VA | U.S. Department of Veterans Affairs

Pain Management
Opioid Safety
VA Educational Guide (2014)

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

Pain Management
Opioid Safety

VA Educational Guide (2014)

VA | U.S. Department of Veterans Affairs

VA Academic Detailing Service
Real Provider Resources
Real Patient Results

Your Partner in Enhancing Veteran Health Outcomes

VA Academic Detailing Service Email Group:

PharmacyAcademicDetailingProgram@va.gov

VA Academic Detailing Service SharePoint Site:

https://vaww.portal2.va.gov/sites/ad

Chronic Pain Management: Reducing Harm While Helping the Hurting Veteran

An Educational Aid to Improve Care and Safety with Opioid Therapy

According to the Centers for Disease Control and Prevention (CDC), unintentional overdose deaths parallel per capita sales of opioid analgesics and are now the leading cause of injury deaths among 25–65 year olds in the United States (U.S.).[1,2]
This is of particular concern in our Veteran population where there is a high incidence of posttramatic stress disorder (PTSD), major depressive disorder (MDD), alcohol use and suicide attempts. All of these disorders are associated with high dose opioid utilization leading to an increased risk of overdose compared to the general population.[3,4]

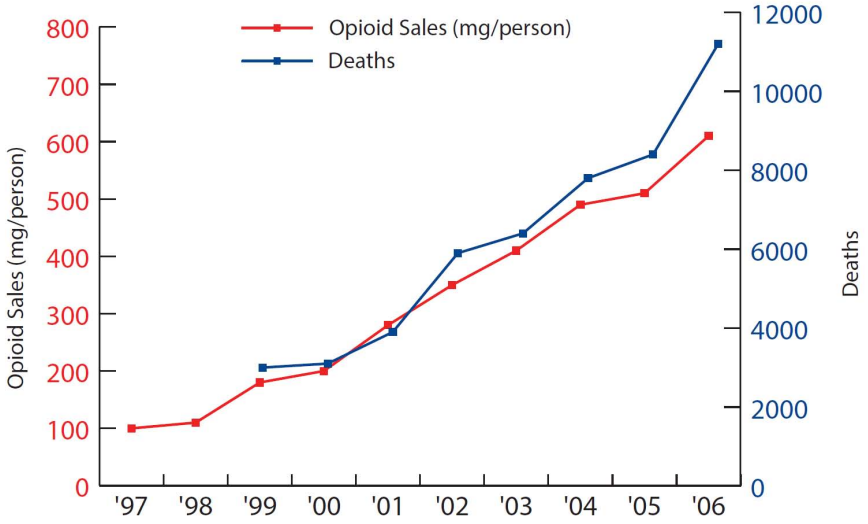
Concerns with Increasing Opioid Use

- ➔ Drug overdose death rates have increased 102% from 1999 to 2010[2]
- ➔ In 2010, 78% of the drug overdose deaths in the United States were unintentional and 60% were related to prescription medications[2]
- ➔ In 2011, more than 1.4 million Emergency Department visits were related to pharmaceuticals[2]

Opioid medications are associated with dependence, tolerance, abuse, and risk of accidental overdose. Other methods of managing pain should be utilized prior to considering opioid therapy and continued if patients progress to opioid therapy.

More than one hundred people die from drug overdoses every day in the United States. Most deaths are caused by prescription medications.

Unintentional Overdose Deaths in the U.S.[1, 2]



Unintentional overdose deaths parallel per capita sales of opioids in morphine equivalents by year.

Veterans are twice as likely to die from accidental overdose compared to the non-Veteran population.[4] Assessment of risk factors is important in our Veteran population especially in returning combat Veterans. Often they present to primary care seeking relief from both physical and psychological pain.[5] **Psychological distress may lead to inappropriate use of opioid medications in patients with mental health disorders. Caution should be used in this high risk population.**

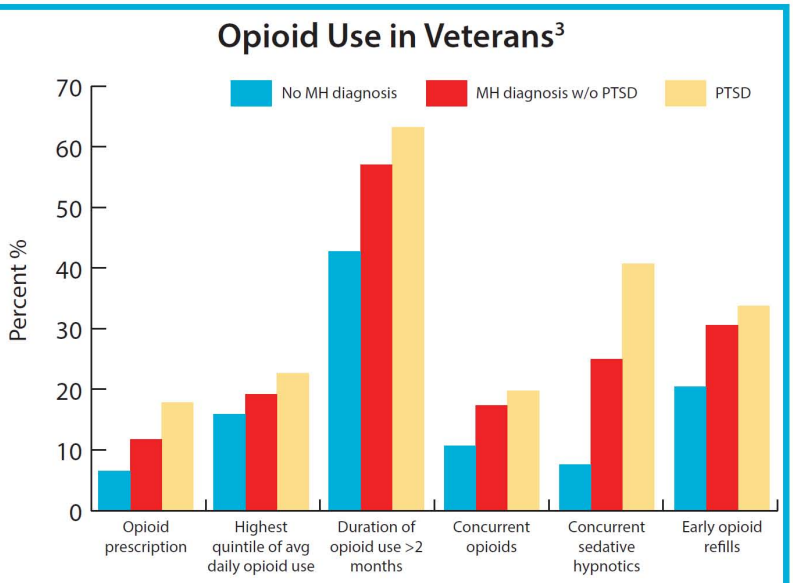
Veterans with Posttramatic Stress Disorder are more likely to:[3]

- ➔ Be prescribed opioids at higher doses
- ➔ Receive opioids and sedative hypnotics (including benzodiazepines) concurrently
- ➔ Combinations lead to increased risk of unintentional overdose

Opioid use in mental health populations is associated with:[3]

- ➔ Opioid-related, alcohol, and non-opioid drug related accidents and overdoses
- ➔ Self-inflicted injuries and violence related injuries
- ➔ Higher incidence of wounds or injuries

Iraq and Afghanistan Veterans who received a new non-cancer pain diagnosis within 1 year of VA entry followed x 1 yr to evaluate whether an opioid was prescribed for ≥20 consecutive days. Patients with mental health (MH) disorders were significantly more likely to receive opioids than Veterans without a MH diagnosis (17.8% for Posttramatic Stress Disorder (PTSD) vs 6.5% for no MH diagnosis, adjusted RR, 2.58; 95% CI 2.49–2.67 and 11.7% for non-PTSD MH disorder, adjusted RR, 1.74; 95% CI 1.67–1.82). Veterans with PTSD were significantly more likely to be in the highest quintile for dose (22.7% vs 15.9%, adjusted RR 1.42, 95% CI 1.31–1.54), receive more than 1 type of opioid concurrently (19.8% vs 10.7%, adjusted RR 1.87, 95% CI 1.70–2.06), receive concurrent sedative hypnotics (40.7% vs 7.6%, adjusted RR 5.46, 95% CI 4.91- 6.07), and obtain early opioid refills (33.8% vs 20.4%, adjusted RR 1.64, 95% CI 1.53–1.75) than Veterans without a MH diagnoses.



