



POCKET GUIDE FOR CLINICIANS FOR MANAGEMENT OF CHRONIC PAIN

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TABLE OF CONTENTS

Introduction.....	1
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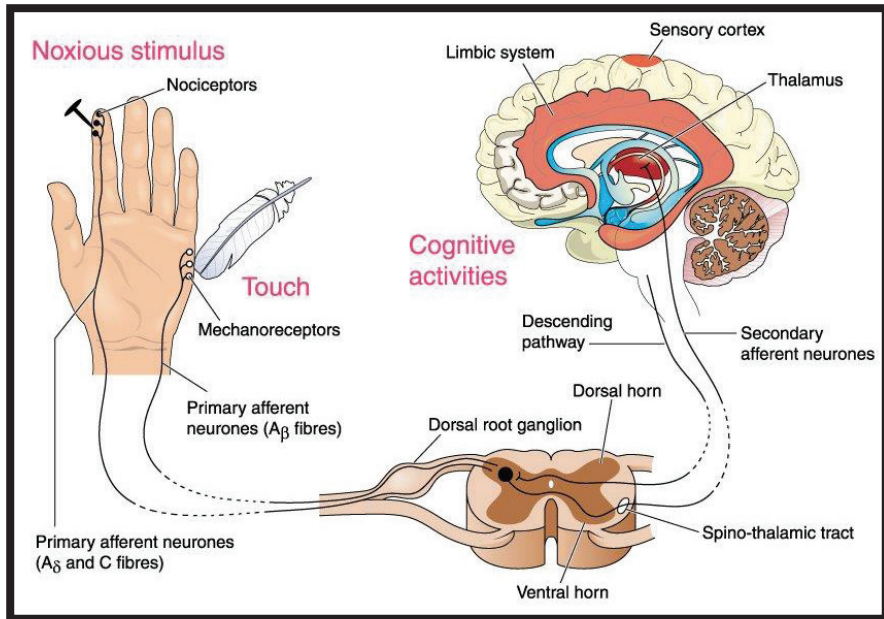
Categories

1. Types and Mechanism of Pain.....	3
2. Chronic Pain and Psychiatric Co-morbidity	11
3. Assessment of Pain	17
4. Stepped Care Model of Care	25
5. Pharmacological Interventions	33
6. Non-Pharmacological Interventions	45
7. Opioid and Substance Use Disorders	53
8. Opioid Safety and Risk Assessment	63
9. Opioid Education and Naloxone Distribution Program.....	77
10. References and Resources.....	83

Introduction

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

Pain is the most common physical symptom affecting 100 million Americans, more than diabetes, heart disease and cancer combined. Providers in virtually any patient care 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 billions including incremental health care costs and lost productivity. Most importantly, it affects the quality of life placing emotional and financial burden on individuals and their families¹.



TYPES AND MECHANISMS OF PAIN

Pain can be classified based on pain physiology, type of tissue involved and time course³.

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 somato-sensory 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, post-herpetic neuralgia, carpal tunnel syndrome.
- **Central:** Spinal cord injury, phantom limb (post-amputation), 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 one type of pain in a given patient. In addition, 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 obvious cause. Examples include acute pain secondary to trauma, burns and infarction.

Chronic pain: Generally refers to pain that persists beyond normal tissue healing time, for three 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 Pain⁴:

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.

- **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 three 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 - site of synaptic modulation and transmission.

Ascending tracts: Spinothalamic tracts transmit nerve stimuli through dorsal horn of spinal cord to 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 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 then relayed to multiple areas of the brain.

Pain Perception: 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:** Inhibition of synaptic transmission by activation of A β fibers by light touch.
- **Descending:** Projections from brain stem nuclei to dorsal horn result in modulation of nociception.
 - Inhibition occurs through release of neurotransmitters such as serotonin, norepinephrine and opioids.
 - Facilitation can occur as a result of fear and anxiety.

Sensitization: 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:** Mild noxious stimulus resulting 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 resulting in referred pain to the area of skin.

Sympathetically Maintained Pain: Complex Regional Pain Syndrome (CRPS):

Development of spontaneous pain in the region of nerve injury which may be of a burning quality beginning after a delay of hours to days or even weeks and may be accompanied by swelling of the extremity, periarticular bone loss, and arthritic changes in the distal joints. CRPS can be produced by a variety of injuries, including fractures of bone, soft tissue trauma, myocardial infarction, and stroke and 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 CO-MORBIDITY

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

Depression: The estimated current or 12 month prevalence of depressive symptoms or mood disorder is more than 20% in individuals with arthritis, migraine headache and pelvic pain and more than 50% in fibromyalgia, temporomandibular joint pain, chronic back pain and abdominal pain. The prevalence of major depressive disorders, dysthymia and bipolar disorders range from 2%-61%, 1%-9%, and 1%-21%, respectively, across all chronic pain groups. Individuals with chronic neck or low back pain are 2 to 2.5 times more likely to experience an episode of depression at 6 and 12month follow-up. Conversely, pain free individuals with depression are 3 to 4 times more likely to develop neck or low back pain than individuals without depression. Some studies also suggested a dose response relationship between intensity of pain and severity of depression. Functional imaging studies in individuals with fibromyalgia, abdominal and low back pain suggested alterations in brain regions responsible for processing emotional stimuli such as the Anterior Cingulate Cortex (ACC) and the Prefrontal Cortex (PFC).

