abuse Allergic reaction, WBC < 3000 Platelet < 100,000 RBC < 4x10 ⁶
Gabapentin	100 to 1200 mg PO TID	Somnolence, ataxia, dizziness, headache, tremor	Morphine increases and antacids decrease levels	Dose adjustment for renal failure
Pregabalin	50 to 200 mg PO TID		Orlistat and calcifediol decrease the levels	Hypersensitivity
NMDA Receptor Na+ Channel Blockers				
Ketamine	Not used in primary care settings	Hypersalivation, hypertension, tachycardia, bad dreams		

Table 5. Pharmacology of Opioid analgesics.

Alkaloids	Semisynthetic	Synthetic	Opioid peptides
Morphine Codeine Thebaine Noscapine Papaverine	Hydromorphone Oxycodone Diacetylmorphine (heroin) Naloxone Naltrexone Etorphine	Methadone, fentanyl, meperidine, tramadol, levorphanol, butorphanol, alfentanil, sufentanil, remifentanil, nalbuphine	Endorphin Enkephalin Dynorphin

Opioids can be classified based on their pharmacodynamics profile, as:

1. Full agonists: High potency, maximal response even with low receptor occupancy - morphine, fentanyl, sufentanil
2. Partial agonists: High affinity for low response - buprenorphine
3. Mixed agonists/antagonists: Agonist at κ -receptors and antagonists at μ receptors - pentazocine, butorphanol
4. Antagonists: No response - naloxone, naltrexone

Opioids act on μ , δ , and κ opioid receptors that are widely distributed in central and peripheral nervous systems and the gastrointestinal tract. The analgesic effect of opioids is due to activation of μ opioid receptors, which in turn activates the intracellular signaling system that leads to release of norepinephrine and serotonin,

resulting in decreased neuronal excitability and pain inhibition. Opioids are effective through multiple routes of administration such as systemic (oral, IV, SC or IM), spinal (intrathecal or epidural) and peripheral (intra-articular or topical).

Table 6. Equianalgesic narcotic conversions.

Medication	Equianalgesic Doses	
	Parenteral	Oral (Conversion factor for MED)
Morphine	10 mg	30 mg
Codeine	120 mg	200 mg (0.15)
Fentanyl	0.1 mg	Transdermal (2.4)
Hydrocodone	N/A	30 mg (1)
Hydromorphone	1.5 mg	7.5 mg (4)
Oxycodone	N/A	20 mg (1.5)
Methadone	5 mg	10 mg (4 to 12 depending on the dose: 1 to 20mg - 4; 21 to 40 mg - 8; 41 to 60 mg -10 and 61 to 80 mg - 12)
Tramadol	100 mg (IV)	150 mg (5)
Buprenorphine		0.3 mg SL
Levorphanol	2 mg (single dose, 1 mg for chronic use)	4 mg - single dose, 1 mg for chronic use
Oxymorphone	N/A	10 mg (3)
Tapentadol	N/A	100 mg (Suggested)

Fentanyl Patch	24 hour MED	Patch
	45 mg	12mcg/hr
	90 mg	25mcg/hr
	180 mg	50 mcg/hr
	360 mg	100 mcg/hr

The wide distribution of opioid receptors also explains the numerous adverse effects of the opioids, such as euphoria, dysphoria sedation, respiratory depression, bradycardia, nausea, vomiting, constipation, pruritus, miosis and suppression of endocrine systems. Hence, it is recommended to always start with a low dose and titrate gradually. In addition to the adverse effects, development of opioid tolerance and opioid-induced hyperalgesia are significant challenges in chronic opioid therapy. The degree of tolerance varies among individuals as well as individual opioids, warranting caution with switching from 1 opioid to another to avoid opioid toxicity. In addition, clinical differentiation of opioid tolerance from opioid-induced hyperalgesia can be challenging.

Numerous randomized controlled trials support effectiveness of short-term use of opioids for managing chronic pain, usually for 12 weeks or less. The long-term effectiveness of opioid therapy is, however, limited due to lack of long-term (> 3 months) high-quality studies. Evidence from multiple systematic reviews suggests extensive nonmedical use and abuse of opioids. Yet, use of opioids has

escalated to an epidemic proportion, with an estimated 259 million prescriptions for opioids in the United States in 2012, presenting serious risks, including OUD, overdose, and a marked increase in opioid-related death rate.²⁰ Long-acting opioids and a combination of long-acting and short-acting opioids contribute to increasing fatalities, with approximately 60% of fatalities originating from opioids prescribed within the guidelines, and approximately 40% of fatalities occurring in the 10% of individuals with drug dependence.^{10, 22}

Given the above concerns, the CDC developed guidelines for the safe prescription and monitoring of opioids for management of chronic pain outside of cancer, palliative care and end-of-life care.²⁰

Determining When to Initiate or Continue Opioids for Chronic Pain

- Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks. If opioids are used, combine them with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
- Before starting opioid therapy for chronic pain:
 1. establish treatment goals with everyone, including realistic goals for pain and function, and
 2. consider how therapy will be discontinued if benefits do not outweigh risks. Continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks.

- Before starting and periodically during opioid therapy, collaboratively discuss known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

- When starting opioid therapy for chronic pain, prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
- When opioids are started:
 - Prescribe the lowest effective dosage
 - Use caution when prescribing opioids at any dosage
 - Carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day
 - Avoid increasing dosage to ≥ 90 MME/day, or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
- Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, prescribe the lowest effective dose of immediate-release opioids and prescribe no greater quantity than needed for the expected duration of pain that is severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.

- Evaluate benefits and harms with individuals within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Evaluate benefits and harm of continued therapy every 3 months or more frequently. If benefits do not outweigh harm of continued opioid therapy, optimize other therapies and work with individuals to taper opioids to lower dosages or to taper and discontinue opioids.

Assessing Risk and Addressing Harms of Opioid Use (See Opioid Safety and Risk Assessment)

- Before starting and periodically during continuation of opioid therapy, evaluate risk factors for opioid-related harm. Incorporate strategies to mitigate risk, including offering naloxone when factors that increase risk for opioid overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present.
- Review the individual's history of controlled substance prescriptions, using state prescription drug monitoring program (PDMP) data to determine whether the person is receiving opioid dosages or dangerous combinations resulting in high risk for overdose. Review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.

- When prescribing opioids for chronic pain, use urine drug testing before starting opioid therapy, and consider urine drug testing at least annually to assess for prescribed medications, as well as other controlled prescription drugs and illicit drugs.
- Avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible.
- Offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for individuals with OUD.

* All recommendations are category A (apply to everyone except active cancer treatment, palliative care, and end-of-life care) except Urine drug testing recommendation (designated category B, with individual decision making required); see full guideline for evidence ratings.

NONPHARMACOLOGICAL INTERVENTIONS



Potential resources to assist individuals in managing chronic pain extend well beyond traditional and leading-edge biomedical and pharmacological interventions. The following treatment modalities are commonly available at a variety of sites and may constitute important treatment options for diverse chronic pain patients.

