Montana Utilization and Treatment Guidelines

F7. Medications - Chronic Pain Disorder

F.7 Medications There is no single formula for pharmacological treatment of patients with chronic nonmalignant pain. A thorough medication history, including use of alternative and over the counter medications, should be performed at the time of the initial visit and updated periodically. Appropriate application of pharmacological agents depends on the patient's age, past history (including history of substance abuse), drug allergies and the nature of all medical problems. It is incumbent upon the physician to thoroughly understand pharmacological principles when dealing with the different drug families and their respective side effects, bioavailability profiles, and primary reason for each medication's usage.

Control of chronic non-malignant pain is expected to involve the use of medication. Strategies for pharmacological control of pain cannot be precisely specified in advance. Rather, drug treatment requires close monitoring of the patient's response to therapy, flexibility on the part of the prescriber and a willingness to change treatment when circumstances change. Many of the drugs discussed in the medication section were licensed for indications other than analgesia, but are effective in the control of many types of chronic pain. Consensus regarding the use of opioids has generally been reached in the field of cancer pain, where nociceptive mechanisms are generally identifiable, expected survival may be short, and symptomatic relief is emphasized more than functional outcomes. In injured workers, by contrast, central and neuropathic mechanisms frequently overshadow nociceptive processes, expected survival is relatively long, and return to a high level of function is a major goal of treatment. Approaches to pain, which were developed in the context of malignant pain, therefore may not be transferable to chronic non-malignant pain.

All medications should be given an appropriate trial in order to test for therapeutic effect. Trials of medication requiring specific therapeutic drug levels may take several months to achieve, depending upon the half-life of the drug. It is recommended that patients with chronic nonmalignant pain be maintained on drugs that have the least serious side effects. For example, patients need to be tried or continued on acetaminophen and/or antidepressant medications whenever feasible as part of their overall treatment for chronic pain. It is recommended that use of opioid analgesic and sedative hypnotic medications in chronic pain patients be used in a very limited manner, with total elimination desirable whenever clinically feasible.

The preceding principles do no apply to chronic headache patients. These patients should be referred to a physician specializing in the diagnosis and treatment of headache and facial pain.

For the clinician to interpret the following material, it should be noted that: (1) drug profiles listed are not complete; (2) dosing of drugs will depend upon the specific drug, especially for off-label use; and (3) not all drugs within each class are listed, and other drugs within the class may be appropriate. Clinicians should refer to informational texts or consult a pharmacist before prescribing unfamiliar medications or when there

is a concern for drug interactions.

The following drug classes are listed in alphabetical order, not in order of suggested use.

F.7.a Alpha-Acting Agents

Noradrenergic pain-modulating systems are present in the central nervous system, and the alpha-2 adrenergic receptor may be involved in the functioning of these pathways. Alpha-2 agonists may act by stimulating receptors in the substantia gelatinosa of the dorsal horn of the spinal cord, inhibiting the transmission of nociceptive signals. Spasticity may be reduced by presynaptic inhibition of motor neurons. Given limited experience with their use, they cannot be considered first-line analgesics, but a trial of their use may be warranted in many cases of refractory pain.

Clonidine (Catapres)

A) Description – Central alpha 2 agonist.
B) Indications – Sympathetically mediated pain, treatment of withdrawal from opioids. Intravenous regional anesthesia with clonidine for administration prior to surgery to prevent recurrence of CRPS in patients who have previously had CRPS. It may also be considered in patients undergoing surgery who are considered at increased risk for CRPS.
C) Major Contraindications – Severe coronary insufficiency, renal impairment.
D) Dosing and Time to Therapeutic Effect – Increase dosage weekly to therapeutic effect.
E) Major Side Effects – Sedation, orthostatic hypotension, sexual dysfunction, thrombocytopenia, weight gain, agitation, rebound hypertension with cessation.
F) Drug Interactions – Beta adrenergics, tricyclic antidepressants.
G) Recommended Laboratory Monitoring – Renal function.