Anxiety: Similar to depression, a bidirectional relationship exists between chronic pain and anxiety, particularly in individuals with migraine headaches. Individuals with migraines are 2 to 3 times more likely to be diagnosed with Generalized Anxiety Disorder (GAD), Panic Disorder (PD), agoraphobia and Post Traumatic Stress Disorder (PTSD), while individuals with anxiety disorders are twice as likely to develop migraine headaches than individuals without anxiety

disorders. Functional imaging studies suggested activation of overlapping brain regions (Thalamus, ACC and PFC) by both chronic pain and anxiety.

Substance use: Individuals with chronic pain are also at risk for other substance use disorders (SUD), with the highest prevalence rates for patients with fibromyalgia, chronic spinal pain and arthritis. Similar to 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 (Opiate Use Disorder [OUD] not specified) ranges from 1% to 25%. From a neurobiological perspective, the medical prefrontal cortex is involved in processing of pain and the development of SUD as a key component in the reward pathway.

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 of the 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 treatment⁷.












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

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.

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, greater pain related anxiety and suffering.

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, are more likely to use opioids, and use higher doses of opioids.

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.			

ASSESSMENT OF PAIN

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

Some helpful tips for an effective approach include:

1. Accept patient's self-reported pain as accurate
2. Allow patients to describe their pain in their own words as much as possible
3. Utilize active listening with observation of behavior and body language
4. Involve the family in the process when the patient is a limited historian e.g., an elderly patient with cognitive impairment

Every patient who presents with pain requires a basic evaluation within the primary care setting. Patients 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.

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

P- Provokes and Palliates:

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

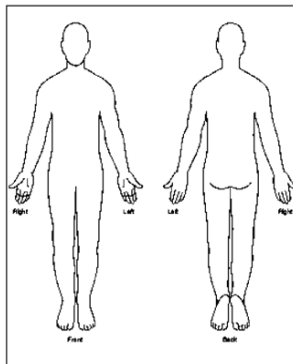
Q-Quality: Sharp/dull/stabbing/burning/crushing
(helps differentiate the type or cause of pain-see Types of Pain section)

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?



Past Medical History:

1. Past 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, including:
 - Anxiety, depression, somatoform disorders, PTSD, ADHD 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 including:
 - 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:

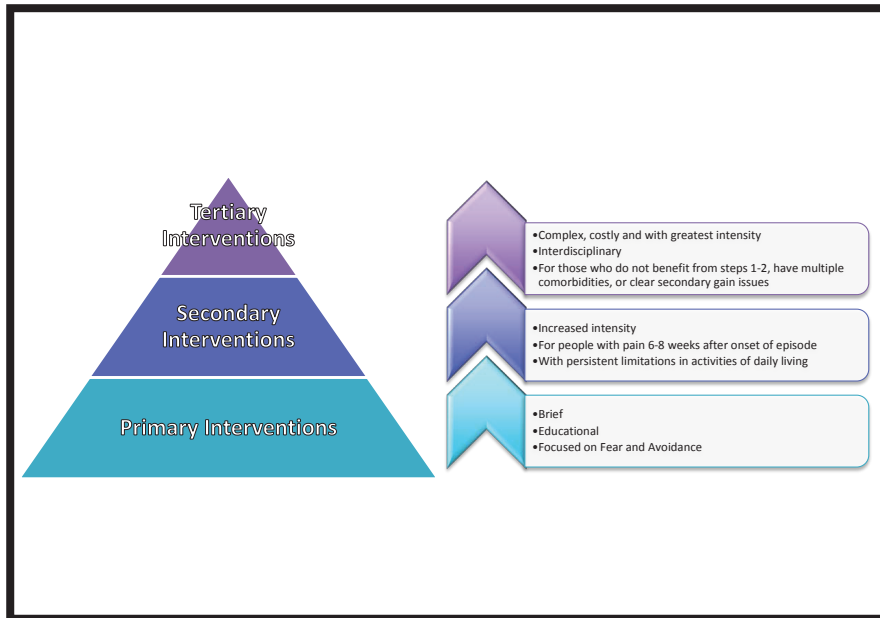
Common assessment tools often used for psychological assessment of pain patient include:

1. McGill Pain Questionnaire (Melzac): Widely used, relatively brief, assesses location, degree, and a variety of emotional modifiers
2. West Haven-Yale Multidimensional Pain Inventory (WHYMPI; Kerns, Turk, & Rudy): Gives comprehensive evaluation of interference and disability, longer time
3. Pain Outcomes Questionnaire (POQ; Clark, Gironde, and Young): Standardized with VA patient samples, designed for use as repeated assessment measure, has intake, discharge, and follow-up versions, measures different pain impacts across domains including:
 - ADLs, Pain-Related Fears, Mobility Problems, Negative Affect, Vitality, and Pain Severity
4. The Minnesota Multiphasic Personality Inventory (second ed.) “MMPI-2”: This well known and widely used personality inventory, although not a pain assessment tool, can give a basic understanding of the patient’s personality and how he or she generally views the world, 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 exaggeration
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, ADLs 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 health care 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 interference and disability and may become high utilizers of medical services.