Psychological Therapies

Cognitive Behavioral Therapy (CBT) for pain developed from successes of CBT in treating depression and anxiety disorders and was informed by multidimensional models of pain that emphasize cognitive, emotional and behavioral factors. CBT typically incorporates strategies for enhancing awareness of the interaction of these factors in the pain experience and with regard to an individual's functioning. CBT also stresses the refinement and use of multiple cognitive and behavioral skill sets relevant to enhanced coping, increased activity, augmented functioning, improved mood and better quality of life.²³

CBT for pain may be offered in individual or small-group modalities, typically involving multiple sessions over a limited timeframe of several weeks, although brief therapies may also be offered. CBT for pain is supported by a strong evidence base. Within the VA system, a specific 11-session protocol for individual treatment, "Cognitive Behavioral Therapy for the Management of Chronic Pain" (CBT-CP) is offered at many sites by therapists who have been trained and mentored in its use through the national VA evidence-based psychotherapies (EBP) training rollout.

Acceptance and Commitment Therapy (ACT), pronounced as the word, act) **for pain** is another CBT approach that enjoys a significant evidence base supporting outcomes of enhanced functioning, improved satisfaction, and higher self-rated quality of life. ACT is intended to promote cognitive flexibility and support individual ability to commit action to the pursuit of values-driven

goals while accepting rather than struggling with ongoing thoughts and emotions.²³ ACT for pain may be available in individual or group formats.

Physical Medicine and Rehabilitation

Physical therapy (PT) and **occupational therapy (OT)** are specialties within the area of Physical Medicine and Rehabilitation. PT seeks to promote functioning, range of motion, mobility and quality of life through physical interventions including stretching, weight-training and exercise that address specific goals identified through appropriate examination and diagnosis. PT services may include in-house treatments but often also focus on training individuals to perform effective physical procedures at home or on their own. OT seeks to help develop, regain or maintain skills and activities of work, recreation, and daily living in persons with physical or cognitive barriers to these goals. As a patient-centered practice with focus on environmental adaptations, skills training, task modification, and activity restructuring, OT may be of value in the rehabilitation and activity recovery efforts of persons with chronic pain.²⁴

Complementary, Alternative, and Integrative Medicine (CAIM) Approaches

CAIM has been used to refer to practices and products that currently are not part of mainstream medicine but may show promise, or in some cases, evidence-based success in assisting individuals to manage long-standing conditions with impacts on functioning and quality of life. CAIM is consistent

with the biopsychosocial perspective and Whole Health.²⁴ Increasingly, CAIM modalities have been incorporated and promoted in healthcare systems targeting chronic pain, including VHA, to expand treatment options and address aspects of pain that formerly were not a main focus of intervention.

In considering appropriateness of CAIM resources, it is important to consider the evidence base for effectiveness as well as potential for individual benefit and harm. Many CAIM treatments lack formal clinical trials to assess effectiveness and safety. Moreover, in the case of certain CAIM modalities, it should be recognized that local medical center policies and procedures may apply, guiding or restricting use and availability.

Acupuncture involves insertion of extremely fine needles through the skin at selected strategic points on the body. Its most common use is for treatment of pain. Full response may develop over multiple sessions, and relief may not be lasting. Acupuncture was developed within traditional Chinese medicine with putative mechanism of altered energy flow and balance within the body, but has been increasingly subject to study within Western medicine.²⁴ Many people with chronic pain have found it helpful and well-tolerated; it has been increasingly offered through the VHA in recent years.

Battlefield acupuncture is a subtype of auricular (ear-related) acupuncture that has found widespread utilization in military and medical contexts throughout the Department of Defense and in many Veterans Affairs²⁵ medical centers. In this procedure, individuals undergo insertion of 5 auricular semi-permanent (ASP) needles at specific points in the outer ear. The ASP needles typically

remain in place for 4 or 5 days, sometimes much longer. Pain relief may be noted within a few minutes, and research findings to date suggest that therapeutic effects may be sustained for 30 days or more in some cases.²⁶ The treatment can also be repeated.

Biofeedback training can supplement training in relaxation or other processes relevant to self-management of chronic pain, by monitoring select responses within the body (such as heart-rate variability, respiration, peripheral blood flow, and galvanic skin response) through use of sensors, and presenting immediate feedback in visual, auditory or other formats to facilitate the learning of improved control over those responses. Studies have confirmed that biofeedback training can promote improved stress response and quicker recovery following stress exposure. Although multimodal biofeedback training may be offered in office visits, there are now many small and relatively inexpensive devices that can be easily used by individuals with chronic pain at home.²⁷

Cranial electrotherapy stimulation (CES) for pain involves use of special portable stimulators to propagate small-intensity complex alternating current waveforms through the cranium, or sometimes other parts of the body, with the intention of triggering biochemical or related responses that may have a facilitative impact on altered mood states or anxiety associated with pain and, possibly, with pain transmission and processing itself. A common methodology uses small earlobe clip electrodes connected to a portable, battery-powered CES unit delivering 20- to 60-minute treatments. Other versions employ handheld post electrodes that can be applied adjacent to painful areas in the

body. The published outcome evidence for CES and related electrotherapy stimulation is controversial, but the procedure is considered safe and has been embraced by individuals receiving care and clinicians in many settings, including VHA. Because it is relatively nondemanding of individual effort, it can represent an option for trial when other treatment modalities are limited.²⁸

Chiropractic treatment can offer a pain relief alternative for certain conditions affecting muscles, joints and connective tissues. Chiropractic practitioners as a group comprise the largest population of CAIM clinicians. They may use hands-on manipulations to promote or restore alignment and mobility in joints restricted by trauma, degenerative changes, or repetitive stress. Other techniques such as electrical muscle stimulation, ultrasound, or applications of heat and cold may be employed as well. Chiropractic treatments are often combined with counseling regarding exercise and wellness issues. The majority of treated referrals typically involve low back pain. As with other treatment approaches, initial examination and assessment by the referring provider is important for evaluating the appropriateness and applicability of specific chiropractic treatments.²⁴

Meditation practice is the most commonly available CAIM modality within the VHA treatment system and can have great applicability to the management of chronic pain conditions. The term may refer to a variety of practices intended to promote relaxation or self-regulation of body and mind. “Mindful” meditation emphasizes open experiencing of events and perceptions during the present moment, in a nonjudgmental fashion. Mindfulness training has been associated

with increased ability to alter aspects of pain experiences and serves as a core process within more comprehensive cognitive behavioral approaches such as ACT. The “mantra” meditation technique involves silent repetition of a word, sound, or phrase that holds personal meaning. It is being investigated as a means of altering response to chronic stressors such as pain. Many individuals with chronic pain report benefit from increased awareness of rhythms, including movement of breath in and out of the body during regular meditative practice.²³

Neurofeedback training, or electroencephalographic biofeedback, is a specialized type of biofeedback that monitors and provides feedback specifically related to ongoing brain wave signals. Neurofeedback can address health issues, including chronic pain, by helping individuals to alter brain wave patterns. This technique can promote shifts in cognition or mood relevant to management of certain pain presentations such as neuropathic pain.²⁴

Relaxation training may include meditative techniques but also includes well-studied calming strategies such as abdominal (diaphragmatic) breathing, progressive muscle relaxation, guided imagery, and autogenics (reliable use of visualization to trigger the “relaxation response”). Learning to reliably use visualization is a useful self-management skill for many individuals with chronic pain, who may experience high levels of sympathetic arousal and “fight-or-flight” response as a function of pain escalation.²⁴

Repetitive transcranial magnetic stimulation³⁰ (rTMS) is a safe, noninvasive technique that can stimulate the brain cortex by producing magnetic pulses.