Tizanidine (Zanaflex)

A) Description – Alpha 2 adrenergic agonist.
B) Indications – Spasticity, musculoskeletal disorders.
C) Major Contraindications – Hepatic disease.
D) Dosing and Time to Therapeutic Effect – As needed (PRN) or titrate to effective dose.
E) Major Side Effects – Hypotension, sedation, hepatotoxicity, hallucinations and psychosis, dry mouth.
F) Drug Interactions – Alcohol, oral contraceptives, and acetaminophen. Use with caution with other alpha agonists.
G) Recommended Laboratory Monitoring – Hepatic and renal function.

F.7.b Anticonvulsants

Although the mechanism of action of anticonvulsant drugs in neuropathic pain states remains to be fully defined, they appear to act as nonselective sodium channel blocking agents. A large variety of sodium channels are present in nervous tissue, and some of these are important mediators of nociception, as they are found primarily in unmyelinated fibers and their density increases following nerve injury. While the pharmacodynamic effects of the various anticonvulsant drugs are similar, the pharmacokinetic effects differ significantly. Carbamazepine has important effects as an inducer of hepatic enzymes and may influence the metabolism of other drugs enough to present problems in patients taking more than one drug. Gabapentin and oxcarbazepine, by contrast, are relatively non-significant enzyme inducers, creating fewer drug interactions. Because anticonvulsant drugs may have more problematic side-effect profiles, their use should usually be deferred until antidepressant drugs have failed to relieve pain.

Gabapentin (Neurontin)

A) Description – Structurally related to gamma-aminobutyric acid (GABA) but does not interact with GABA receptors.
B) Indications – Neuropathic pain.
C) Relative Contraindications – Renal insufficiency.
D) Dosing and Time to Therapeutic Effect – Dosage may be increased over several days.
E) Major Side Effects – Confusion, sedation.

F) Drug Interactions – Oral contraceptives, cimetidine, antacids.
G) Recommended Laboratory Monitoring – Renal function.

Pregabalin

A) Description – Designed as a more potent successor to gabapentin.
B) Indications – Neuropathic pain, fibromyalgia
C) Dosing and Time to Therapeutic Effect – Initiate medication at a low dose and gradually increase. Duration of use for patients with neuropathic pain may be as long as indefinitely, although many of these patients do not require indefinite treatment as the conditions usually either resolve or improves.
D) Major Side Effects – elevated risks for CNS-sedating adverse effects.
E) Drug Interactions – pregabalin has not been reported to cause clinically relevant pharmacokinetic drug interactions.
F) Recommended Laboratory Monitoring – Careful monitoring of employed patients is indicated due in part to elevated risks for CNS-sedating adverse effects.

Oxcarbazepine (Trileptal)

A) Description – The mechanism of action resembles that of carbamazepine, but has an advantage in being a less potent inducer of hepatic enzymes. Controlled trials of its effectiveness in chronic pain are lacking.
B) Indications – Neuropathic pain.
C) Major Contraindications – Hypersensitivity to carbamazepine.
D) Dosing and Time to Therapeutic Effect – Dosage may be increased weekly.
E) Major Side Effects – Sedation, visual disturbances.
F) Drug Interactions – Oral contraceptives, valproic acid, carbamazepine.
G) Recommended Laboratory Monitoring – Drug levels, renal and hepatic function.

Carbamazepine (Tegretol)

A) Description – Anticonvulsant structurally related to tricyclic antidepressants.
B) Indications – Trigeminal neuralgia and other neuropathic pain.
C) Major Contraindications – Bone marrow depression, hypersensitivity to tricyclic antidepressants.
D) Dosing and Time to Therapeutic Effect – Dosage levels typically exceed those utilized for seizure prophylaxis. Titrate to desired effect.
E) Major Side Effects – Aplastic anemia, agranulocytosis, nausea, diplopia, pulmonary sensitivity, inappropriate antidiuretic hormone, dysphoria, disequilibrium.
F) Drug Interactions – Many interactions have been reported including, but not limited to, macrolide antibiotics, valproic acid, SSRI's, propoxyphene, doxycycline, bupropion, anticoagulants, and acetaminophen.
G) Recommended Laboratory Monitoring – Drug levels, renal and hepatic function, complete blood count.

