AMDG
AGENCY MEDICAL DIRECTORS' GROUP

Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain:

an educational pilot to improve care and safety with opioid treatment

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Introduction

This guideline is part of a year-long educational pilot to improve care and safety when treating chronic non-cancer pain with opioids. Sponsored by the Agency Medical Directors' Group (AMDG), the guideline was developed by the Interagency Workgroup on Practice Guidelines[1] in collaboration with actively practicing physicians who specialize in pain management. It is intended as a resource for primary care providers treating patients who receive health care through state agency programs. It does not apply to the treatment of acute pain, cancer pain, or end-of-life (hospice) care.

Providers prescribing opioids should be aware of the delicate balance between the undertreatment and overtreatment of chronic non-cancer pain. Because high dose opioid treatment can be ineffective and/or unsafe, providers must pay ongoing attention to adverse outcomes of chronic opioid use (Ballantyne 2003).

Recent studies indicate an increase in accidental deaths associated with the use of prescription opioids since 1999 (CDC 2005, Franklin 2005, Paulozzi 2006). At the same time, there has been a dramatic increase in the average daily morphine equivalent dose (MED) of the most potent (Schedule II) long-acting opioids (Franklin 2005). In Washington State, the overall number of opioid-related deaths more than doubled between 1995 and 2004, and prescription opioid-related deaths now exceed non-prescription opioid-related deaths. (Sabel 2006).

The purpose of Part I of the dosing guideline is to assist the primary care provider who does not specialize in pain medicine in prescribing opioids for adults in a safe and effective manner when:

- Instituting or transitioning opioid treatment from acute to chronic non-cancer pain;
- Assessing and monitoring opioid treatment for chronic non-cancer pain; and
- Weaning opioids if an opioid trial fails to yield improvements in function as well as pain.

The purpose of Part II of the guideline is to assist primary care providers in treating patients whose morphine equivalent dose (MED) already exceeds 120 mg per day.

[1] Washington State Department of Corrections; Health; Labor and Industries; Social and Health Services; and Health Care Authority

I. Guidelines for initiating, transitioning, and maintaining oral opioids for chronic non-cancer pain

Part I of the dosing guideline will assist the primary care provider who does not specialize in pain medicine in prescribing opioids for adults in a safe and effective manner when:

- Instituting or transitioning opioid treatment from acute to chronic non-cancer pain;
- Assessing and monitoring opioid treatment for chronic non-cancer pain; and
- Weaning opioids if an opioid trial fails to yield improvements in function and pain.

Dosing threshold for pain consultation

In order to improve the quality of care in the state of Washington, the state agencies, in collaboration with the physician panel, reviewed the available evidence and made the following recommendations:

- In general, the total daily dose of opioid should not exceed 120 mg of oral morphine equivalents.
- Rarely, and only after pain management consultation, should the total daily dose of opioid be increased above 120 mg oral morphine equivalents.
- Safety and effectiveness of opioid therapy for chronic non-cancer pain should be routinely evaluated by the prescriber.
- Assessing the effectiveness of opioid treatment should entail tracking and documenting both functional improvement and pain relief.
- A specialty consultation may be considered at any time if there is evidence of frequent adverse effects or lack of response to an opioid trial.

Table 1. Summary of Recommendations

Prescribing opioid doses up to 120mg/day MED: (Cumulative daily dose when using one or more opioids. See Table 2 for specific opioid thresholds.)	Before exceeding 120mg/day MED dose threshold: (Cumulative daily dose when using one or more opioids. See Table 2 for specific opioid thresholds.)
• No pain management consultation needed if the prescriber is documenting sustained improvement in both function and pain. • Consider specialty consultation[2] if frequent adverse effects or lack of response is evident in order to address: o Evidence of undiagnosed conditions; o Presence of significant psychological condition affecting treatment; and o Potential alternative treatments to reduce or discontinue use of opioids.	• Seek pain management consultation[3] to address: o Potential alternative treatments to opioids; o Risk and benefit of a possible trial with opioid dose above 120mg/day MED; o Assistance with ongoing documentation of improvement in function and pain; and o Schedule for follow up with pain management specialist, if necessary.