These pulses facilitate changes in cortical activity at the stimulation site and at distant areas. rTMS has been shown to reduce the effects of various pain conditions as well as symptoms associated with major depressive disorder. It helps modulate abnormal brain activities to reduce pain, and the mechanism of this technique is based on the modification of neuronal excitability. It is thought that rTMS induces alteration in cortical and subcortical brain regions related to pain modulation and processing (i.e., orbitofrontal cortices, medial thalamus, anterior cingulate, periaqueductal gray matter) and reduces chronic pain by triggering descending inhibitory neural pathways.

Transcutaneous electrical nerve stimulation (TENS) is the most common form of electrical stimulation for pain; individuals typically receive a TENS unit to use at home, featuring electrodes that they place noninvasively in relevant body area such as the low back. Electrical stimulation is propagated through the skin, with individual control of intensity. TENS can help block pain transmission signals along nerves in the affected area, and there is evidence that it may additionally release endogenous endorphins to reduce local pain response. TENS units are commonly available, and many individuals receiving pain management services find them useful as a self-management tool.²⁹

OPIOID AND SUBSTANCE USE DISORDERS



Management of chronic pain in individuals with a history of SUD can be challenging due to a number of factors including:

- Concerns about possible relapse of substance use
- Chronic opioid therapy-induced central sensitization resulting in increased pain perception and opioid-induced hyperalgesia
- Difficulty in differentiating between physiological dependence due to development of tolerance and addiction

- Legitimization of opioid abuse by individuals with SUD

DSM-5 Diagnosis of OUD includes a problematic pattern of opioid use, leading to clinically significant impairment or distress, as manifested by at least 2 of the following in a 12-month period³¹:

1. Opioids are often taken in larger amounts or over a longer period than intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. There is a craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use results in a failure to fulfill major role obligations at work, school, or home.
6. Opioid use continues, despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.

8. Opioids are used recurrently in situations in which they are physically hazardous.
9. Opioid use continues, despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance occurs (NOT one of the criteria for counting, when opioids are taken under medical supervision).
11. Withdrawal occurs (NOT one of the criteria for counting, when opioids taken under medical supervision).

Severity: is determined as follows: **2-3 mild; 4-5 moderate; 6+ severe**

The goals for treatment are management of SUD in addition to the goals for chronic pain, i.e., functional restoration and pain relief.

The relevant clinical issues to be considered are management of the following:

1. OUD and SUD
2. Safe taper of the opioids
3. Opioid withdrawal
4. Chronic pain with alternate interventions
5. Opioid therapy if necessary

Long-term use of Opioid Analgesics (LTOA: ICD-10 Z79.891)

Some patients take opioid analgesics as prescribed and develop physiological opioid dependence with development of tolerance and opioid withdrawal symptoms. They may experience difficulty in tapering or discontinuing opioids even when the risks outweigh the benefits and with no evidence of improvement in functional status. Long-term use of opioid analgesics may be an appropriate billing diagnosis if individuals do not meet DSM-5-TR criteria for OUD, per se. This is not a formal psychiatric diagnosis, per DSM-5-TR, and may be used only for billing purposes.

Complex persistent opioid dependence³² is proposed as another clinical entity for those who have physiological dependence on opioids with persistent desire to use opioids for pain management without craving or compulsive and harmful use. Opioid tapering for this group may fail or become highly protracted. Further research is needed to validate complex persistent opioid dependence-based approaches to manage high-dose opioid therapy.

Management of OUD and SUD in Individuals with Chronic Pain

Essential elements of assessment of SUD and OUD include^{33, 34}:

1. Comprehensive psychiatric assessment including substance use history
2. Comprehensive risk assessment for opioid misuse and abuse, including history of risk factors for addiction (see opioid safety and risk assessment section)

- 3. Detailed assessment of pain including delineation of nociceptive, emotional, cognitive and behavioral components
- 4. Assessment of degree of functionality

Table 7. Guidelines for management of chronic pain with comorbid SUD. ³⁵

	Low Risk (Gr I)	Medium Risk (Gr II)	High Risk (Gr III)
UDT Frequency	1 to 2 yrs.	6 to 12 months	3 to 6 months
PDMP*/year	Twice	3 times	4 times
Opioid use	> 50 MED, if needed	> 50 MED occasionally	Avoid or use rarely Very low dose (10 mg) Avoid dose increase
Addressing aberrant behavior	Counseling Reevaluate	Counseling Reevaluate	Taper opioids

UDT = Urine Drug Test; PDMP = Prescription Drug Monitoring Program;
MED = Morphine equivalent dose

Please refer to next section on **Opioid Safety and Risk Assessment** for the risk categorization proposed by Gourley et al.³⁶

Individuals with SUD and OUD require interventions in addition to the above risk stratification including:

1. Referral to appropriate specialist services such as substance use treatment programs
2. Relapse prevention using
 - Careful monitoring
 - Cognitive behavioral interventions for pain management
 - Stress management and psychosocial supports
3. Early identification of relapse

Opioid Tapering

The safest pain treatment strategy for individuals with OUD or SUD is a non-opioid and non-benzodiazepine approach. It is not uncommon for individuals with comorbid SUD and OUD to be on a fairly high dose of opioids. Abrupt discontinuation of opioid medication can place individuals at high risk of opioid withdrawal and often complicates comorbid medical and psychiatric conditions.

Hence, some flexibility should be employed with the speed of taper, allowing the individual to adjust to the schedule.

The following strategies can be helpful to ensure smooth transition³⁷:

1. Active listening
2. Reassuring the individual in your care and addressing the fear of abandonment
3. Educating the individual receiving care regarding the risks and concerns related to chronic opioid therapy and SUD
4. Assisting individuals in setting goals for pain management as well as opioid tapering
5. Offering medications for management of withdrawal symptoms
6. Offering other pharmacological and nonpharmacological interventions for pain management.
7. Facilitating referral to specialty services

The following opioid tapering guidelines are proposed to facilitate safe tapering³⁸:

Table 8. Opioid tapering guidelines for safe tapering.