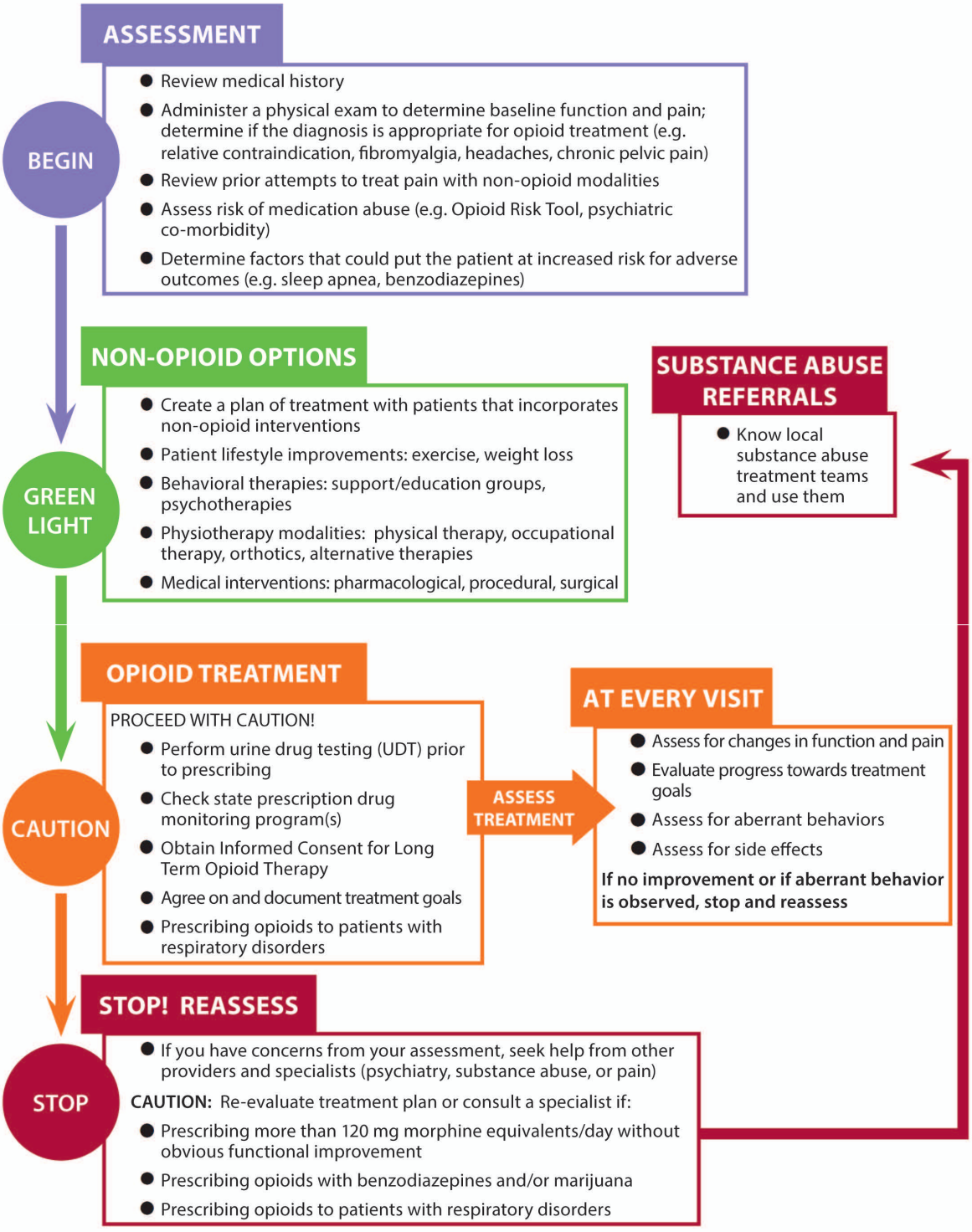
It is important to manage pain safely and effectively

- ➔ Chronic pain is the most common cause of work disability[6]
- ➔ More than 50% of male VA patients in primary care report chronic pain; the prevalence may be even higher in female Veterans[6]

However…

- ➔ Chronic opioid use may not always improve function and quality of life[7-10]
- ➔ The judicious use of opioids should be considered as only one part of the treatment plan

Chronic Pain Treatment Strategies[6,11,12]



Adapted from: Southern Oregon Opioid Prescribing Guidelines[12]

Setting Expectations for Pain Management

It is important to inform the patient that the goal is to assist them in returning to a satisfying, productive life. However, complete pain relief may not be a realistic goal.

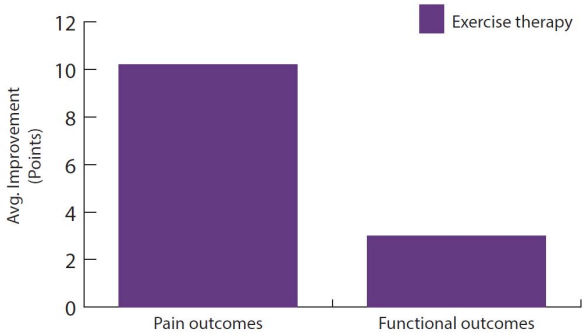
Set Realistic Patient Expectations[6]			
Goal	**Pain Reduction**	**Improve Function**	**Minimize Side Effects**
• Education	• Total pain relief is rare • Goal is to take the "edge off" and reduce the pain by 20–30% • Expect a 2–3 point reduction on a 10 point pain scale	• Ultimate goal to improve quality of life (QOL) • Degree of pain that interferes with QOL is highly personal • Measure improvement with a QOL scale	• Educate on potential side effects and risks associated with chosen treatment(s)

Providing patient education is as important as the appropriate selection of treatment modalities. Inform your patients of potential pain management issues to increase the likelihood of adherence to treatment plans and self-care.