Topiramate

A) Description – While there is no basis for use of most anti-convulsant agents in nociceptive pain, there is quality evidence that topiramate is effective for the treatment of chronic LBP (Muehlbacher 06), which warrants generating a separate recommendation regarding its use.
B) Indications – Failure of multiple other modalities including different NSAIDs; aerobic, specific stretching, and strengthening exercises; tricyclic anti-depressant s; distractants; and manipulation if indicated. It is somewhat recommended for limited use as a fourth- or fifth-line agent in select patients with chronic LBP. Topiramate is not recommended for treatment of radicular or neuropathic pain including peripheral neuropathy.
C) Dosing and Time to Therapeutic Effect – Begin with a dose of 50mg and increase by 50mg a week. The most appropriate steady-state dose is 300mg. Duration of use for patients with chronic persistent pain may be indefinite although most of these patients do not require indefinite treatment as the condition usually either resolves or improves, particularly if there is compliance with elements of a functional restoration program.

Indications for Discontinuation – Resolution, development of adverse effects, failure to adhere to a restoration program.

D) Major Side Effects – Topiramate may cause significant neurocognitive problems, glaucoma, weight loss, or kidney stones.

E) Recommended Laboratory Monitoring – Careful monitoring of employed patients is indicated due to elevated risks for CNS-sedating adverse effects.

F.7.c Antidepressants Antidepressants are classified into a number of categories based on their chemical structure and their effects on neurotransmitter systems. Their effects on depression are attributed to their actions on disposition of norepinephrine and serotonin at the level of the synapse; although these synaptic actions are immediate, the symptomatic response in depression is delayed by several weeks. When used for chronic pain, the effects may in part arise from treatment of underlying depression, but may also involve additional neuromodulatory effects on endogenous opioid systems, raising pain thresholds at the level of the spinal cord.

Pain responses may occur at lower drug doses with shorter times to symptomatic response than are observed when the same compounds are used in the treatment of mood disorders. Neuropathic pain, diabetic neuropathy, post-herpetic neuralgia, and cancer-related pain may respond to antidepressant doses low enough to avoid adverse effects that often complicate the treatment of depression.

Tricyclics (e.g., amitriptyline [Elavil], nortriptyline [Pamelor, Aventyl], doxepin [Sinequan, Adapin])

A) Description – Serotonergics, typically tricyclic antidepressants (TCAs), are utilized for their serotonergic properties as increasing CNS serotonergic tone can help decrease pain perception in non-antidepressant dosages. Amitriptyline is known for its ability to repair Stage 4 sleep architecture, a frequent problem found in chronic pain patients and to treat depression, frequently associated with chronic pain.

B) Indications – Chronic musculoskeletal and/or neuropathic pain, insomnia. Second line drug treatment for depression.

C) Major Contraindications – Cardiac disease or dysrhythmia, glaucoma, prostatic hypertrophy, seizures, suicide risk.

D) Dosing and Time to Therapeutic Effect – Varies by specific tricyclic. Low dosages are commonly used for chronic pain and/or insomnia.

E) Major Side Effects – Anticholinergic side effects including, but not limited to, dry mouth, sedation, orthostatic hypotension, cardiac arrhythmia, weight gain.

F) Drug Interactions – Tramadol (may cause seizures), Clonidine, cimetidine, sympathomimetics, valproic acid, warfarin, carbamazepine, bupropion, anticholinergics, quinolones.

G) Recommended Laboratory Monitoring – Renal and hepatic function. EKG for those on high dosages or with cardiac risk.

Selective serotonin reuptake inhibitors (SSRIs) (e.g., citalopram [Celexa], fluoxetine [Prozac], paroxetine [Paxil], sertraline [Zoloft]).

A) Description – SSRIs are characterized by the predominance of inhibition of serotonin reuptake at the pre-synaptic nerve terminal.

B) Indications – Depression, chronic pain with depression and/or anxiety. Less effective than tricyclic antidepressants for neuropathic pain.

C) Major Contraindications – Allergy to SSRIs.