Speed of Taper	Indications
<i>Stop Now</i>	Suspected diversion
<i>Fast (Days)</i>	Inpatient admission (SI, medical reasons) Non-prescribed medication or substance use (cocaine, alcohol) Social/Legal concerns Medical: Prolonged QTc
<i>Slow (Weeks) High risk individuals</i>	Combined use with benzodiazepines Substance induced mood disorder, SUD or high risk for SUD (MJ), high risk for aberrant behavior Mild traumatic brain injury Persistent psychiatric disorders (PTSD, ADHD, bipolar disorder, schizophrenia) with no follow-up Medical: Pregnancy, central sensitization states, opioid-resistant conditions
<i>Slowest (Months)</i>	High risk comorbidity: Probable obstructive sleep apnea, sedatives Mental health relative risk: sexual trauma, comorbid MH issue Substance misuse: Past hx, Family hx., nonprescribed medication use, Moderate opioid risk score, tobacco use of > 1PPD, negative UDS screenscreenTest (UDT) Social/legal: Family history, disruptive behavior Medical: Lack of continuity of care, lack of improvement in pain

SI = Suicidal ideation; MJ = Marijuana; ADHD = attention deficit hyperactivity disorder; MH = mental health; hx = history; PPD = Packs per day; UDS = Urine Drug Screen

Complications from opioids:
Hyperalgesia, cognitive impairment, LTOT bowel syndrome, sleep disorders, erectile dysfunction

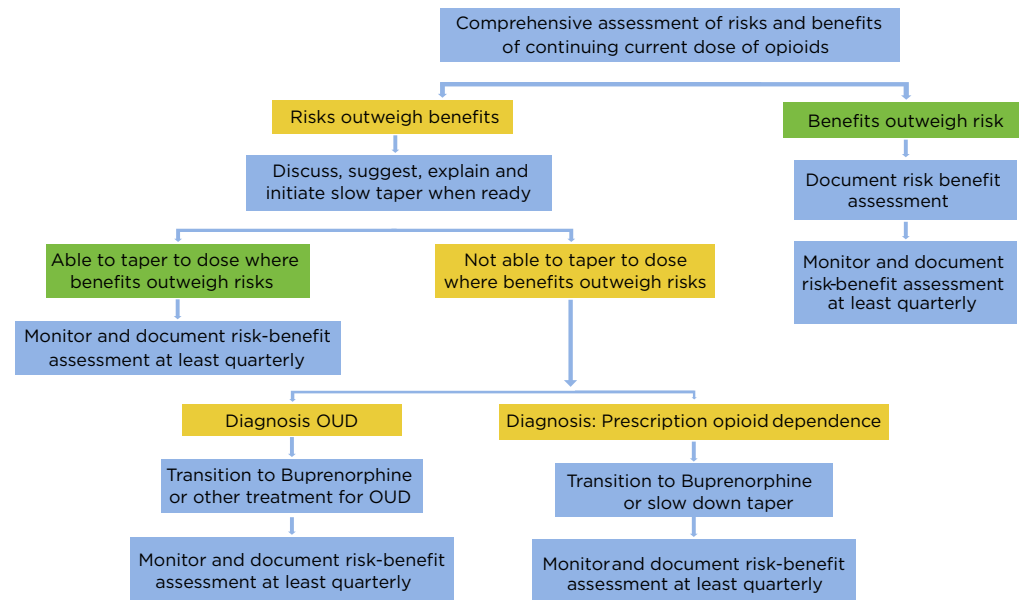
Potential complications from opioids: Age >65, fall risk, renal dysfunction, liver dysfunction

ADDITIONAL CONSIDERATIONS:

1. Taper long-acting opioids prior to short-acting opioids.
2. Taper benzodiazepines prior to opioid initiation.



Figure 1. Clinical Pathway for Consideration of Tapering in Patients using Opioids for > 90 days^{39, 40}



Management of Opioid Withdrawal

Opioid withdrawal is not life threatening but can be very distressing with anxiety, insomnia, yawning, chills, anorexia, muscle cramps, nausea, diarrhea, miosis and elevated heart rate and blood pressure. Ineffective management of withdrawal can lead to dose escalation, development of tolerance and even accidental overdose and death. A detailed initial psychiatric assessment and collateral information from external resources are necessary to stratify the risk of opioid use and guide the treatment team in determining the individualized treatment plan in the most appropriate setting.

The following medications can be used to manage withdrawal symptoms:

1. Clonidine 0.1 mg PO TID for the autonomic symptoms of opioid withdrawal can be titrated over a week and can be used for several weeks.
2. Methocarbamol 750mg PO TID or cyclobenzaprine 10mg PO TID or baclofen 5 to 20 mg PO Q 6 hours for muscle spasms
3. Ibuprofen 800mg PO TID for pain
4. Loperamide 4mg PO x 1 for first loose stool and 2mg x 1 for each additional loose stool
5. Ondansetron 8mg PO TID for nausea (avoid Phenergan as it can potentiate the effects of opioids)

6. Hydroxyzine palmoate 25 mg or diphenhydramine 25 mg PO Q6 hours and at bedtime for anxiolytic effect and insomnia
7. Trazodone 25-50mg PO HS for insomnia (avoid benzodiazepines and zolpidem)

Management of Chronic Pain with Alternative Interventions

See sections on pharmacological and nonpharmacological management of chronic pain.

Management of Opioid Therapy

Treatment of OUD includes 3 stages -

1. Stabilization: Usually achieved by substitution with long-acting opioids to address the reinforcing and euphoric aspects of drug use
2. Detoxification: A safe taper of opioids to minimize withdrawal symptoms
3. Maintenance (relapse prevention)

Several pharmacological agents are available for maintenance treatment including:

1. Full agonists: Methadone, morphine sulphate

- 2. Partial agonists: Buprenorphine, buprenorphine/naloxone, buprenorphine film and depot implant
- 3. Antagonists: Naloxone (IV use only), naltrexone and depot naltrexone.

Methadone and buprenorphine are first-line medications for treatment of opioid dependence and opioid detoxification.

Psychosocial interventions including CBT, seeking safety therapy, contingency management, motivational enhancement and other supportive interventions play an important role in all stages of treatment.

Liquid methadone is a long-acting synthetic opioid that can be dispensed for OUD only by federally licensed treatment facilities, as part of an addiction treatment program. Any physician can prescribe methadone tablets for managing pain. It can be administered once daily. It has 80% bioavailability with a half-life of 7 to 65 hours. It is available as oral tablets and solution and as injectable solution. The doses for opioid maintenance are usually higher (60 to 80 mg/day, can be up to 130 mg/day) than for pain relief (2.5 to 10 mg QID). Methadone’s side-effect profile includes cardiotoxicity (QT prolongation and risk for torsades de pointe), cognitive deficits, respiratory depression and hypogonadism.

Buprenorphine has agonistic activity at μ receptors (analgesic effect at low doses) and antagonistic activity at “k” opioid receptors.³⁹ It has a long half-life of 24 to 60 hours (see Table 9 below).