[2] For information on specialty consultations, see page 6.
[3] For information on pain management consultations, see page 7.

Morphine equivalent dose calculation

For patients taking more than one opioid, the morphine equivalent doses of the different opioids must be added together to determine the cumulative dose (see Table 3 on page 11 for MEDs of selected medications). For example, if a patient takes six hydrocodone 5mg / acetaminophen 500mg and two 20mg oxycodone extended release tablets per day, the cumulative dose may be calculated as follows:

1) Hydrocodone 5mg x 6 tablets per day = 30mg per day.
2) Using the Equianalgesic Dose table on page 11 of this guideline, 30mg Hydrocodone = 30mg morphine equivalents.
3) Oxycodone 20mg x 2 tablets per day = 40mg per day.
4) Per Equianalgesic Dose table, 20mg oxycodone = 30mg morphine so 40mg oxycodone = 60mg morphine equivalents.
5) Cumulative dose is 30mg + 60mg = 90mg morphine equivalents per day.

An electronic opioid dose calculator can be downloaded at www.agencymeddirectors.wa.gov/opioiddosing.asp

When to consider prescribing opioids

- Other conservative measures have failed (e.g. NSAIDs, tricyclic antidepressants, antiepileptics and non-pharmacologic therapies) and opioids have not been tried.
- Patient has demonstrated sustained improvement in function and pain level in previous opioid trial.
- Patient has no relative contraindication to the use of opioids (e.g. active alcohol or other substance abuse).

Principles for prescribing opioids

- Single prescriber
- Single pharmacy
- Patient and prescriber sign opioid agreement
- Lowest possible effective dose should be used
- Be cautious when using opioids with conditions that may potentiate opioid adverse effects (including COPD, CHF, sleep apnea, history of alcohol or substance abuse, elderly, or history of renal or hepatic dysfunction).
- Do not combine opioids with sedative-hypnotics, benzodiazepines or barbiturates for chronic non-cancer pain unless there is a specific medical indication for the combination.
- Assess function and pain status routinely (see *Tools for assessing function and pain*, page 5).
- Monitor for medication misuse (for a list of drug-seeking behaviors, see *Reasons to discontinue opioids or refer for addiction management*, page 10).
- Random urine drug toxicology screening to objectively assure compliance (see *Urine drug toxicology screening*, page 6).

Instituting opioid treatment for chronic non-cancer pain

Prior to initiating chronic opioid therapy, the prescriber should comprehensively assess the risks and benefits of treatment. The prescriber is responsible for routinely monitoring the safety and effectiveness of opioid therapy in providing pain relief and improving function.

When instituting opioid therapy, both provider and patient should discuss and agree on:

- Risks and benefits of opioid therapy supported by an opioid agreement;
- Treatment goals and provider's established criteria to evaluate the effectiveness of opioid therapy; and
- A follow-up plan with specific time intervals to monitor treatment.

Treatment goals must include improvements in both function and pain while monitoring for and minimizing adverse effects (see *Principles for prescribing opioids*, page 4).

Depression and anxiety disorders are frequently associated with the use of opioids (Sullivan 2005). Extreme caution should be used, and a specialty consultation is strongly encouraged, prior to prescribing opioids when patients have a history of significant psychological conditions such as conversion disorder, somatization, borderline personality, mood disorder, PTSD, or history of alcohol or other substance abuse.

Transitioning opioid treatment from acute pain to chronic non-cancer pain

- **Acute pain** is self-limiting and lasts from a few days to a few weeks following trauma or surgery.
- **Chronic pain** persists beyond the anticipated healing period for the specific disease condition.

The level of pain during an acute phase does not necessarily and accurately predict the pain level in a chronic phase. Thus, opioid dosing for chronic treatment should be assessed and adjusted accordingly (see *Instituting opioid treatment for chronic non-cancer pain*, page 4).