Nonpharmacological Treatment Strategies[11]

- ➔ **Psychosocial interventions**
  - ❖ Cognitive-Behavioral Therapy (CBT)
  - ❖ Pain school
  - ❖ Behavioral groups
  - ❖ Support groups
- ➔ **Educational interventions** to improve self-management
- ➔ **Family interventions**, community support
- ➔ **Rehabilitation therapies** including physical therapy and occupational therapy
- ➔ **Exercise**
- ➔ **Specialty procedures** (e.g. injections, nerve blocks, ablations, neuromodulation)
- ➔ **Complementary and alternative therapies** as available (e.g. acupuncture, massage, tai chi)

Excercise Therapy vs. No Treatment[13]



Meta-analysis of pain outcomes at the earliest follow-up included 23 exercise groups with an independent comparison and adequate data. Pooled weighted mean improvement of 10.2 points (scale of 100) for exercise therapy vs. no treatment. At the earliest follow-up, an observed mean positive effect of 3.00 points was seen with exercise therapy vs. no treatment for functional outcomes.

Nonpharmacological treatment strategies are effective and should be an integral part of treatment for Veterans with pain.

Pharmacological Treatment Strategies

Acetaminophen

- ➔ Recommended as first-line therapy for the treatment of osteoarthritis and chronic lower back pain[14,15]
- ➔ Moderately more effective than placebo for pain relief and safe at recommended doses[16]
- ➔ Caution patients about acetaminophen in over-the-counter and combination products

Acetaminophen[17,18]		
Usual Adult Dosing	**Maximum Dose**	**Comments**
650–1000 mg po every 4–6 hours as needed (see dosing limits)	**3 gm/day in healthy patients** **2 gm/day in hepatic impairment**	**No platelet (<2 gm/day) or anti-inflammatory effect. Adjust dose in alcoholic or hepatic disease. Not associated with GI ulcers (<2 gm/day).**

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Available evidence suggests that all NSAIDs have anti-inflammatory, analgesic and antipyretic effects and have similar efficacy to one another.[17-20] However, individual patients may report that a particular product works better for them than others in the same class.

- ➔ Strategies for preventing gastrointestinal (GI) toxicity:
  - ❖ Add a proton pump inhibitor, high dose H2 blocker (e.g. ranitidine >300mg/day) or misoprostol for patients at an increased risk of GI toxicity[21,22]
  - ❖ PPIs reduce upper GI bleeding to a greater degree than do H2 blockers[21,22]

GI Toxicity Risk Factors:[22]

- ➔ Age >65
- ➔ History of GI bleed or peptic ulcer
- ➔ Use of steroids, anticoagulants, or other NSAIDs including aspirin
- ➔ Helicobacter pylori infection

The risk of GI bleeding increases as the number of risk factors increase.

- Minimizing cardiac risk
  - NSAIDs are associated with cardiovascular side effects such as hypertension, stroke and myocardial infarction[17]
  - Current evidence indicates that selective COX-2 inhibitors may have a greater risk; populations to avoid use includes patients with a history of cardiovascular disease or high baseline cardiovascular risk[20]
  - Naproxen may have the lowest risk of cardiac side effects[20]

Other Medications Used to Treat Pain

- Anticonvulsants
- Antidepressants
  - Tricyclic antidepressants (TCAs)
  - Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Topical analgesics

Systematic Review of Effectiveness in Diabetic Neuropathy[23-29]		
	Agent (# high quality trials)	**% Pain reduction, compared to placebo**
Antidepressants (TCAs)	**Amitriptyline (3)**	**58–63%**
	Desipramine (2)	**31–32%**
	Nortriptyline (1)	**46%**
Antidepressants (SNRIs)	**Venlafaxine (2)**	**23%**
	Duloxetine (3)	**8–13%**
Antiepileptics	**Gabapentin (2)**	**11%**
	***Pregabalin (4)**	**11–13%**
Topicals	**Capsaicin (2)**	**13–40%**
	Lidocaine patch (2)	**20–30%**

* Currently not on VA National Formulary but are available through the nonformulary request process; imipramine, carbamazepine and phenytoin are additional options with evidence for use.

Non-opioid analgesics are recommended 1st line for chronic pain. If the Veteran fails non-drug and non-opioid treatment interventions, a trial of opioid therapy may be added if potential benefits outweigh risks.

Opioid Universal Precautions: Reducing the Risk of Opioid Medications

- ➔ **Reserve opioids** for patients with severe pain when all of the following criteria are met:
  - ❖ Inadequate response to non-opioid measures (e.g. a team based multimodal approach, non-opioid analgesics, physical therapy)
  - ❖ Potential benefits are likely to outweigh risks
  - ❖ Clear and measurable treatment goals are established
  - ❖ Patient agrees to participate in a comprehensive pain care plan
- ➔ **Assess** for factors that could put the patient at increased risk of adverse outcomes
  - ❖ Medical conditions in which opioid therapy can exacerbate symptoms (sleep apnea, chronic obstructive pulmonary disease, congestive heart failure, elderly, or history of renal or hepatic dysfunction)
  - ❖ Benzodiazepines or other sedative hypnotic medications

Contraindications to Initiation of an Opioid Therapy Trial for Chronic Pain[6]	
1. **Severe respiratory instability**	5. **Co-administration of drugs capable of inducing life-limiting drug-drug interactions**
2. **Acute psychiatric instability or uncontrolled suicide risk**	6. **QTc interval >500 milliseconds (for methadone)**
3. **Diagnosed non-nicotine substance use disorder not in remission and not in treatment**	7. **Prior adequate trials of specific opioids that were discontinued due to intolerance, serious adverse effects that cannot be treated, or lack of efficacy**
4. **True allergy to opioids**	8. **Active diversion of controlled substances**

- ➔ **Screen for risk factors** of addiction and misuse and obtain a baseline urine drug test (UDT)
  - ❖ Screening tools like the Opioid Risk Tool (ORT) or the Screener and Opioid Assessment for Patient with Pain-Revised (SOAPP-R), may be useful for predicting risk of future aberrant drug-related behaviors
  - ❖ Before initiating therapy, obtain data from your state prescription drug monitoring program (PDMP)

Regardless of the use of screening tools, patients may be classed into three different categories of risk stratification.