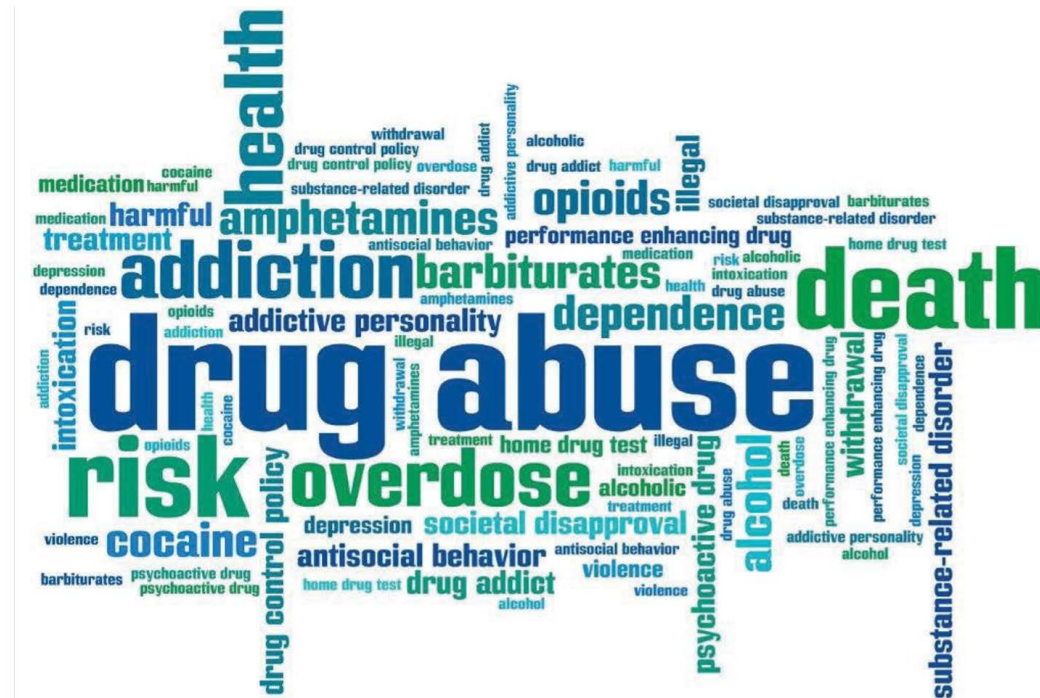
Table 9. Mechanism of action of buprenorphine.

μ Opioid receptor	δ Opioid receptor	k-Opioid receptor	ORL1
Partial agonist	Antagonist	Antagonist	Agonist
<ul style="list-style-type: none"> • Potent analgesia • Ceiling on respiratory depression and euphoria • Limited impact on GI motility • Limited physical dependence, abuse potential and withdrawal symptoms • Reduced impact on the HPA axis and immunosuppression • Reduction in suicidal thoughts, anxiety and depression • Limited dysphoria 	<ul style="list-style-type: none"> • Antiopioid effects • Myocardial protection • Limited impact on GI motility • Limited respiratory depression 	<ul style="list-style-type: none"> • Reduced depression, dysphoria, suicidal tendencies, anxiety and hostility • Limited potential for addiction and tolerance • Reduced immunosuppression 	<ul style="list-style-type: none"> • Enhanced spinal analgesia • Reduced supraspinal analgesia • Diminished opioid-rewarding effects • Limited potential for tolerance

GI = gastrointestinal, HPA = Hypothalamic Pituitary Axis,
 Management of opioid withdrawal symptoms requires $\leq 50\%$ mu-opioid receptor availability with buprenorphine trough plasma concentrations ≥ 1 ng/mL, which can be achieved by a dose of 4mg . However, management of reinforcing

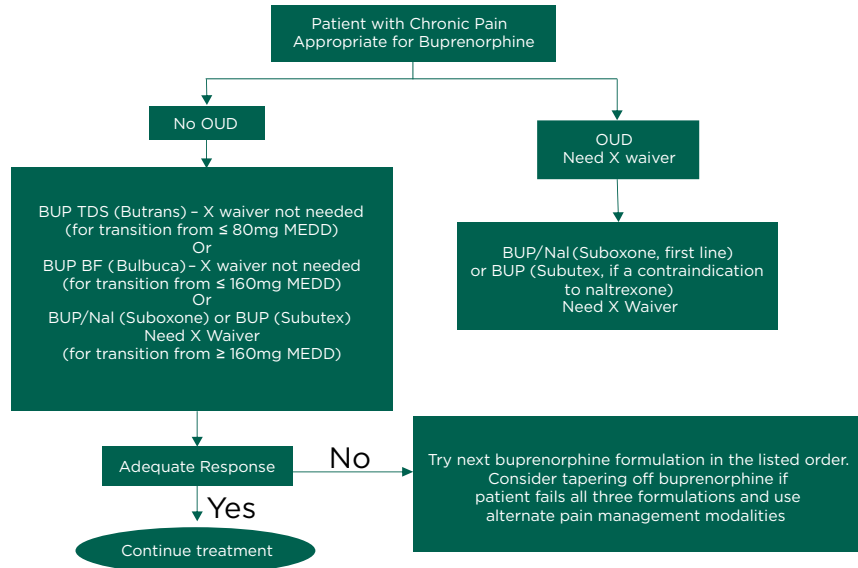
and euphoric effects of opioids in OUD requires <20% mu-opioid receptor availability with buprenorphine trough plasma concentrations ≥ 3 ng/mL, thus requiring a higher dose.²¹ Dosages of 4 to 16 mg (up to 32) mg/day are usually given for opioid maintenance therapy. Buprenorphine/naloxone combination medication has less potential for abuse due to deterrent properties of naloxone, thus decreasing the risk of diversion. Unlike methadone, buprenorphine does not prolong the QT interval. A buprenorphine/naloxone film is also introduced to address safety and diversion issues and improve retention. Buprenorphine-related fatalities are almost exclusively related to combined use with other psychotropic agents or drugs, especially benzodiazepines.⁴⁰

Indication	Formulation	Dosing
<i>Pain</i>	Buccal Film (Belbuca)	75 - 900 mcg/day, BID dosing
	Transdermal Patch (Butrans)	5-20 mcg/hr., weekly
<i>Opioid Use Disorder</i>	Sublingual tablet (Subutex) Sublingual film (Suboxone)	8-24mg/day
	Extended-release injection (Sublocade)	100-300mg monthly



OPIOID SAFETY AND RISK ASSESSMENT

Figure 2. Example of guidelines for assessment of OUD



You should always review updates to your own institutional and national guidelines.