Tools for assessing function and pain

The key to effective opioid therapy for chronic non-cancer pain is sustained functional improvement (Loeser 1989, Devulder 2005). While there is no universally accepted tool to assess opioid treatment, it is important to use a tool that monitors both function and pain. An assessment of function should consistently measure the same elements to adequately determine the degree of progress. The following are functional assessment tools that may be helpful in monitoring your patient's progress:

- **SF36 Health Survey**
  http://www.npecweb.org/clinicaltoolbox.asp?id=26&selMenu=15,0
- ***Quick*Dash** for musculoskeletal disorders of the upper extremities
  http://www.dash.iwh.on.ca/assets/images/pdfs/quickdash_q.pdf
- **Quality of Life Scale**
  http://www.npecweb.org/clinicaltoolbox.asp?id=26&selMenu=15,0
- **Oswestry Disability Index**
  http://www.chirogeek.com/001_Oswestry-Disability-level.htm
- **Neck Disability Index**
  http://www.chirogeek.com/001_Neck-Disability-Index.htm
- **Short Musculoskeletal Function Assessment. (**See Swiontkowski et al.)

Assessing effects of opioid treatment

Long-term opioid treatment is associated with the development of tolerance to its analgesic effects (White 2004). Evidence is accumulating that opioid treatment may also paradoxically induce abnormal pain sensitivity, including hyperalgesia and allodynia (Mao 2002, Ossipov 2005, King 2005). Thus, increasing opioid doses may not improve pain control and function.

The prescriber should assess the risks and benefits of their patient's current opioid therapy. This assessment should include:

- Function and pain status (see *Tools for assessing function and pain*, page 5);
- Possible adverse effects of current opioid doses;
- Potential psychological condition affecting treatment;
- Possible drug combinations or conditions that may potentiate opioid adverse effects (such as COPD, CHF, sleep apnea, history of alcohol or substance abuse, advanced age, or history of renal or hepatic dysfunction); and
- Any relative contraindication to the use of opioids (active alcohol or other substance abuse, see *Urine drug toxicology screening*, below).

If function and pain do not improve after a sufficient opioid trial, consider discontinuing opioids (see *Weaning opioids*, page 7). When there is evidence of significant adverse effects from opioid therapy, the provider should reduce the opioid dose and reassess the patient's status.

Otherwise, if no reasons for dose reduction or discontinuation are identified, and the prescriber feels (with support of objective measures of pain and function) that the patient is benefiting from current therapy, continuation would be appropriate. Ongoing therapy, however, entails ongoing assessment. The screening described above should be done on a regular basis to assess progression of therapy as the patient's condition changes over time.

Urine drug toxicology screening

Urine drug toxicology screening can improve the prescriber's ability to safely and appropriately manage opioid treatment. Urine toxicology can verify if the patient is taking the prescribed medications. It can also identify if other psychoactive substances are consumed, but not reported, which may impact the patient's safety, function and treatment. The NIDA 5 (National Institute on Drug Abuse) is the most commonly used basic urine drug test that screens for five common drug classes:

- Cannabinoids (marijuana, hash)
- Cocaine (crack)
- Amphetamines (methamphetamines, speed)
- Opioids (heroin, opium, codeine, morphine)
- Phencyclidine (PCP)

The NIDA 5 does not screen for many other drugs of abuse, such as barbiturates, benzodiazepines, hydrocodone, methadone, oxycodone, propoxyphene, or other synthetic drugs. An expanded urine drug toxicology panel can be ordered to screen for these substances.

Positive results from a urine toxicology screen should be interpreted with caution. Over-the-counter medication may occasionally cause a positive result, particularly in the amphetamines and opioids classes. In some circumstances a positive result may require confirmatory tests and consultation with a certified Medical Review Officer (MRO). To locate a MRO in your area, submit a search at the following website:
http://www.aamro.com/registry_search.html

Specialty consultation

Specialty consultation is recommended for ongoing severe pain symptoms with no improvement in function despite treatment with opioids. Consultation should address possible undiagnosed conditions, psychological conditions affecting treatment, and alternative treatments. The type of consultation obtained should be determined by the patient's presenting signs and symptoms. Consultation may be with, but not limited to, a physician specializing in psychiatry, neurology, anesthesiology, pain, physical medicine and rehabilitation, orthopedics, addiction medicine, rheumatology, or oncology.