D) Time to Produce Therapeutic Effect – 3 to 4 weeks.

E) Major Side Effects – Insomnia, gastrointestinal (GI) distress, sexual dysfunction.

F) Drug Interactions – Multiple drug interactions have been reported, including non-sedating antihistamine. May be used in combination with TCAs but therapeutic TCA levels (as used for depression) are known to increase when used in combination with SSRIs and may persist for at lease 5 weeks after discontinuance. Tramadol should not be used with SSRIs due to potential for seizures.

G)Recommended Laboratory Monitoring – Renal and hepatic function.

Duloxetine

A) Description: duloxetine is often placed in the SSRI class of medications, but duloxetine is a mixed norepinephrine and serotonin inhibitors. Duloxetine is the newest of these medications with a mechanism of action that is thought to be more similar to that of TCAs. Duloxetine has been approved for management of painful diabetic peripheral neuropathy. May be moderately costly.

B) Indications – for limited use in select patients with diabetic peripheral neuropathy or patients with CRPS who failed multiple other modalities including trials of tricyclic anti-depressants, anti-convulsant agents, and NSAIDs. Duloxetine should be considered a third-line agent

C) Major Side Effects – CNS adverse effects are elevated with this medication.

Atypical Antidepressants/Other Agents

A) Description – Venlafaxine, (Effexor), nefazadone (Serzone), trazodone (Deseryl), and mirtazapine (Remeron) share adjuvant analgesic effects with tricyclic antidepressants. They differ in their side effect and drug interaction profiles.

B) Indications – Venlafaxine is approved for generalized anxiety disorder, bupropion for smoking cessation.

C) Major Contraindications – Seizures, eating disorders.

D) Major Side Effects – Depends on the drug, but commonly include GI distress, drowsiness, sexual dysfunction less than other classes except trazadone, which may cause priapism. Hypertension (venlafaxine).

E) Drug Interactions – Drug specific. Prolongation of cardiac output (QT) interval with rare arrhythmias associated with nefazadone and non-sedating antihistamines.

F) Recommended Laboratory Monitoring – Drug specific.

F.7.d Hypnotics and Sedatives Sedative and hypnotic drugs decrease activity, induce drowsiness, and moderate agitation. Many drugs produce these effects incidental to their usual intended effects, similar to the side effects of many antihistamines and antidepressants. Due to the habit-forming potential of the benzodiazepines and other drugs found in this class, they are not routinely recommended but may be useful in some patients with chronic pain.

Most insomnia in chronic pain patients should be managed primarily through behavioral interventions with medications as secondary measures (refer to Section F.4, Disturbances of Sleep).

Zaleplon (Sonata)

A) Description – A nonbenzodiazepine hypnotic.

B) Indications – Insomnia.

C) Dosing and Time to Therapeutic Effect – Time of onset is 30 to 60 minutes. Due to rapid elimination, may be taken as little as 4 hours before awakening.

D) Major Side Effects – Dizziness, dose-related amnesia.

E) Drug Interactions – Increases sedative effect of other central nervous system (CNS) depressant drugs. Use low dose if on cimetidine.

F) Recommended Laboratory Monitoring – Hepatic function.

Zolpidem (Ambien)

A) Description – A nonbenzodiazepine hypnotic, which does not appear to cause rebound insomnia. It has little respiratory depression and insignificant anxiolytic or muscle relaxant activity.

B) Indications – Short-term use for insomnia

C) Time to Therapeutic Effect – Onset of action is 30 to 60 minutes

D) Major Side Effects – Dizziness, dose-related amnesia.

E) Drug Interactions – Increases sedative effect of other CNS depressant drugs.

F) Recommended Laboratory Monitoring – Hepatic function.

F.7.e Skeletal Muscle Relaxants Skeletal Muscle Relaxants are most useful for acute musculoskeletal injury or exacerbation of injury. Chronic use of benzodiazepines is discouraged due to their habit-forming potential and due to seizure risk following abrupt withdrawal.