Level of risk and appropriate treatment settings for opioid management[6,30]

Risk of Misuse	Condition/Situation	Treatment Setting for Opioid Therapy (OT)
Low (no moderate to high risk characteristics) **(ORT = 0–3; SOAPP-R ≤17)**	• Diagnosis with concordant physical exam, medical imaging, laboratory findings • High levels of pain acceptance and active coping strategies • Well motivated patient willing to participate in multimodal treatment plan • Attempting to function at normal levels and making progress towards treatment goals • UDT and PDMP are appropriate • No aberrant drug related behaviors (ADRB) (e.g. lost prescriptions, multiple requests for early refills, unauthorized dose escalation, apparent intoxication, frequent accidents etc.)	• Provide OT in primary care setting in conjunction with multimodal treatment plan • PDMP and UDT yearly or more often as indicated • Follow up interval should be no longer than 2–4 weeks after opioid dosage modification and no longer than 6 months for patients on stable opioid doses
Moderate (high risk characteristics absent) **(ORT = 4–7)**	• Diagnosis with concordant physical exam, medical imaging, laboratory findings and pain in >3 regions of body • Moderate co-morbid psychological and medical problems well-controlled by active treatment • Risk factors for medication misuse/ abuse (e.g. history of substance use) • Any positive UDT or PDMP with no repeat behavior • Moderate levels of pain acceptance and coping strategies	• Provide OT in primary care setting with escalated monitoring and caution • Perform updated risk/benefit assessment • Increase frequency of follow up and monitoring to determine stability or if there is a pattern of ADRB • Consider consultation with addiction or behavioral health specialist • PDMP and UDT every 6 months or more often as indicated
High **(ORT ≥8; SOAPP-R >17)**	• Widespread pain without objective signs and symptoms • Unstable or untreated substance abuse or psychiatric disorder or high suicide or homicide risk • History of or current troublesome aberrant drug related behaviors • Unwilling to participate in multimodal therapy and not functioning close to a normal lifestyle • Pattern of repeat positive PDMP or UDT (or failure to submit)	• For one or more high risk situations/conditions, OT not appropriate until further evaluation and treatment of high risk finding can occur; consider tapering OT • For high risk ORT/SOAPP-R, consider an advanced structured pain clinic • Consider non-opioid treatment strategies • Co-manage with SUD or behavioral health specialist

Evaluate Patients for Suicidality[6]

- ❖ Patients with chronic pain have an increased risk of suicide
  - o **Assess** patient for risk factors including mental health diagnoses, past suicide attempts, intentional self-harm, traumatic brain injury, and psychosocial factors (e.g. recent job loss, legal charges etc.)
  - o **Ask** about suicidal ideation, intent, plan, and past attempts
  - o **Refer** as needed for treatment of depression and other mental health disorders, and provide patients with supportive psychological therapy and safe drug treatment

When starting an opioid medication in a patient with a pain syndrome:[6]

1. **Discuss the patient information guide "Taking Opioids Responsibly"** which includes the risks, side effects and potential benefits of opioid therapy and support this with the opioid pain care agreement **"Consent for Long-Term Opioid Therapy for Pain"**
   - o VHA opioid prescribers must complete the patient education and informed consent process (VHA Directive 1005). This requirement does not apply to patients receiving short-term opioids, patients enrolled in hospice, or patients receiving long-term opioids for cancer pain.

Serious Risks of Opioid Therapy[6]	
• Respiratory suppression • Addiction/dependence • Death	• Fatal drug interactions

Potential Adverse Effects of Opioid Therapy[6]	
Common Adverse Effects	**Pointers for Management**
• Confusion • Constipation • Dizziness • Dry mouth • Dyspepsia • Endocrine dysfunction • Headache • Hyperalgesia • Nausea and vomiting • Pruritus • Sexual dysfunction • Sedation • Sweating • Tiredness • Tolerance	• Many side effects spontaneously resolve with development of tolerance • Anticipate and consider preventive treatment for common side effects • Slowly titrate the opioid dose, modify the dosage regimen, treat symptoms, and rotate the opioid agents to successfully treat most side effects • Consider possible drug-to-drug interactions with other medications that have been prescribed for the patient

Patients Should Be Informed of and Regularly Assessed for Adverse Effects Caused by Opioid Analgesics

2. Obtain a baseline **urine toxicology screen** and emphasize the requirement of urine drug testing.
    - o Inform the patient of the reasons for testing
    - o Expectations of random testing
    - o Consequences of unexpected results

Recommended Frequency of Urine Drug Testing (UDT)[31]	
Risk category	**Recommended UDT frequency**
Low risk	**Periodic (at least 1/year)**
Moderate risk	**Regular (e.g. at least 2/year)**
High risk or opioid doses >120 morphine equivalents/day	**Frequent (e.g. 3–4/year)**
Aberrant behavior	**At time of visit and continuous assessment throughout treatment (address aberrant behaviors in person or with a telephone discussion)**

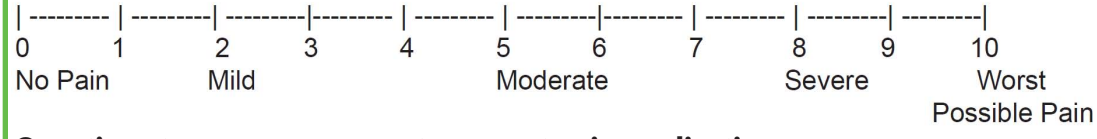
Urine drug testing should be done at least annually for patients on chronic opioid therapy. When used with a proper level of understanding they can improve your ability to safely and appropriately manage opioid therapy.

3. **Inform the patient of the treatment goals**, which must include improvement in both function and pain while monitoring for and minimizing adverse effects.

Measure pain intensity with a Numeric Rating Scale (NRS) and include the following:[6]

- ➔ Current pain ("On a scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is your current pain level?")
- ➔ Most and least pain in the last week
- ➔ "Usual" or "average" pain in the last week

Numeric Rating Scale (NRS)[6,32]



Questions to assess response to current pain medication:

- "What is your intensity of pain after taking your current treatment/medication?"
- "How long does your pain relief last after taking your medication?"

It is important to evaluate pain intensity and patient function at each visit.