Von Korff and Moore (2001) proposed the Stepped-Care Model for pain to stratify resource utilization for management of back pain, using a three-tiered approach to maximize benefit for the patient and promote return to the highest level of functioning achievable. At the base of this system were educational strategies designed to challenge fears associated with reinjury or symptom exacerbation perpetuated through inactivity and activity avoidance. This model suggests that Step One interventions should be available to all patients with a goal of addressing specific worries associated with the pain condition through self-care educational materials distributed in Primary Care. Gatchel (2005) expanded upon this by emphasizing the role of potential 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 patient will likely require more intensive treatment. The Veterans Affairs Administration (VA) has adopted the Stepped-Care model on a national level and now mandates a variety of actions and programs to expand its implementation (VHA DIRECTIVE 2009-053).

Diagram of Stepped Care Model

The model can be thought of in terms of treatment implementation, in terms of the complexity of the patient and the condition, or more broadly in terms of the interaction of the treatment and the patient. Otis, Macdonald, and Dobscha (2006) and the VA suggest treatments for Step One patients should be done within the Primary Care setting with input from consultative services for diagnostic or treatment purposes.

Step One

Step One is often characterized as care for patients 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. They require a basic medical evaluation (see Assessment of Pain) to assess for the cause of the pain and to make specific, and appropriate, treatment recommendations, and address any specific concerns on the part of the patient, 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 for most individuals to 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. They 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 done in an individual or a group format. Frequently, these interventions involve providers who are co-located or integrated into Primary Care.

Interventions:

Medical: Management within primary care setting

Psychological

Step Two

Step Two is characterized as patients who continue to have activity limitations at 6 to 8 weeks (Von Korff & Moore, 2001) for acute conditions, or 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 patients have moderate to high levels of pain-related interference, which may lead to disability. Additionally, patients with chronic pain conditions with comorbid psychological or psychiatric conditions such as Post Traumatic Stress Disorder 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 a Step Two patient.

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 made. Evaluation and treatment is 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. Relevant patients are frequently physically deconditioned and pain is clearly affected by low to minimal levels of activity and marked fear and pain avoidance. There are significant psychosocial factors associated with the experience of pain with high levels of pain-related catastrophizing and possible secondary gains (either financial or psychological). 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 opiate medication, which is used not only to treat 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 opiate based medication, opiate misuse or abuse, and significant “acting out” or hostile behaviors.

(Opiate 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

Studies have shown that several pharmacological agents (Opioid and non-opioid) are effective for chronic pain management, most regimens ranging from 2 weeks to 6 months.

Commonly used pharmacological agents include:

Analgesic Medication	Mechanism of action	Examples	Type of Pain
Non Opioids	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
Opioids	Act by binding to μ -opioid receptors in the brain	Morphine, Codeine, Hydrocodone	
Adjuvants			
<i>Antidepressants</i>	Block reuptake of serotonin and Norepinephrine	Amitriptyline, Nortriptyline, Venlafaxine, Duloxetine	Neuropathic pain Fibromyalgia
<i>Anticonvulsants</i>	Modulation of Ion channels	Topiramate, Valproic acid Carbamazepine, Gabapentin, Pregabalin,	Migraine Neuropathic pain Fibromyalgia
<i>Muscle Relaxants</i>	Direct action on CNS CNS and other unknown mechanism	Baclofen, Tizanidine, Methocarbamol, Cyclobenzaprine,	Fibromyalgia, muscle spasms, Tension headache
<i>Topical Agents</i>	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.
<i>Beta-Blockers</i>			

Choosing an appropriate medication for management of pain depends on a number of factors such as diagnosis, intensity and duration of pain, medical and psychiatric co-morbidities, treatment setting, past medication trials, drug interactions, side effect profile, 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 function and quality of life while minimizing the risk of addiction, and considering when and how to discontinue Opioid therapy if benefits do not outweigh risks.

Pharmacology of Non Opioid 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 increase cardiovascular risk such as myocardial infarction and stroke.

Drug	Dose mg	Adverse effects	Drug interactions	Contraindications (Absolute and relative)
Nonselective, Acidic Drugs (NSAIDs)				
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 cardio-protection	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

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 Anticonvulsants and other non-opioid analgesics

Drug	Dose mg	Adverse effects	Drug interactions	Contraindications
Antiepileptics				
Carbamazepine	200 - 500 mg PO BID (Trigeminal Neuralgia)	Diplopia, Ataxia, Stevens -Johnson syndrome, SIADH	Avoid grape fruit juice 2 D6 inducer, increased metabolism of contraceptives	Allergic reaction, WBC < 3000 Platelet < 100,000 RBC < 4x10 ⁹
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		

Pharmacology of Opioid Analgesics

The term "Opioids" refers to a broad class of drugs such as:

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 gastrointestinal tract. Analgesic effect of Opioids is due to activation of μ opioid receptors, which in turn activates 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).