Assessment of OUD (misuse, abuse and addiction) in Primary Care can be a challenge, including difficulty in determining an individual's current frequency and past history of use. OUD assessment in Primary Care may be negatively affected by the lack of a universally accepted definition for addiction in the context of opioid treatment for chronic pain. Some of the usual criteria such as tolerance and dependence become irrelevant, as they are often the inevitable consequences of chronic opioid therapy. The American Pain and Addiction Societies identified 4 criteria for addiction: impaired control over drug use, compulsive use, continued use despite harm and craving.³⁶

Prediction of future inappropriate use of opioids is often considered difficult, despite the availability of several tools to assess the risk and severity of addiction. Diagnostic tools such as the Addiction Severity Index and Structured Clinical Interview for *DSM*²⁵ require skilled administration experts and significant time to administer. Some brief screening tools such as CAGE are designed to screen for active problems with substances but not to predict future problems and were not designed to screen for OUD. Several risk-assessment tools have been developed to overcome such challenges and are currently in clinical practice, but none has been validated across medical settings. Review of external sources of information such as biological tests (e.g., urine drug screen), medical records, collateral information from family, prescription monitoring programs, payer opioid prescription data and screening for other risk factors is recommended.

Essential elements of opioid safety and risk assessment include³⁷:

- 1. Past and current substance use
- 2. Psychiatric assessment
- 3. Aberrant drug-related behaviors (please see table below)
- 4. Opioid assessment screening tools
- 5. Risk factor stratification



Figure 3. Aberrant behaviors indicating abuse of opioids prescribed for chronic pain.

	Forged prescription		Solicited opioids from other providers
	Sold prescription		Used nonprescribed opioids > once
	Abused prescribed drug		Sought euphoria from opioids
	Canceled clinic visit		Wanted opioids for anxiety
	No show or no follow-up		Abnormal positive drug screen for 2 or more substances
	Requested early refills		Resisted therapy changes/alternative therapy
	Unauthorized ER visits		Repeatedly reported lost or stolen prescriptions
	Concurrent inappropriate use of alcohol		Requested refills without clinic visit
	Injected drug use		Previously discharged from practice
	Overdose		Third party required to manage individual's medications
	Abnormal urine/blood screen		Unauthorized dose escalation

ER = emergency room

Opioid assessment screening tools: Despite limited evidence for reliability and accuracy, screening for opioid-related risk is recommended to identify and minimize the risk for aberrant behavior. Some tools commonly used in clinical practice include those on the following pages.

Opioid Risk Tool³⁷

1. Family History of Substance Abuse

	Mark each box that applies	Female	Male
Alcohol	<input type="checkbox"/> <input type="checkbox"/>	1	3
Illegal drugs	<input type="checkbox"/> <input type="checkbox"/>	2	3
Prescription drugs	<input type="checkbox"/> <input type="checkbox"/>	4	4

2. Personal History of Substance Abuse

Alcohol	<input type="checkbox"/> <input type="checkbox"/>	3	3
Illegal drugs	<input type="checkbox"/> <input type="checkbox"/>	4	4
Prescription drugs	<input type="checkbox"/> <input type="checkbox"/>	5	5

3. Age (Mark box if 16 – 45)

☐ ☐ 1 1

4. History of Preadolescent Sexual Abuse

☐ ☐ 3 0

5. Psychological Disease

Attention Deficit Disorder, Schizophrenia	<input type="checkbox"/> <input type="checkbox"/>	2	2
Obsessive-Compulsive Disorder, Bipolar, Depression	<input type="checkbox"/> <input type="checkbox"/>	1	1

TOTAL _____

Total Score Risk Category: Low Risk 0 – 3 Moderate Risk 4 – 7 High Risk > 8

D.I.R.E. Score: Patient Selection for Chronic Opioid Analgesia³⁸

For each factor, rate the individual's score from 1-3, based on the explanations in the right- hand column. Score Factor Explanation:

Diagnosis	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, nonspecific back pain 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis
Intractability	1 = Few therapies have been tried, and the individual takes a passive role in the pain-management process. 2 = Most customary treatments have been tried, but the individual is not fully engaged in the pain-management process, or barriers prevent full engagement (insurance, transportation, medical illness). 3 = Individual is fully engaged in a spectrum of appropriate treatments but with inadequate response.
Risk	R= Total of P+C+R+S (see below)

<u>Psychological:</u>	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder 3 = Good communication with clinic. No significant personality dysfunction or mental illness
<u>Chemical Health:</u>	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse 2 = Chemical coper (uses medications to cope with stress) or history of CD in remission 3 = No CD history. Not drug-focused or chemically reliant
<u>Reliability:</u>	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through 2 = Occasional difficulties with compliance but generally reliable. 3 = Highly reliable individual with meds, appointments &
<u>Social Support:</u>	1 = Life in chaos. Little family support and few close relationships; loss of most normal life roles 2 = Reduction in some relationships and life roles 3 = Supportive family/close relationships. Involved in work or school and no social isolation
<u>Efficacy score</u>	1 = Poor function or minimal pain relief, despite moderate-to-high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient info – hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

CD = Chemical dependence

Total score = D + I + R + E

Score 7-13: Not a suitable candidate for long-term opioid analgesia
Score 14-21: May be a candidate for long-term opioid analgesia

Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP®-R)

The Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0 is a tool for clinicians to help determine how much monitoring an individual on long-term opioid therapy might require.³⁹ It is a quick and easy-to-use questionnaire designed to help providers evaluate an individual's relative risk for developing problems when placed on long-term opioid therapy. It has 14 items, each item scored on 5-point scale.

The following are some sample questions given to individuals who are on or being considered for medication for their pain.

	Never	Seldom	Sometimes	Often	Very often
	0	1	2	3	4
How often have you felt a need for higher doses of medication to treat your pain?					
How often have you counted pain pills to see how many are remaining?					
How often have you been concerned that people will judge you for taking pain medication?					
How often have you taken more pain medication than you are supposed to?					
How often have you felt a craving for medication?					
How often have others expressed concern over your use of medication?					
How often have any of your close friends had a problem with alcohol or drugs?					
How often have any of your close friends had a problem with alcohol or drugs?					
How often have you felt consumed by the need to get pain medication?					
How often have you run out of pain medication early?					
How often have you attended an AA or NA meeting?					
How often have others suggested that you have a drug or alcohol problem?					

How often have you had to borrow pain medications from your family or friends?					
How often have you been treated for an alcohol or drug problem?					

Note: You may access the SOAPP-R Version 1.0 at <https://www.txpain.org/pdf/forms/SOAPP.pdf>

Risk-factor stratification: Gourlay et al.³⁰ proposed a “Universal Precautions” approach to decrease risks related to chronic opioid therapy, and stratified individuals into 3 groups (see opioid safety and risk assessment section). The purpose of stratification is to determine the intensity of monitoring required and not to deny pain treatment to high-risk individuals.