Function should be assessed using objective documentation and patient report on a monthly basis during the titration phase and every one to six months after the patient is stable on opioids.[6]

Improving QOL

Quality of Life Scale (QOL)[33]	
Printed by permission of the American Chronic Pain Association, 2013. **http://www.theacpa.org/uploads/documents/Life_Scale_3.pdf** or **www.theacpa.org/uploads/documents/Quality_of_Life_Scale.pdf**	
0	**Stay in bed all day. Feel hopeless and helpless about life.**
1	**Stay in bed at least half of the day. Have no contact with outside world.**
2	**Get out of bed but don't get dressed. Stay home all day.**
3	**Get dressed in the morning. Minimal activities at home. Contact with friends via phone, email.**
4	**Do simple chores around the house. Minimal activities outside the home two days a week.**
5	**Struggle but fulfill daily home responsibilities. No outside activity. Not able to work/volunteer.**
6	**Work/volunteer limited hours. Take part in limited social activities on weekends.**
7	**Work/volunteer for a few hours daily. Can be active at least five hours a day. Can make plans to do simple activities on weekends.**
8	**Work/volunteer for at least six hours daily. Have energy to make plans for one evening of social activity during the week. Active on weekends.**
9	**Work/volunteer/be active eight hours daily. Take part in family life. Outside social activities limited.**
10	**Go to work/volunteer each day. Normal daily activity each day. Have a social life outside of work. Take an active part in family life.**

Assess overall patient satisfaction with pain management by asking about function and pain at each visit.

Objective Documentation of Function	Overall Patient Function
• Physical therapy progress notes • Employment records • Exercise diaries • Family reports • Clinician observations • Numerical rating scales (Pain /Quality of Life Scale)	• Employment • Enjoyment of life • Emotional distress (depression and anxiety) • Housework, chores, hobbies and other day-to-day activities • Sleep • Mobility • Self-care behaviors • Sexual function • Side effects

Discussing Pain Management

Clear non-confrontational communication from the start is important in pain management. Set realistic expectations with the patient and put them in writing (pain agreement).

- ❖ Inform the patient that the goal is to assist them in returning to a productive life
  - o Complete pain relief is not a realistic goal
- ❖ Discuss a long-term plan and the importance of sticking to it
  - o Exacerbation is not a reason to change the plan

Samples of Non-Confrontational Rephrasing	
Avoid "hot phrases"	**Use helpful phrases**
Pain/opioid contract	**Informed consent for long term opioid therapy**
There's nothing wrong with you	**We can't measure pain with tests**
Accept your pain	**Expect pain to be a small part of your life and it won't be a large part**
You'll have to live with the pain	**I want to help you live better with pain**
Nothing can be done	**"No medical solutions" does not mean no solution**
Degenerative	**These are normal changes that occur when we get older**

High-Dose Opioid Analgesics

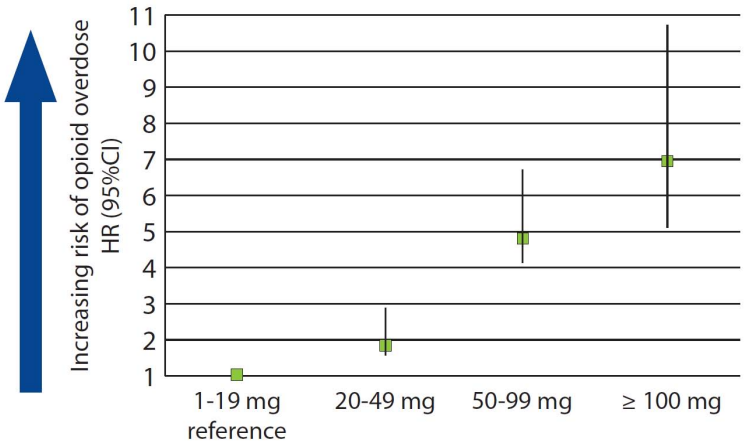
Literature indicates that increased doses of opioid medications are associated with increased risk of mortality.[4,34-38] It is important to use the lowest effective dose to reduce the rate of complications, including accidental overdose and side effects.

Escalating opioid doses does not always result in improved pain and functioning.

High-Dose Opioid Analgesics

- A 9-fold increase in opioid overdoses has been reported in patients receiving high dose opioids (≥100 mg morphine equivalent dose (MED) compared to low dose (<20 mg MED))[35]
- Patients receiving morphine equivalent doses of more than 120 mg/day were more likely to have alcohol or drug-related encounters (alcohol or drug intoxication, withdrawal, or overdose)[38]
- A reduction in the proportion of patients receiving ≥120 mg MED/day resulted in a 50% reduction in opioid related deaths[39]
- Opioid induced hyperalgesia may present as:[40]
  - Treatment effect diminishing in the absence of disease progression
  - Increased levels of pain with increasing dosages
- Studies indicate that patients with severe pain on high-dose opioid analgesics can achieve both reduced pain and improved mood with dose reduction[7,42-45]

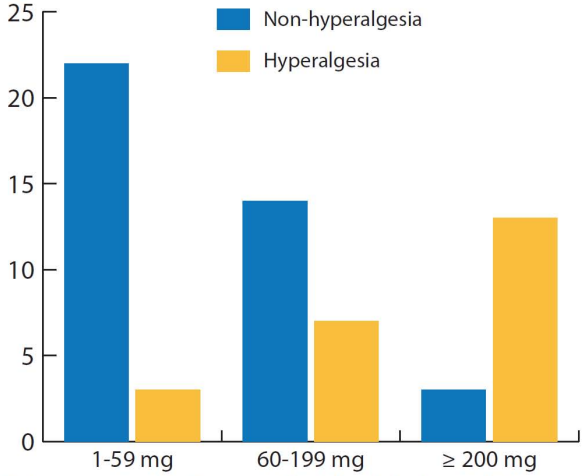
Risk of Death by Prescription Opioid Overdose for Chronic Non-Cancer Pain[67]



Data shows all unintentional prescription opioid overdose deaths (n = 750) in a random national sample of Veterans Health Administration patients (n = 154,684) from 2004–2008. The risk of opioid overdose increased when opioid dose was equivalent to 50 mg/day or more of morphine. Mortality risk related to opioid doses at or above 100 mg day MED, compared with less than 20 mg/day, was increased seven fold.

With overwhelming evidence for the misuse, abuse and risk of overdose along with limited efficacy of chronic opioid therapy, it is important to re-examine high-dose opioids (>120 mg/day MED) and to consider consultation or dose reduction rather than further escalation of the dose.

Clinical Pain Stimulus and Opioid-Induced Hyperalgesia[41]



Eighty-two cancer patients reported pain levels before and after receiving a local anesthetic injection (LAI). LAI specific pain intensity, unpleasantness, and behavior pain score were significantly higher in the opioid group compared to the non-opioid group. In addition patients post-injection scores were higher in the high dose (≥200 MED/day) versus the low dose group ($p < 0.05$).