Chronic opioid treatment can be challenging in patients with symptoms suggestive of mood, anxiety, and psychotic disorders. Consider psychiatric and/or psychological consultation for intervention if a psychological condition is affecting treatment. Patients with signs of alcohol or other substance abuse should be referred to an addiction specialist (see *Referrals for addiction management or opioid agonist treatment*, page 10).

Pain management consultation

Although pain may be relieved at oral morphine doses up to 120 mg per day, pain relief is not necessarily associated with psychological or functional improvement (Moulin 1996). Because sustained functional improvement is so critical to effective opioid therapy for chronic non-cancer pain, the prescriber should ensure that the patient meets the following conditions before considering a dosage above 120mg/day MED:

- There are no significant psychological issues or evidence of drug-seeking behaviors, AND
- The patient has demonstrated improvement in function and pain level previously at a lower dose.

If these conditions are met, the prescriber may seek a pain management consultation for a possible trial with opioid doses above 120mg/day MED.

Consultation with a specialist does not necessitate transfer of the patient's care or on-going opioid prescribing. However, the consultant should advise the prescribing provider on a pain management plan that may include alternative treatments to reduce or discontinue use of opioids; adequate explanation of the risks and benefits of a possible trial with opioid dosing above 120mg/day MED; and the need for ongoing documentation of improvement in function and pain.

If you need to find a pain management specialist, you may find it helpful to contact one of the following organizations that offer credentialing or certification in pain medicine:

- American Academy of Pain Management and American Board of Pain Medicine
- American Board of Anesthesiology with certification of added qualifications in pain management
- American Board of Physical Medicine and Rehabilitation
- American Board of Psychiatry and Neurology

In addition, you can find a non-exclusive list of pain specialists at www.agencymeddirectors.wa.gov/opioiddosing.asp

Weaning opioids

Not all patients benefit from opioids, and a prescriber frequently faces the challenge of reducing the opioid dose or discontinuing the opioid altogether. From a medical standpoint, weaning from opioids can be done safely by slowly tapering the opioid dose and taking into account the following issues:

- A decrease by 10% of the original dose per week is usually well tolerated with minimal physiological adverse effects. Some patients can be tapered more rapidly without problems (over 6 to 8 weeks).
- If opioid abstinence syndrome is encountered, it is rarely medically serious although symptoms may be unpleasant.
- Symptoms of an abstinence syndrome, such as nausea, diarrhea, muscle pain and myoclonus can be managed with clonidine 0.1 – 0.2 mg orally every 6 hours or clonidine transdermal patch 0.1mg/24hrs (Catapres TTS-1™) weekly during the taper while monitoring for often significant hypotension and anticholinergic side effects. In some patients it may be necessary to slow the taper timeline to monthly, rather than weekly dosage adjustments.
- Symptoms of mild opioid withdrawal may persist for six months after opioids have been discontinued.
- Consider using adjuvant agents, such as antidepressants to manage irritability, sleep disturbance or antiepileptics for neuropathic pain.
- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids.
- Referral for counseling or other support during this period is recommended if there are significant behavioral issues.
- Referral to a pain specialist or chemical dependency center should be made for complicated withdrawal symptoms.

Recognizing and managing behavioral issues during opioid weaning

Opioid tapers can be done safely and do not pose significant health risks to the patient. In contrast, extremely challenging behavioral issues may emerge during an opioid taper (Passik 2006).

Behavioral challenges frequently arise in the setting of a prescriber who is tapering the opioid dose and a patient who places great value on the opioid he/she is receiving. In this setting, some patients will use a wide range of interpersonal strategies to derail the opioid taper. These may include:

- Guilt provocation ("You are indifferent to my suffering")
- Threats of various kinds
- Exaggeration of their actual suffering in order to disrupt the progress of a scheduled taper

There are no fool-proof methods for preventing behavioral issues during an opioid taper, but strategies implemented at the beginning of the opioid therapy are most likely to prevent later behavioral problems if an opioid taper becomes necessary (see *Instituting opioid treatment for chronic non-cancer pain*, page 4).