Equianalgesic Narcotic Conversion Table

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)

<i>Fentanyl Patch</i>	<i>24 hour MED</i>	<i>Patch</i>
	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 (OIH) are significant challenges in chronic Opioid therapy. The degree of tolerance varies among individual patients as well as individual Opioids, warranting caution with switching from one Opioid to another to avoid Opioid toxicity. In addition, clinical differentiation of Opioid tolerance from OIH can be challenging.

Numerous randomized controlled trials support effectiveness of short term use of Opioids for management of 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 proportions with an estimated 259 million prescriptions for Opioids in United States in 2012, presenting serious

risks including Opioid use disorder, overdose and a marked increase in Opioid related death rate¹³. 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 patients with drug dependence¹⁰.

Given above concerns, CDC developed following guidelines for safe prescription and monitoring of Opioids for management of chronic pain outside of cancer, palliative care and end of life care¹³:

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

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

4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients 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)

8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should 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.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should 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.
10. When prescribing opioids for chronic pain, clinicians should 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.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

* All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline for evidence ratings.



NON - PHARMACOLOGICAL INTERVENTIONS

Potential resources to assist patients in managing chronic pain extends 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 and interplay of these factors in the pain experience and functioning, but 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. CBT for pain may be offered in individual or small group modalities, typically involving multiple sessions over a limited time frame 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 therapies (EBT) training rollout.

Acceptance and Commitment Therapy (ACT), pronounced as the word, “act”) ***for pain*** is another cognitive therapy approach which enjoys a significant evidence base supporting outcomes of enhanced functioning, improved patient

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. 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 (PM&R). 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 patients 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.

Integrative Medicine

Complementary and alternative medicine (CAM) 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 patients to manage longstanding conditions with impacts on functioning and quality of life, consistent with the biopsychosocial perspective. Increasingly,

CAM modalities have been incorporated and promoted in healthcare systems targeting chronic pain, including VA, to expand treatment options and address aspects of pain that formerly were not a main focus of intervention. With this movement, the term “integrative medicine” also has gained traction, reflecting a blending of mainstream, semi-mainstream, and alternative practices.

In considering appropriateness of CAM and integrative medicine resources, and as stressed throughout this handbook generally, it is important to consider presence or absence of underlying evidence base for effectiveness as well as potential for patient benefit or harm. Many CAM treatments lack formal clinical trials to assess effectiveness and safety. Moreover, in the case of certain CAM modalities, it should be recognized that local medical center policies and procedures may apply, guiding or restricting use and availability.

Meditation training or practice is the most commonly available CAM modality within the VA treatment system, and may 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. As examples, “mindful” meditation emphasizes open experiencing of events and perceptions in a non-judgmental and non-imperative fashion, and has been shown to be capable of altering pain experience. The “mantram” meditation technique involves silent repetition of a word, sound or phrase that holds personal meaning, and is being investigated as a means of altering response to chronic stressors such as pain. Many chronic pain patients report benefit from learning to allow increased awareness of rhythms such as movement of breath in and out of the body, during regular meditative practice.

Relaxation training may include meditative techniques but also includes well-

studied calming strategies such as abdominal (diaphragmatic) breathing, progressive muscle relaxation, autogenics, and guided imagery. Learning to trigger the “relaxation response” reliably is a useful self-management skill for many chronic pain patients, who may experience high levels of sympathetic arousal and “fight or flight” response as a function of pain escalation.

Biofeedback training can supplement training in relaxation or other processes relevant to self-management of chronic pain, by monitoring select responses within the body 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 multi-modal biofeedback training may be offered in office visits, there are now many small and relatively inexpensive devices that can find ready use by chronic pain patients in or out of the home.

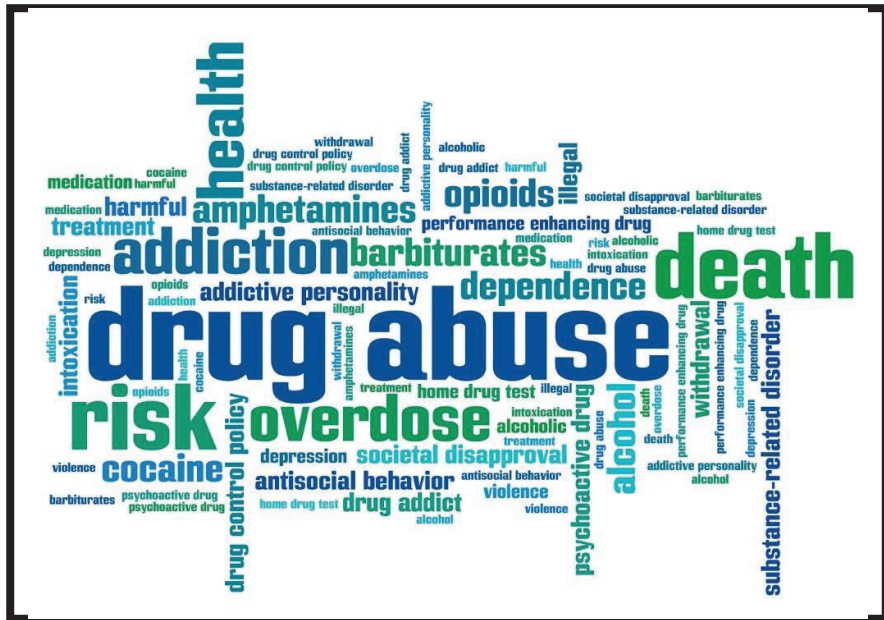
Chiropractic treatment can offer a pain relief alternative for certain conditions affecting muscles, joints and connective tissues. Chiropractic practitioners as a group comprise the largest population of CAM providers. They may use hands on manipulations to promote or restore alignment and mobility 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.