Ways to Avoid Dose Escalation

Opioid rotation

When Opioids Should Be Switched[49]	
• **Inadequate analgesia** • **Side effects** o Sedation o Somnolence o Delirium o Nausea	• **Drug interactions** • **Hyperalgesia** • **Route of administration** • **Onset of activity**

- ➔ Consider when there is a failure to maintain or improve functional goals
- ➔ Goal is to avoid further dose escalation and minimize potential adverse events
- ➔ Evidence though limited indicates that 50–80% of patients with chronic pain who respond poorly to one opioid maintain or improve pain control after being rotated to another opioid[46-48]
- ➔ Opioid rotation can also be used to switch patients from short-acting opioids to long-acting medications[48]

Single-Step Rotation[6]	Step-Wise Rotation[68]
Commonly used tapering strategy	**May be preferable when rotating from high doses of opioids. More complex than single-step; consider consulting with advanced pain care provider for assistance**
Determine new opioid target dose using equianalgesic conversion protocol*	**Determine new opioid target dose using equianalgesic conversion protocol***
Stop the current opioid-Start new opioid dose: **Timing for the first dose of the new opioid is based on the original's anticipated decline in plasma level and the new opioid's onset of action**	**Reduce the original opioid in several steps with overlapping increase of the new opioid in similar increments** **Example: Reduce the original opioid by 10–30% per week while increasing the new opioid by 10–30% per week; Process is usually completed in 3–4 weeks**
Provide sufficient immediate release opioid during the rotation process in case dosing changes prove insufficient; this minimizes risk of the patient self-medicating, which can be fatal.	

*When converting to a new opioid, the **starting dose should be 50–67% of the calculated 24 hour equianalgesic dose** due to incomplete cross-tolerance.[6]

A notable exception to this general rule is methadone because of its unique pharmacokinetic/pharmacodynamic profile. Methadone has a long and highly variable half-life, with shorter duration of analgesia which contributes to unpredictable accumulation of methadone. This can lead to potentiality life-threatening, and in many cases, fatal respiratory depression, particularly during sleep.[50,51] Inexperienced clinicians should consult with an expert before initiating methadone, even in an opioid-tolerant patient. See pocket cards for suggested equianalgesic doses.

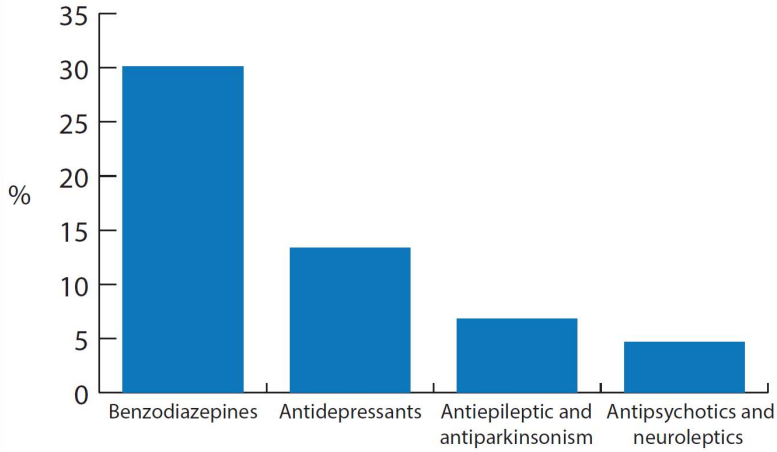
Consider rotating between opioids as it may improve efficacy, reduce side effects, and prevent dose escalation in patients who are receiving long-term opioid therapy.

Lethal Drug Combinations

Other medications when co-administered with opioids may result in potentially fatal outcomes specifically, medications with sedative properties like benzodiazepines.

- In about one-half of the deaths involving opioid analgesics, more than one type of drug was specified as contributing to the death, with benzodiazepines being the most frequent[53]
- Extra precautions need to be taken with methadone:
  - Benzodiazepines increase the risk of sleep apnea when given with methadone[54,55]
  - Benzodiazepines have been associated with an increased risk of death due to methadone toxicity[56]
- Inhibitory GABA receptors are highly concentrated in the medullary respiratory centers thus benzodiazepines can potentiate the effects of opioids on respiration frequency[57,58]
- It has been suggested that benzodiazepines enhance the positive "euphoric" effects of opioids making them commonly abused combination[58]

Concomitant Pharmaceuticals Commonly Involved in Opioid Overdose[52]



CDC recently reported that among overdose deaths involving opioid analgesics, the pharmaceuticals most often involved in these deaths were benzodiazepines, followed by antidepressants, antiepileptic and anti-parkinsonism, and antipsychotics and neuroleptics. The majority of these deaths were unintentional (74.3%) vs. suicide (17.1%) or undetermined intent (8.4%).

Given the risks of co-medication with benzodiazepines and opioid medications, clinicians should avoid this combination.

Opioid Reduction and Discontinuation

Reduction and discontinuing opioids should only be done after a discussion with the patient. Once a plan is created, both written and verbal instructions should be provided to the patient and their family to ensure successful taper and/or discontinuation.[6,59] If a patient is resistant, be prepared for unwanted behaviors from the patient and consider contacting your local patient advocate in advance.

Make the decision to discontinue or refer to a pain specialist

Consider tapering opioids in patients with:[6,60-62]

- **Side effects or medical complications**
- **Stable patients with reduced pain levels**
- **Opioid misuse and addiction**

Consider referring to a pain specialist:

- **Inadequate analgesia**

Stop the opioid immediately and educate patient about potential withdrawal if there are clear signs of unsafe or illegal behaviors

Discuss the alternative options for therapy

When the risks outweigh the benefits of opioid therapy:[6]

- **Discuss non-opioid and non-pharmacologic alternatives for the treatment of pain**
- **Document and offer referral to addiction specialist for patients who demonstrate behaviors that suggest addiction to prescribed opioids or other substances**
- **Discuss pharmacotherapy options for the treatment of opioid and/or alcohol dependence**
- **Refer patients with co-occurring psychiatric disorders to appropriate behavioral health providers**

Opioid reduction and/or discontinuation strategies:[6,31, 28,64-66]

- ➔ As with the decision to taper, the pace of the dosage reduction is related to risk stratification and is variable, the greater the perceived degree of risks the quicker the pace
- ➔ A slower opioid dose reduction is recommended for patients who have been on opioids for long duration and/or high doses and risks are considered manageable
  - ❖ A gradual dosage reduction of 10–25% every 1–4 weeks can be used based on the individual patient's needs and provider preference
  - ❖ The initial dosage reduction may be greater than 25% in selected patients (such as high dosage patients)
- ➔ Higher risk requires a faster discontinuation rate (see pocket cards for details)
- ➔ Stop prescribing opioids when there are clear signs of unsafe or illegal behaviors
- ➔ Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids

Consider Use of Adjuvant Medications During Taper [18, 31,64-66]	
Withdrawal symptoms (not as effective for anxiety, restlessness, insomnia, and muscle aches)	Sample dosing: Clonidine 0.1–0.6 mg oral every 6 hours; hold dose if blood pressure <90/60 mmHg (0.1 mg–0.2 mg QID is commonly used in the outpatient setting)
Anxiety, dysphoria, lacrimation, rhinorrhea	Hydroxyzine 25–50 mg three times a day as needed
Myalgias	NSAIDs or acetaminophen (see pocket cards)
Sleep disturbance	Trazodone (50–100 mg) or gabapentin (300–800 mg) as needed
Nausea	Antiemetics (e.g. prochlorperazine 5–10 mg every 4 hours as needed)
Diarrhea	Bismuth subsalicylate (524 mg every 0.5–1 hr, max: 4192 mg/day); loperamide (4 mg then 2 mg after each loose stool, max 16 mg/day)

Online resources:

National pain management website: **www.va.gov/painmanagement**

VA Clinical Practice Guideline Website: **http://www.healthquality.va.gov/**

These are general recommendations only; specific clinical decisions should be made by the treating physician based on an individual patient's clinical condition.

This summary was written by:

Sarah J. Popish, Pharm.D., BCPP
Daina L. Wells, Pharm.D., BCPS, BCPP
Hope Kimura, Pharm.D.
Monica Yee, Pharm.D.
Melissa L. D. Christopher, Pharm.D.

We thank our expert reviewers:

Michael Craine, Ph.D.
Aram S. Mardian, MD
Jeremiah McKelvey, Pharm.D.
Joseph Pruitt, Pharm.D.
Ilene Robeck, MD
Friedhelm Sandbrink, MD

REFERENCES:

1. Centers for Disease Control and Prevention. Policy Impact: Prescription Painkiller Overdoses. Page last updated: December 19, 2011. Available at: **http://www.cdc.gov/homeandrecreationalsafety/rxbrief/index.html**.
2. Drug Overdose in the United States: Fact Sheet. Page last updated September 9, 2013. Available at: **http://www.cdc.gov/homeandrecreationalsafety/overdose/facts.html**.
3. Seal KH et al. Association of Mental Health Disorders with Prescription Opioids and High-Risk Opioid Use in US Veterans of Iraq and Afghanistan. JAMA 2012; 307:940-7.
4. Bohnert AS, Ilgen MA, Galea S, McCarthy JF, Blow FC. Accedental poisoning mortality among patients in the Department of Veterans Affairs Health System. Med Care 2011;49: 393–396.
5. Hoge CW. Interventions for war-related posttraumatic stress disorder: meeting Veterans where they are. JAMA. 2011;306(5):549-551.
6. Management of Opioid Therapy for Chronic Pain. VA/DoD Clinical Practice Guideline. May 2010. Available at: **http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf**.
7. Gross DP, Stephens B, Bhambhani Y, Haykowsky M, Bostick GP, Rashiq S. Opioid prescriptions in Canadian workers' compensation claimants prescription trends and associations between early prescription and future recovery. Spine 2009; 34:525-531.
8. Becker N, Sjogren P, Bech P, Olsen AK, Eriksen J. Treatment outcome of chronic non-malignant pain patients managed in a Danish multidisciplinary pain centre compared to general practice: A randomised controlled trial. Pain 2000;84:203-211.
9. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333.
10. Sjøgren P, Grønbæk M, Peuckmann V,Ekholm O. A population-based cohort study on chronic pain: The role of opioids. Clin J Pain 2010; 26:763-769.
11. Pain Management. Department of Veterans Affairs Veterans Health Administration Directive 2009-053. October 28, 2009.
12. Southern Oregon Opioid Prescribing Guidelines; A provider and community resource. Available at: **http://www.southernoregonopioidmanagement.org/wp-content/uploads/2014/05/OPG_Guidelines.pdf#=85**. Accessed online October 17, 2013.
13. Hayden JA, et al. Meta-Analysis: Exercise Therapy for Nonspecific Low Back Pain. Ann Intern Med 2005; 142:765-75.
14. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc 2009; 57:1331-46.
15. Barkin RL et al. Management of Chronic Noncancer Pain in Depressed Patients. Postgraduate Medicine 2011; 123:143-54.
16. Towheed TE, Maxwell L, Judd MG et al. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev. 2006(1):CD000396.
17. Munir MA, et al. Nonopioid Analgesics. Med Clin N Am 2007; 91:97–111.
18. Micromedex Drugdex Evaluations. Thomson Micromedex. Greenwood Village, CO. Available at: **http://www.micromedexsolutions.com/micromedex2/librarian**. Accessed March 19, 2012.
19. Roelofs PD et al. Non-steroidal Anti-inflammatory Drugs for Low Back Pain. Cochrane Database Syst Rev. 2008(1):CD000396.

20. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007;115(12):1634-1642.
21. Rostom A, Dube C, Wells G, et al. Prevention of NSAID-induced gastroduodenal ulcers. Cochrane Database Syst Rev, 2002(4)CD002296.
22. Abraham NS. Hlatky MA. Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation 2010; 122.
23. Bril V, England J, Franklin GM, et al. Evidence-based Guideline: Treatment of Painful Diabetic Neuropathy Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM R. Apr;3(4):345-352 e321.
24. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992 May 7;326(19):1250-6.
25. Collins SL, Moore RA, McQuayHJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. J Pain Symptom Manage. 2000 Dec;20(6):449-58.
26. Sindrup SH, Gram LF, Skjold T, et al. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. Br J Clin Pharmacol. 1990 Nov;30(5):683-91.
27. Kvinesdal B, Molin J, Frøland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. JAMA. 1984 Apr 6;251(13):1727-30.
28. Argoff CE. Topical analgesics in the management of acute and chronic pain. Mayo Clin Proc. 2013 Feb;88(2):195-205. doi: 10.1016/j.mayocp.2012.11.015.
29. Gilron I, Bailey JM, Tu D, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial Lancet. 2009 Oct 10;374(9697): 1252-61. doi: 10.1016/S0140-6736(09)61081-3. Epub 2009 Sep 30.
30. Manchikanti L, Salahadin A, Atluri A, et al. American society of interventional pain physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part 2-guidence. Pain Psysician 2012; 15:S67-S116.
31. Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An educational aid to improve care and safety with opioid therapy 2010 Update. Available at: **http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf**. Accessed July 9, 2013.
32. National Pain Management Coordinating Committee, Veterans Health Administration Pain as the 5th vital sign tool kit: **www.va.gov/painmanagement/docs/toolkit.pdf**. Accessed: July 9, 2013.
33. Quality of Life Scale. American Chronic Pain Association, 2013. Available at: **http://www.theacpa.org/uploads/documents/Life_Scale_3.pdf**. Accessed July 9. 2013.
34. Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid overdose related deaths. JAMA 2011; 305:1315-1321.

35. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. Ann Intern Med 2010; 152:85-92.

36. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD. A history of being prescribed controlled substances and risk of drug overdose death. Pain Med 2012; 13:87-95.

37. Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Med 2011; 5:E13-E22. 366.

38. Braden JB, Russo J, Fan MY, Martin BC, DeVries A, Sullivan MD. Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 2010; 170:1425-1432.

39. Franklin GM, Mai T, Turner JA, et al. Bending the Prescription Opioid Dosing and Mortality Curves: Impact of the Washington State Opioid Dosing Guideline 2012. Am. J. Ind. Med. 55:325–331.

40. Lee M Silverman S, Hansen H, Patel V Manchikanti L. A Comprehensive Review of Opioid-Induced Hyperalgesia. Pain Physician 2011; 14:145-161.

41. Kim SH, Yoon DM, Choi KW, Yoon KB. High-dose daily opioid administration and poor functional status intensify local anesthetic injection pain in cancer patients. Pain Physician. 2013;16(3):E247-56.

42. Rome JD, Townsend CO, Bruce BK, Sletten CD, Luedtke CA, Hodgson JE. Chronic noncancer pain rehabilitation with opioid withdrawal: Comparison of treatment outcomes based on opioid use status at admission. Mayo Clinic Proceedings 2004; 79:759-768.

43. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. J Opioid Manag 2006; 2:277-282.

44. Miller NS, Swiney T, Barkin RL. Effects of opioid prescription medication dependence and detoxification on pain perceptions and self-reports. Am J Ther 2006; 13:436-444.

45. Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK. Withdrawal of analgesic medication for chronic low-back pain patients: improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. Am J Phys Med Rehabil 2008; 87:527.

46. Mercadante S, Bruera E. Opioid switching: A systematic and critical review. Cancer Treat Rev 2006;32:304–15.

47. Mercadante S, Ferrera P, Villari P, et al. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009;37:632–41.

48. Thomsen AB, Becker N, Eriksen J. Opioid rotation in chronic non-malignant pain patients. A retrospective study. Acta Anaesthesiol Scand 1999;43(9):918-23.

49. Sirinivas NR. Opioid rotation in clinical practice. Adv Ther 2012;29:849-863.

50. Cousins G, Teljeur C, Motterlini N, et al. Risk of drugrelated mortality during periods of transition in methadone maintenance treatment: A cohort study. J Subst Abuse Treat 2011;41:252-60. 569.

51. Modesto-Lowe V, Brooks D, Petry N. Methadone deaths: Risk factors in pain and addicted populations. J Gen Intern Med 2010;25:305-9.

52. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical Overdose Deaths, United States, 2010, JAMA. 2013;309(7):657-659.

53. Warner M, Chen LH, Maukuc DM. Increase in fatal poisonings involving opioid analgesics in the United States, 1999-2006. NCHS Data Brief. 2009;22(22)1-8.

54. Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. Aust N Z J Public Health. 2002 Aug; 26(4):358-62.

55. Webster LR, Choi Y, Desai H, Webster L, Grant BJ. Sleep-disordered breathing and chronic opioid therapy. Pain Med 2008 May-Jun;9(4):425-32.

56. McCowan C, Kidd B, Fahey T. Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study. BMJ 2009 Jun 16;338:b2225.

57. Skatrud JB, Begle RL, Busch MA. Ventilatory effects of single, high-dose trizolam in awake human subjects. Clin Pharmacol Ther 1988;44:684-689.

58. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opiod and benzodiazepine combination use. Drug and Alcohol Dependence 2012;125:8-18.

59. VA/DOD Opioid Tapering Fact Sheet 23May2013. Available at: **http://www.healthquality.va.gov/guidelines/Pain/cot/OpioidTaperingFactSheet23May2013v1.pdf**. Accessed online 7/8/13.

60. Miller NS, Swiney T, Barkin RL. Effects of opioid prescription medication dependence and detoxification on pain perceptions and self-reports. Am J Ther. 2006 Sep-Oct;13(5):436-44.

61. Kahan M, Mailis-Gagnon A, Wilson L, et. al. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. Can Fam Physician. 2011 Nov; 57(11):1257-66, e407-18.

62. Wang H, Akbar M, Weinsheimer N, et. al. Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. Pain Med. 2011 Dec;12(12):1720-6. doi: 10.1111/j.1526-4637.2011.01276.x. Epub 2011 Nov 14.

63. University of Michigan Health System. Discontinuing Opioids. UMHS Guidelines for Clinical Care May 2009. Available at: **http://www.med.umich.edu/1info/FHP/practiceguides/**. Accessed July 9, 2013.

64. Charney DS, Sternberg DE, Kleber HD, et. al. The clinical use of clonidine in abrupt withdrawal from methadone. Effects on blood pressure and specific signs and symptoms. Arch Gen Psychiatry. 1981 Nov;38(11):1273-7.

65. Mattick RP, Hall W. Are detoxification programmes effective? Lancet. 1996 Jan 13; 347(8994):97-100.

66. Kral L.A. Safely Discontinuing Opioid Analgesics. 66. Kral L.A. Safely Discontinuing Opioid Analgesics. Pain Treatment Topics: March 2006. Available at: **http://www.nhms.org/sites/default/files/Pdfs/Safely_Tapering_Opioids.pdf**. Accessed online July 9. 2013.3.

67. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC. Association between opioid prescribing patterns and opioid over dose related deaths. J AMA 2011; 305:1315-1321.

68. Webster L, Fine P. Overdose deaths demand a new paradigm for opioid rotation. Pain Medicine. 2012;13:571-574

VA Academic Detailing Service

Real Provider Resources
Real Patient Results

U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint.

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

VA Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

VA Academic Detailing Service SharePoint Site:
https://vaww.portal2.va.gov/sites/ad

Created July 2014