Part II: Guidelines for optimizing treatment when opioid doses are greater than 120 mg MED per day

Part II of this dosing guideline will assist the provider in optimizing treatment:

- When assessing effectiveness of opioid therapy in patients whose total morphine equivalent dose exceeds 120 mg per day;
- When reducing the total daily opioid dose; and
- When discontinuing opioid therapy.

Assessing effects of opioid doses greater than 120 mg MED per day

As previously stated, ongoing opioid treatment requires ongoing assessment to optimize therapy. This is important in light of the development of hyperalgesia and other abnormal pain sensitivity with chronic high dose opioid treatment. If, after using the guidelines under *Assessing effects of opioid treatment* (page 5), the prescriber feels that current treatment is not benefiting the patient, a dose reduction or discontinuation is warranted. However, if current treatment is benefiting the patient as demonstrated by objective measures of pain and function, it may be appropriate to continue, while establishing a plan to monitor therapy as the patient's condition changes over time (see *Principles for prescribing opioids,* page 4).

How to discontinue opioids or reduce and reassess at lower doses

Treatment with opioids, even at high doses, does not guarantee freedom from chronic pain, and some patients may actually do better on lower doses of opioids (Mao 2002, Ballantyne 2003). A decrease by 10% of the original dose per week is usually well tolerated. Behavioral issues or physical withdrawal symptoms can be a major obstacle to an otherwise beneficial dose reduction (see *Weaning opioids,* page 7, and *Recognizing and managing behavioral issues during opioid weaning,* page 8).

The prescriber should assess the patient's status after discontinuing or reducing the opioid dose to less than 120mg MED per day. If the chosen assessment tool indicates improved patient status, other than subjective pain complaints, or if there is improvement in opioid-related side effects, maintain the patient off opioids or at the new reduced dose and reassess at a later time.

Conversely, if there is evidence of functional and symptomatic deterioration following opioid taper, the prescriber can resume prior dosing or strongly consider consulting with a pain management specialist to evaluate additional therapeutic options.

Referrals to pain centers

A referral for counseling or other support during opioid taper or dose reduction is recommended if there are significant behavioral issues. In addition, a multidisciplinary pain program may be considered when appropriate to address the psychosocial and cognitive aspects of chronic pain together with patients' physical rehabilitation (Guzman 2002).

Recognizing aberrant behaviors during opioid treatment

Patients who exhibit aberrant behaviors may or may not be at risk for opioid abuse. There is no universally accepted screening tool to predict aberrant behaviors with opioid treatment for chronic pain. However, it is important to identify aberrant behaviors as they can affect the medical management of your patients (see *Reasons to discontinue opioids or refer for addiction management,* page 10).

Patients with a co-morbid psychiatric condition or addiction are at higher risk of uncontrolled opioid use despite their attempts to follow the treatment plan (Streltzer 2001, Streltzer 2006, Passik 2006). Prescribers should seek a

consultation with an addiction specialist if there is co-morbid substance dependence or abuse.

Reasons to discontinue opioids or refer for addiction management

- No improvement in function or pain after opioid trial;
- Opioid treatment produces significant adverse effects; or
- Patient exhibits drug-seeking behaviors or diversion:
  - Selling prescription drugs
  - Forging prescriptions
  - Stealing or borrowing drugs
  - Frequently losing prescriptions
  - Aggressive demand for opioids
  - Injecting oral/topical opioids
  - Unsanctioned use of opioids
  - Unsanctioned dose escalation
  - Concurrent use of illicit drugs
  - Failing a drug screen
  - Getting opioids from multiple prescribers

Referrals for addiction management or opioid agonist treatment

A patient who exhibits overt signs of alcohol or substance use disorder as defined in the current edition of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM) should be referred to an addiction specialist for appropriate treatment. Prognosis is poor for patients with a DSM diagnosis of opioid dependence or opioid abuse who do not receive opioid agonist therapy, such as methadone or buprenorphine (Sees 2000, Kakko 2003).