Transcutaneous Electrical Nerve Stimulation (TENS) is the most common form of electrical stimulation for pain; patients typically receive a TENS unit to use at home, featuring electrodes that they place noninvasively in relevant body area such as low back. Electrical stimulation is propagated through the skin, with patient 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 patients find them useful as a self-management tool.

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 may or 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, yielding mixed scientific outcome support and alternative proposals for mechanisms of action. Many chronic pain patients have characterized it as helpful and well-tolerated, and it has been increasingly offered through VA in recent years.

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 utilizes small earlobe clip electrodes connected to a portable, battery-powered

CES unit delivering 20-60 minute treatments. Other versions employ hand held 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 patients and providers in many settings including VA. Because it is relatively non-demanding of patient effort it can represent an option for trial when other treatment modalities are limited.



OPIOID AND SUBSTANCE USE DISORDERS

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

1. Concerns about possible relapse of substance abuse
2. Chronic Opioid therapy induced central sensitization resulting in increased pain perception and Opioid induced hyperalgesia.
3. Difficulty in differentiating between physiological dependence due to development of tolerance and addiction
4. Legitimization of Opioid abuse by patients with SUD.

DSM 5 Diagnosis of Opioid Use Disorder is a problematic pattern of opioid use, leading to clinically significant impairment or distress as manifested by at least 2 of the following in a 12month period.

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. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use 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. Recurrent opioid use in situations in which it is physically hazardous.

9. Continued opioid use 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 (NOT one of the criteria for counting, when opioids taken under medical supervision).
11. Withdrawal (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 in this patient population are management of SUD in addition to the goals for all patients with chronic pain, i.e., functional restoration and pain relief.

The relevant clinical issues to be considered are:

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

Management of OUD and SUD in patients with Chronic Pain

Essential elements of assessment of SUD and OUD include:

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

Gourlay. et al proposed “Universal Precautions” approach to decrease risks related to chronic Opioid therapy, and stratified patients in to 3 groups (See Opioid safety and risk assessment section). Atluri et al proposed the following guidelines for management of chronic pain with comorbid SUD¹⁷:

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

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

1. Referral to appropriate specialist services such as Substance Dependence Treatment Program.
2. Relapse prevention using
 - Careful monitoring
 - Cognitive behavioral interventions for pain management
 - Stress management and psychosocial supports
3. Early identification of relapse

**SDMP: State drug monitoring program*

Opioid Tapering

The safest pain treatment strategy for patients with OUD and or SUD is a non-Opioid and non-benzodiazepine approach. It is not uncommon for patients with comorbid SUD and OUD to be on fairly high dose of Opioids. Abrupt discontinuation of opiate medication can however place patient at high risk of opiate withdrawal, and often complicates co-morbid medical and psychiatric conditions. Hence, some flexibility should be employed with the speed of taper, allowing the patient to adjust to the schedule.

The following strategies can be of help to ensure smooth transition for the patient¹⁴:

1. Active listening
2. Reassuring the patient and address their fear of abandonment
3. Educate the patient regarding the risks and concerns related to chronic Opioid therapy and SUD
4. Assisting patient in setting goals for pain management as well as Opioid tapering
5. Offer medications for management of withdrawal symptoms
6. Offer other pharmacological and nonpharmacological interventions for pain management.
7. Facilitate referral to specialty services

The following Opioid Tapering Guidelines are proposed to facilitate safe tapering²⁶:

<i>Speed of Taper</i>	<i>Indications</i>
<i>Stop Now</i>	Suspected diversion
<i>Fast (Days)</i>	Inpatient admission (SI, medical reasons) Non-prescribed medication or substance abuse (cocaine, alcohol) Social/Legal concerns Medical: Prolonged QTc
<i>Slow (Weeks)</i> <i>High risk patients</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 co-morbidity: Probable Obstructive sleep apnea, sedatives Mental health relative risk: sexual trauma, co-morbid MH issue Substance misuse: Past Hx, Family Hx., Non prescribed medication use, Moderate Opioid risk score, Tobacco use of > 1PPD Social/Legal: Family Hx, Disruptive behavior, -ve UDT Medical: Lack of Continuity of care, lack of improvement in pain

Complications from Opioids: Hyperalgesia, cognitive impairment, LTOT bowel syndrome, sleep disorders, ED

Potential Complications from Opioids: Age >65, fall risk, renal dysfunction, liver dysfunction

Additional considerations:

1. Taper down long acting Opioids prior to short acting Opioids
2. Taper down Benzodiazepines prior to Opioid initiation.