Table 11. Risk factors associated with chronic opioid therapy.⁴⁰

Age of 18 to 24 years	Early prescription refills
Male sex	Escalating dosage
12 or more opioid prescriptions	Hospital visits and psychiatric outpatient visits
Use of 3 or more pharmacies	Diagnosis of nonopioid substance abuse, depression, PTSD and/or hepatitis

Monitoring for inappropriate opioid use

Everyone taking chronic opioid therapy needs to be monitored regularly, with the intensity dependent on risk stratification, to ensure safe and effective use of opioids. Monitoring must include the following:

1. Opioid assessment screening tool
2. Urine drug testing (UDT)
3. Prescription drug-monitoring program data
4. Opioid treatment agreement
5. Universal precautions

UDT: UDT is an essential component of risk management in chronic opioid therapy and must be implemented from the beginning with ongoing follow-up. Benefits include:

1. Facilitates objective assessment of treatment adherence
2. Identifies possible inappropriate drug use
3. Is noninvasive
4. Is cost effective
5. Detects most drugs for 1 to 3 days after exposure, including illicit drugs
6. Improves individual care

However, a test may occasionally have an unexpected result. Differential analysis of this situation includes consideration of clerical error, false-positive result due to use of another product or medication, drug misuse, SUD, psychiatric comorbidity, pseudo-addiction or drug diversion. Confirmatory testing may sometimes be necessary to determine the accuracy of the result. It is important to discuss any unexpected results with the individual, separate the motive from the aberrant behavior, and review treatment plans, which may include a referral to a specialist in addiction medicine, increase in the frequency of UDTs, or a taper or discontinuation of the opioids if the individual receiving care is nonadherent with the treatment plan. Open communication with the individual, seeking their interpretation of the results, and review of previously agreed-upon goals of treatment are often beneficial.



Table 12. UDT detection times of common drugs of misuse and False positive.⁴¹

Drug	Approximate Retention Time	False positive UDT results
Amphetamines	48 hours	Brompheniramine, alpha-agonist catecholamines (nasal inhaler), phenylpropanolamine, B-agonists, Chlorpromazine, Promethazine, Trazodone, Dopamine congeners (bupropion, L-dopa, carbidopa), Ranitidine, Beta-blockers, Pseudoephedrine, phenylephrine,
Barbiturates	Short acting: 24 hours Long acting: 2 -3 weeks	Naproxen, ibuprofen
Benzodiazepines	3 days 4-6 weeks after use for >1 year	Sertraline
Cannabinoids	Moderate use (X4/week): 5 days Heavy use (daily): 10 days Chronic use: Up to 6 weeks	Ibuprofen, Naproxen
Cocaine	2-4 days	
Ethanol	2-4 hours	
Methadone	About 30 days	Diphenhydramine, Doxylamine, Quetiapine, Thioridazine, Chlorpromazine, Clomipramine, Verapamil
Opiates	2 days	Quinolones
Phencyclidine (PCP)	About 8 days Chronic use: Up to 30 days	Venlafaxine, Ibuprofen, Dextromethorphan
Propoxyphene	6-48 hours	

Table 13. Drug testing traps.

Drug	Screening cut- off concentrations ng/ml	Confirmation cut-off concentrations ng/ml	Urine detection time	Immunoassay - (I) Chromatography - (C)
Hydrocodone	300	50	1 - 2 days	I & C
Oxycodone	100	50	1 - 3 days	I & C, specify request
Morphine	300	50	3 - 4 days	I & C
Methadone	300	100	5 - 10 days	I & C, specify request
Hydromorphone	300	100	1 - 2 days	I & C, specify request
Meperidine	300	100	1 - 2 days	I & C, specify request
Codeine	300	50	1 - 3 days	I & C
Heroin	10	25	1 - 3 days	I & C
Buprenorphine	5	10	1 - 10 days	I & C, specify request
Benzodiazepines	200	20 - 50	Up to 30 days	I
Barbiturates	200	100	2 - 10 days	I & C
Amphetamine	1,000	100	2 - 4 days	I & C

Prescription drug monitoring programs collect statewide data for individuals prescribed controlled substances. Data include the name of the controlled substances prescribed, including quantity and dates when issued and filled, name(s) of the prescribing physician(s), and dispensing pharmacies.

The opioid treatment agreement informs individuals about the risks and benefits of opioid therapy and facilitates a mutual agreement of the course and consequences of aberrant behavior.

Universal precautions⁷: The concept of ‘universal precautions’ in pain medicine is derived from the “Infection Prevention” approach by Gourlay et al. to apply the appropriate minimum level of precautions to individuals with chronic pain to reduce stigma, minimize overall risk and improve care, similar to the approach to potentially life-threatening infections. The precautions are outlined as follows:

- 1. Diagnosis with appropriate differential, including psychiatric comorbidity
- 2. Psychological assessment, including risk of addictive disorders
- 3. Informed consent, including risks and benefits
- 4. Treatment agreement
- 5. Pre-and posttrial assessment of pain/function
- 6. Appropriate trial of opioid therapy +/- adjuvants
- 7. Reassessment of pain score and level of function

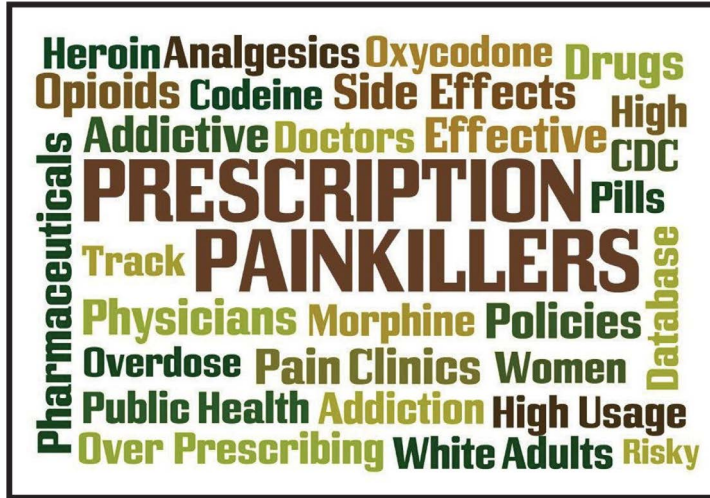
- 8. Regular assessment of the “Four A’s” of pain medicine: analgesia, activity, adverse effects and aberrant behavior
- 9. Periodic review of pain diagnosis and comorbidity, including addictive disorders
- 10.Careful and thorough documentation

Table 14. Triage system to categorize risk per individual needs.³⁰

	Risk factors	Risk Level	Recommended care setting
Group I	No personal or family hx. of SUDor psychopathology	Chronic noncancer pain	Primary care clinics
Group II	Personal or family hx. of SUD Past or current psychiatric disorder	Not addicted to opioids but has high risk	Primary care clinic with specialist support
Group III	Active SUD or major psychopathology Active addiction	Active addiction, significant risk	Specialty care

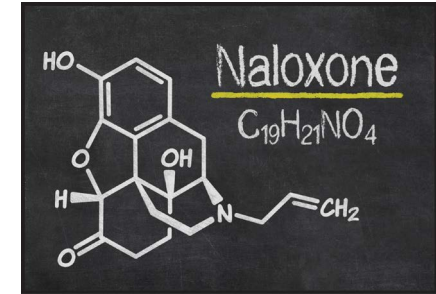
Risk Related to Combined Opioid and Benzodiazepine Use

Benzodiazepines have been used for several decades for management of anxiety, muscle spasticity and insomnia. Their long-term use is discouraged due to concerns related to development of tolerance and dependence. Additionally, benzodiazepines have several serious adverse effects, including sedation, cognitive side-effects, increased risk for falls, CNS and respiratory depression, and life-threatening withdrawal symptoms, including autonomic instability and seizures. Combined use of benzodiazepines and opioids poses additional risk related to cumulative effect. Tapering and eventually stopping benzodiazepines are recommended prior to tapering opioids.