Methadone can only be provided to treat a DSM diagnosis of opioid dependence through a federally licensed opioid treatment program (OTP). A referral for treatment may be made to any one of the licensed OTPs in Washington State:

- http://www1.dshs.wa.gov/DASA/services/certification/GB.shtml and click on Appendix Q.

Buprenorphine or buprenorphine/naloxone may also be prescribed by a qualified physician to treat opioid addiction. Any pharmacy can fill a buprenorphine or buprenorphine/naloxone prescription. To find qualified physicians in Washington, access:

- http://buprenorphine.samhsa.gov/bwns_locator/dr_search.htm

Additional resources

- Department of Social and Health Services (DSHS) Tool Kit to help address drug and alcohol issues in Medicaid patients http://maa.dshs.wa.gov/pharmacy/ToolKit.htm
- DSHS Division of Alcohol and Substance Abuse at 877-301-4557
- List of providers for pain management consultation www.agencymeddirectors.wa.gov/opioiddosing.asp
- Collaborative Opioid Prescribing Education (COPE), an online training to improve doctor-patient communications and collaborative goal-setting.

  http://elearning.talariainc.com/cope

  At a later date the University of Washington may make this course available for continuing medical education credit. For more information, check the UW's site at: http://depts.washington.edu/cme/online/

Table 2. Dosing Threshold for Selected Opioids*			
Opioid	*Recommended dose threshold for pain consult (not equianalgesic)*	*Recommended starting dose for opioid-naïve patients*	*Considerations*
Codeine	800mg per 24 hours	30mg q 4–6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Fentanyl Transdermal	50mcg/hour (q 72 hr)		Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer
Hydrocodone	120mg per 24 hours	5-10mg q 4–6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Hydromorphone	30mg per 24 hours	2mg q 4-6 hours	
Methadone	40mg per 24 hours	2.5-5mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.
Morphine	120mg per 24 hours	Immediate-release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5mg q 4–6 hours Sustained Release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Oxymorphone	40mg per 24 hours	Immediate-release: 5-10mg q 4–6 hours Sustained Release: 10mg q 12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

*Meperidine and propoxyphene products should not be prescribed for chronic non-cancer pain pain.

Acetaminophen warning with combination products

Hepatotoxicity can result from prolonged use or doses in excess of recommended maximum total daily dose of acetaminophen including over-the-counter products.

- Short-term use (<10 days) – 4000 mg/day
- Long-term use – 2500mg/day

Key considerations in dosing long acting opioids

- Monitoring for adequate analgesia and use of "rescue" medications (at least until the long-acting opioid dose is stabilized). All new dosage calculations should include consideration for concurrent utilization of short-acting opioids.
- If the patient is more debilitated, frail and/or has significant metabolic impairments (e.g. renal or hepatic dysfunction), consider starting at the lower end of the conversion dose range.
- Always monitor for adverse effects (nausea, constipation, oversedation, itching, etc.)

Equianalgesic dose table for converting opioid doses

All conversions between opioids are estimates generally based on "equianalgesic dosing" or ED. Patient variability in response to these EDs can be large, due primarily to genetic factors and incomplete cross-tolerance. **It is recommended that, after calculating the appropriate conversion dose, it be reduced by 25–50% to assure patient safety**.

Table 3. MED for Selected Opioids	
Opioid	*Approximate Equianalgesic Dose (oral & transdermal) **
Morphine (reference)	**30mg**
Codeine	200mg
Fentanyl transdermal	12.5mcg/hr
Hydrocodone	30mg
Hydromorphone	7.5mg
Methadone	Chronic: 4mg†
Oxycodone	20mg
Oxymorphone	10mg

*Adapted from VA 2003 & FDA labeling
†Equianalgesic dosing ratios between methadone and other opioids are complex, thus requiring slow, cautious conversion (Ayonrinde 2000)

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