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 can not only stratify the risk of Opioid dependence but also guide the treatment team in determining the individualized treatment plan in the most appropriate setting.

The following medications can be used to manage the withdrawal symptoms:

1. Clonidine 0.1 mg PO TID for the autonomic symptoms of opioid withdrawal, can be titrated up 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 opiates)
6. Hydroxyzine Palmoate 25 mg or Diphenhydramine 25 mg PO Q6 hours and at bed time 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 three 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 of Opioids including

1. Full Agonists: Methadone, Morphine sulphate, Heroin
2. Partial agonists: Buprenorphine, Buprenorphine/Naloxone, Buprenorphine film and depot implant
3. Antagonists: Naloxone (IV use only), Naltrexone and Depot Naltrexone.

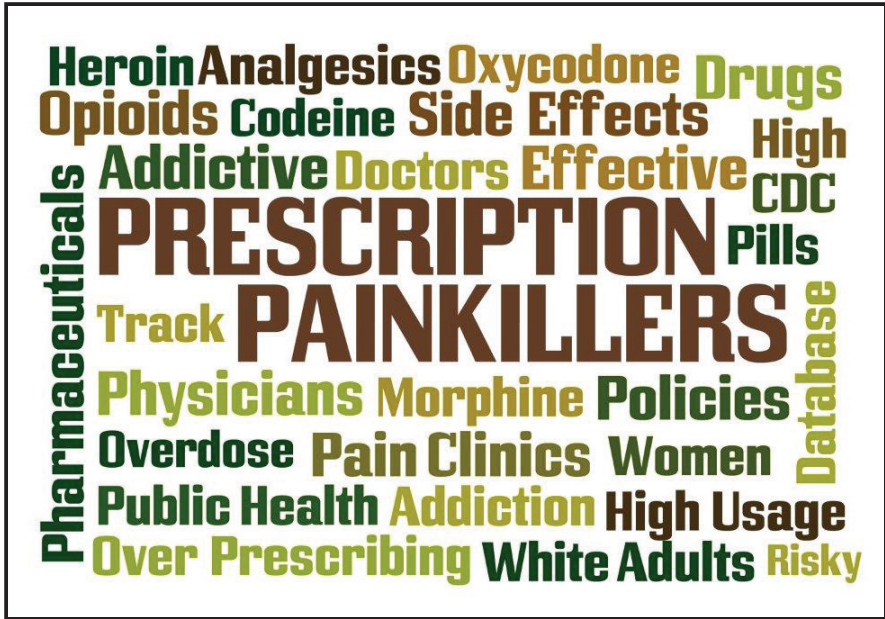
Methadone and Buprenorphine are first line medications for treatment of Opioid dependence and Opioid detoxification.

Psychosocial interventions including Cognitive behavioral therapy, Seeking safety therapy, Contingency management, Motivational enhancement and other supportive interventions play an important role in all stages of treatment.

Methadone is a long acting synthetic Opioid that can be dispensed for Opioid dependence only from federally licensed treatment facilities, as part

of an addiction treatment program. Any physician can prescribe it for the management of pain. It can be administered once daily. It has 80% bioavailability with 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 κ Opioid receptors. It has a long half-life of 24 to 60 hours. Management of Opioid withdrawal symptoms requires $\leq 50\%$ μ -Opioid receptor availability with Buprenorphine trough plasma concentrations ≥ 1 ng/mL which can be achieved by dose of 4mg . However, management of reinforcing and euphoric effects of Opioids in OUD requires $< 20\%$ μ -Opioid receptor availability with Buprenorphine trough plasma concentrations ≥ 3 ng/mL, thus requiring higher dose²¹. 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. Buprenorphine has an added advantage of not prolonging QT interval unlike Methadone. 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 Benzodiazepines²².



OPIOID SAFETY AND RISK ASSESSMENT

Assessment of OUD (misuse, abuse and addiction) in the primary care setting can be a challenge, including difficulty in determining the frequency, 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. American Pain and Addiction Societies identified four criteria for addiction: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Prediction of future abuse of Opioids is often considered difficult despite the availability of several tools to assess the risk and severity of addiction. Diagnostic tools such as Addiction Severity Index and Structured Clinical Interview for DSM 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 opioid abuse. Several risk assessment tools have been developed to overcome such challenges, and are currently in clinical practice, but none have been validated in a variety of 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 include:

1. Past and current substance abuse
2. Psychiatric assessment
3. Aberrant drug related behaviors (Please see table below)

4. Opioid assessment screening tools
5. Risk factor stratification.

Aberrant behaviors indicating abuse of opioids prescribed for chronic pain (table)

Forged prescription	Solicited opioids from other providers
Sold prescription	Used non-prescribed opioids > once
Abused prescribed drug	Seeking euphoria from opioids
Canceled clinic visit	Wanting opioids for anxiety
No show or no follow-up	Abnormal +ve drug screen for 2 or more substances
Requested early refills	Resisted therapy changes/alternative therapy
Unauthorized ER visits	Reported lost or stolen prescriptions
Concurrent abuse of alcohol	Requested refills instead of clinic visit
Injected drug	Was discharged from practice
Overdose and death	Third party required to manage patient's medications
Abnormal urine/blood screen	Unauthorized dose escalation