OPIOID EDUCATION AND NALOXONE DISTRIBUTION PROGRAM

Prescription opioids are 1 of the most common drugs associated with drug overdose, with an overall trend of alarming increase in opioid prescriptions, misuse and overdose deaths. Several primary (prescriber and patient education, avoidance and careful assessment of opioid risk and safety) and secondary (policy initiatives, guidelines and prescription drug monitoring programs) prevention strategies have been implemented.¹⁸ More than 841,000 persons died of opioid overdose since 1999, in the United States. The Centers for Disease Control and Prevention (CDC) has published guidelines intended for primary care physicians posting that nearly half of all dispensed opioids are given in primary care settings.²⁰ Available published estimates of the risk of opioid-related overdose deaths in US Veterans suggest increased risk with morphine equivalent dose (MED) of ≥ 100 mg and with psychiatric comorbidities, including PTSD, chronic noncancer pain, acute pain and SUD. In addition, over half of all stimulant overdoses involved an opioid, often due to the presence of fentanyl or other synthetic opioids, with 9-fold increase in deaths involving stimulants and opioids.²⁰



Several opioid education and naloxone distribution (OEND) programs have been initiated to offer naloxone as a harm-reduction strategy and ensure that individuals at-risk for opioid overdose are educated about overdose and naloxone administration. OEND programs have several additional benefits, including engaging individuals receiving care, empowering family and friends, and keeping individuals alive so they can enter recovery programs for addiction.

Naloxone is a safe and effective specific opioid antagonist that works predominantly at mu-opioid receptors to reverse opioid-mediated effects, including CNS and respiratory depression and hypotension. Naloxone has been used by emergency services and departments for this purpose for decades. It was successful in 98% of opioid overdose rescue attempts made in a community public health OEND program in Massachusetts.⁴²

Naloxone does not have any pharmacological effect in individuals not taking opioids. It is not associated with tolerance or dependence. It has several potential adverse effects, including precipitation of opioid withdrawal in persons with physical dependence on opioids, recurrence of respiratory depression with long-acting opioid overdose and transmission of blood-borne viruses with accidental needle sticks. Rapid administration of naloxone in postoperative care can cause pulmonary edema.

OEND programs have several barriers, including supply shortages, fear of stigma for carrying the injectable, concerns about increased use with perception of naloxone as a safety net and medicolegal concerns. Multiple formulations of naloxone (intranasal and auto-injectors) have made it easier to administer.

The VA OEND Program has a share point site with educational materials: **See Resource list**

OEND candidates are classified below (see Table 15) based on the evidence for effectiveness of the OEND program and the risk factors for opioid-related overdose.⁴³

Direct Association with Benefit	Indirect Association with Potential Benefit	Clinical Judgment of Potential Benefit
Heroin or other IV drug use Substance use High likelihood of opioid overdose or witnessing an overdose	Individual risk factors: SUD, PTSD, other MH diagnosis Heroin or nonmedical opioid use	Individual risk factors: Past suicide attempt, High risk suicide list Cardiac illness, unstable renal, HIV/AIDS or hepatic disease Being ≥ 65 years of age, having cognitive deficits, being debilitated, voluntary caregiver request
	Prescription risk factors: High opioid dose ≥ 50 to 100 mg Long- acting opioid Methadone initiation in opioid- naive individuals Combined use with benzodiazepines	Prescription risk factors: Homebased: Continuous or individual controlled intraspinal infusion Opioid induction, titration or rotation to methadone
	Situational risk: Loss of opioid tolerance Poor access to emergency care Voluntary individual request	Situational risk: Reluctance to call 911 Opioid-related aberrant behavior

Direct Association with Benefit	Indirect Association with Potential Benefit	Clinical Judgment of Potential Benefit
Settings: Medication assisted programs Inpatient detoxification HIV education/prevention Syringe access program SUD treatment programs Community SUD programs Emergency departments Homeless shelters	Settings: Pain management clinics Affordable housing for homeless, or people with mental illness or AIDS	

Table 15. OEND classifications.

IV = intravenous; MH = mental health; COPD = chronic obstructive pulmonary disorder; SUD = substance use disorder

OEND training focuses on teaching individuals, including family and friends, who are likely to be bystanders at an overdose, to recognize an opioid overdose, call emergency medical services (“911”), administer naloxone, perform the “ABCs” (Airway, Breathing and Circulation) of emergency response, and

place the victim in the recovery position. In many cases, just administering naloxone will be enough to prevent a fatal overdose.

Naloxone Kit Contents: 1 pair of gloves, (2) alcohol pads, overdose rescue instructions, laerdal face shield CPR barrier or equivalent, opioid safety brochure among other contents (see Table 16 below).

Table 16. Naloxone Kit Contents.

Intramuscular Kit	Intranasal Kit	Autoinjectors
(2) Naloxone 0.4mg/ml vials (2) syringes,	(2) Naloxone 1 mg/ml (2 ml) prefilled needleless syringe	(2) Naloxone 0.4 mg/ml prefilled autoinjector devices

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RESOURCE MATERIAL: STAFF TRAINING AND RESOURCES

- www.va.gov/painmanagement
- VA OEND SharePoint for Naloxone Training
 - The OEND National Support and Development Work Group develops provider training and patient and provider educational materials.
 - Educational, informational and implementation resources are available to all VA staff via the OEND SharePoint. The link to this SharePoint
- is: [https://vaww.portal2.va.gov/sites/mentalhealth/OEND/SitePages/](https://vaww.portal2.va.gov/sites/mentalhealth/OEND/SitePages/Home.aspx) Home.aspx
- <http://www.pbm.va.gov>
- SAMHSA Opioid Overdose Prevention Toolkit: Contains safety advice for patients and resources for family members. [http://store.samhsa.gov/](http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742) product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742
- Community-Based Overdose Prevention and Naloxone Distribution Program Locator: Identifies programs outside of the VA that distribute naloxone. <http://hopeandrecovery.org/locations/>
- Prescribe to Prevent: Patient resources and videos demonstrating overdose recognition and response, including naloxone administration. • <http://prescribetoprevent.org/video/>
- *Taking Opioids Responsibly*