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 of the tools commonly used in clinical practice are:

Opioid Assessment Screening Tools:

Opioid Risk Tool⁵:

	<i>Mark each box that applies</i>	<i>Female</i>	<i>Male</i>
<i>1. Family History of Substance Abuse</i>			
Alcohol	[]	1	3
Illegal Drugs	[]	2	3
Prescription Drugs	[]	4	4
<i>2. Personal History of Substance Abuse</i>			
Alcohol	[]	3	3
Illegal Drugs	[]	4	4
Prescription Drugs	[]	5	5
<i>3. Age (Mark box if 16 – 45)</i>	[]	1	1
<i>4. History of Preadolescent Sexual Abuse</i>	[]	3	0
<i>5. Psychological Disease</i>			
Attention Deficit Disorder, Schizophrenia	[]	2	2
Obsessive Compulsive Disorder, Bipolar, Depression	[]	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 Analgesia²⁵

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

<u>Diagnosis</u>	<p>1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, nonspecific back pain.</p> <p>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.</p> <p>3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.</p>
<u>Intractability</u>	<p>1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process.</p> <p>2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness).</p> <p>3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.</p>
<u>Risk</u>	(R = Total of P + C + R + S below)
<u>Psychological:</u>	<p>1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues.</p> <p>2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder.</p> <p>3 = Good communication with clinic. No significant personality dysfunction or mental illness.</p>

<u>C</u> hemical Health:	<p>1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse.</p> <p>2 = Chemical coper (uses medications to cope with stress) or history of CD in remission.</p> <p>3 = No CD history. Not drug-focused or chemically reliant.</p>
<u>R</u> eliability:	<p>1 = History of numerous problems: medication misuse, missed appointments, rarely follows through.</p> <p>2 = Occasional difficulties with compliance, but generally reliable.</p> <p>3 = Highly reliable patient with meds, appointments & treatment.</p>
<u>S</u> ocial Support:	<p>1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles.</p> <p>2 = Reduction in some relationships and life roles.</p> <p>3 = Supportive family/close relationships. Involved in work or school and no social isolation.</p>
<u>E</u> fficacy score	<p>1 = Poor function or minimal pain relief despite moderate to high doses.</p> <p>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).</p> <p>3 = Good improvement in pain and function and quality of life with stable doses over time.</p>

___ 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

Source: Miles Belgrade, Fairview Pain & Palliative Care Center © 2005.

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 a patient on long-term opioid therapy might require²⁴. It is a quick and easy-to-use questionnaire designed to help providers evaluate the patients' 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 patients 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?					

*<https://nhms.org/sites/default/files/Pdfs/SOAPP-14.pdf>: For full scale of SOAPP-R Version 1.0”

Risk factor Stratification: The purpose of stratification is to determine the intensity of monitoring required, and not to deny pain treatment to high-risk patients. White et al identified several risk factors such as 18 to 24 years of age, male, 12 or more opioid prescriptions, use of 3 or more pharmacies, early prescription refills, escalating dosage, hospital visits and psychiatric outpatient visits, and diagnosis of non-opioid substance abuse, depression, PTSD and hepatitis⁷.

Monitoring for Opioid abuse:

All patients on chronic opioid therapy need to be monitored regularly, the intensity of which depends 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
3. Prescription monitoring program data
4. Opioid treatment agreement
5. Universal precautions

Urine drug testing (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 compliance
2. Identifies possible drug misuse and abuse
3. Noninvasive
4. Cost effective
5. Detects most drugs for 1 to 3 days after exposure, including illicit drugs
6. Improves patient 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, substance use disorders, psychiatric co-morbidity, pseudoaddiction or drug diversion. A confirmatory testing may sometimes be necessary to determine the accuracy of the result. It is important to discuss any unexpected results with the patient, 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 patient is nonadherent to the treatment plan. Open communication with the patient, seeking their interpretation of the results, and review of previously agreed-upon goals of treatment are often beneficial.

Detection times of common drugs of misuse and False positive UDT		
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	

Drug testing traps:

<i>UDT: Screening and Confirmation cut-off concentrations and detection times for Opioids¹⁴</i>				
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 monitoring programs collect statewide data about prescription drug refill pattern with names of prescribing physicians, dispensing pharmacies and name of the controlled substances prescribed including quantity and dates when issued and filled.

Opioid treatment agreement informs patients about the risks and benefits of opioid therapy, and facilitates a mutual agreement of the course and consequences of aberrant behavior.

*Universal precautions*⁷: The concept of ‘universal precautions’ in pain medicine is derived from “Infection Prevention” approach by Gourlay et al to apply appropriate minimum level of precautions to all chronic pain patients to reduce stigma, minimize the overall risk and improve patient care, similar to the approach to potentially life threatening infections such as HIV. 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 post-trial 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

Gourlay. et al also proposed a triage system to categorize the risk as follows to determine the level of care the patient needs.

	Risk factors	Risk Level	Recommended care setting
Group 1	No personal or family Hx. of substance use disorder (SUD) or psychopathology	Chronic non-cancer 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 Benzodiazepines 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, in addition to 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 pose additional risk related to cumulative effect. Tapering and eventually stopping benzodiazepines is recommended prior to tapering of Opioids.



OPIOID EDUCATION AND NALOXONE DISTRIBUTION PROGRAM

Prescription Opioids are one of the most common drugs associated with drug overdose, with an overall trend of alarming increase in Opioid prescriptions, misuse and overdose deaths. Several Numerous 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 165,000 persons died of Opioid overdose from 1999 to 2014, in United States. Center for Disease Control and Prevention (CDC) has recently published “Guidelines for Prescribing Opioids for Chronic Pain-United States, 2016”, intended for primary care physicians. Nearly half of all dispensed Opioids are given in primary care settings¹³. Available published estimates of the risk of opioid-related overdose deaths in U.S. Veterans suggest increased risk with Morphine equivalent dose (MED) of ≥ 100 mg and with psychiatric co-morbidities including PTSD, chronic non cancer pain, acute pain and SUD.

Several Opioid Education and Naloxone Distribution (OEND) programs have been initiated to offer Naloxone as a harm reduction strategy, and ensure that the individuals at-risk for opioid overdose are educated about overdose and Naloxone administration. OEND programs have several additional benefits including engagement of patients, 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. Naloxone was successful in 98% of opioid overdose rescue attempts made in a community public health OEND program in Massachusetts²⁰.

Naloxone does not have any pharmacological effect in patients not taking Opioids. It is not associated with tolerance or dependence. Naloxone 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 patients 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.

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

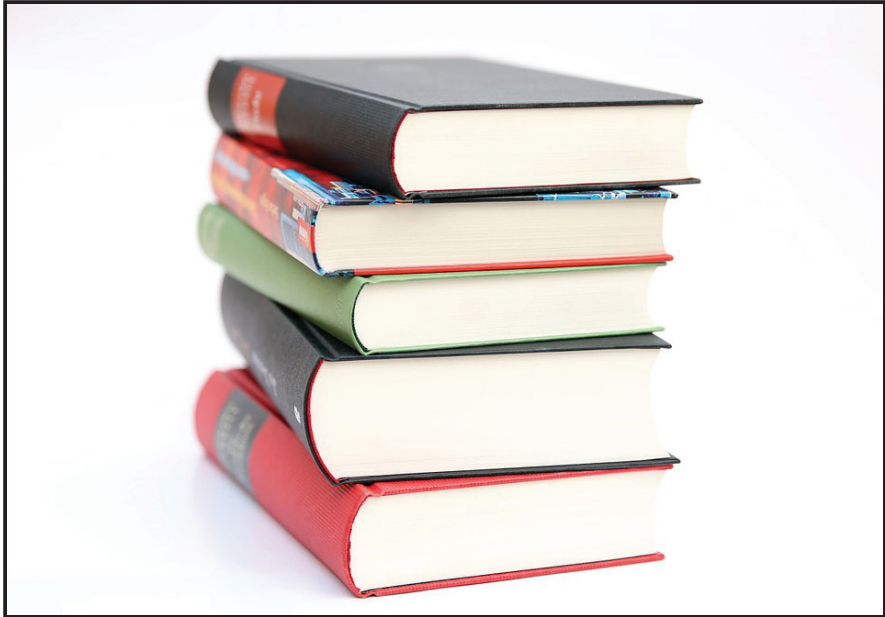
OEND candidates are classified as follows, based on the evidence for effectiveness of the OEND program and the risk factors for Opioid related overdose¹⁹:

<i>Direct Association with Benefit</i>	<i>Indirect Association with Potential Benefit</i>	<i>Clinical Judgment of Potential Benefit</i>
<p>Heroin or other IV drug use Substance use</p> <p>High likelihood of opioid overdose or witnessing an overdose</p>	<p><i>Patient risk factors:</i> SUD, PTSD, other MH diagnosis Heroin or nonmedical opioid use Male, 30-59 years of age COPD, asthma, emphysema, sleep apnea or other respiratory disease</p>	<p><i>Patient risk factors:</i> Past suicide attempt, High risk suicide list Cardiac illness, unstable renal, HIV/AIDS or hepatic disease ≥ 65 years of age, cognitive deficits, debilitated Voluntary caregiver request</p>
	<p><i>Prescription risk factors:</i> High opioid dose ≥ 50 to 100 mg Long acting Opioid Methadone initiation in Opioid naive patients Combined use with benzodiazepines</p>	<p><i>Prescription risk factors:</i> Homebased: Continuous or patient controlled intraspinal infusion Opioid induction, titration or rotation to methadone</p>
	<p><i>Situational risk:</i> Loss of opioid tolerance Poor access to emergency care Voluntary patient request</p>	<p><i>Situational risk:</i> Reluctance to call 911 Opioid related aberrant behavior</p>
<p><i>Settings:</i> Medication assisted programs Inpatient Detoxification HIV education/prevention Syringe access program SUD treatment programs Community SUD programs Emergency departments Homeless shelters</p>	<p><i>Settings:</i> Pain management clinics Affordable housing for homeless, or people with mental illness or AIDS</p>	

OEND training focuses on teaching patients 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 into 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 and the following:

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/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/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](#)*

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