Cyclobenzaprine (Flexeril)
A) Description – Structurally related to tricyclics.
B) Indications – Chronic pain associated with muscle spasm.
C) Major Contraindications – Cardiac dysrhythmias.
D) Dosing and Time to Therapeutic Effect – Variable, onset of action is 1 hour.
E) Major Side Effects – Sedation, anticholinergic, blurred vision.
F) Drug Interactions – Consider interactions similar to tricyclic antidepressants as listed under antidepressant class.
G) Recommended Laboratory Monitoring – Hepatic and renal function.

Carisoprodol (Soma)
A) Description – Mode of action may be central; meprobamate is an active metabolite. Carisoprodol is more commonly abused, because an active metabolite is meprobamate, a potent and highly abused sedative-hypnotic. Regardless, it is recommended that caution be exerted when using any of these agents if there is a history of substance abuse or requests for specific medications. Evidence suggests that Carisoprodol is comparable to cyclobenzaprine.
B) Indications – Chronic pain associated with muscle spasm.
C) Major Contraindications – Sensitivity to meprobamate, renal or hepatic disease.
D) Major Side Effects – Sedation, withdrawal symptoms, abuse potential.
E) Recommended Laboratory Monitoring – Renal and hepatic function.

Metazalone (Skelaxin)
A) Description – Central acting muscle relaxant.
B) Indications – Muscle spasm.
C) Major Contraindications – Hepatic disease, pregnancy, and disposition to drug induced hemolytic anemia.
D) Dosing and Time to Therapeutic Effect – Onset of action 1 hour.
E) Recommended Laboratory Monitoring – Hepatic function.

F.7.f Opioids Opioids are the most powerful analgesics. Their use in acute pain and moderate to severe cancer pain is well accepted. Their use in chronic nonmalignant pain, however, is fraught with controversy and lack of scientific research.

Opioids include some of the oldest and most effective drugs used in the control of severe pain. The discovery of opioid receptors and their endogenous peptide ligands has led to an understanding of effects at the binding sites of these naturally occurring substances. Most of their analgesic effects have been attributed to their modification of activity in pain pathways within the central nervous system; however, it has become evident that they also are active in the peripheral nervous system. Activation of receptors on the peripheral terminals of primary afferent nerves can mediate antinociceptive effects, including inhibition of neuronal excitability and release of inflammatory peptides. Some of their undesirable effects on inhibiting gastrointestinal motility are peripherally mediated by receptors in the bowel wall.

The central nervous system actions of these drugs account for much of their analgesic effect and for many of their other actions, such as respiratory depression, drowsiness, mental clouding, reward effects, and habit formation. With respect to the latter, it is crucial to distinguish between three distinct phenomena: tolerance, dependence, and addiction.

- Tolerance refers to a state of adaptation in which exposure to a drug over time causes higher doses of that drug to be required in order to produce the same physiologic effect.
- Dependence refers to a set of disturbances in body homeostasis that leads to withdrawal symptoms, which can be produced with abrupt discontinuation, rapid reduction, decreasing blood levels, and/or by administration of an antagonist.

- Addiction is a primary, chronic, neurobiologic disease, with genetic, psychological, and environmental factors influencing its development and manifestations. It is a behavioral pattern of drug craving and seeking which leads to a preoccupation with drug procurement and use.

Tolerance and dependence are physiological phenomena, are expected with the continued administration of opioids, and should not deter physicians from their appropriate use. Before increasing the narcotic dose due to a presumption of physiologic tolerance, the physician should review other possible causes for the decline in analgesic effect. Consideration should be given to possible new psychologic stressors or an increase in the activity of the nociceptive pathways.

The use of opioids is well accepted in treating cancer pain, where nociceptive mechanisms are generally present due to ongoing tissue destruction, expected survival may be short, and symptomatic relief is emphasized more than functional outcomes. In chronic non-malignant pain, by contrast, tissue destruction has generally ceased, meaning that central and neuropathic mechanisms frequently overshadow nociceptive processes. Expected survival in chronic pain is relatively long and return to a high level of function is a major goal of treatment. Therefore, approaches to pain developed in the context of malignant pain may not be transferable to chronic non-malignant pain. Opioids are generally not the best choice of medication for controlling neuropathic pain. Tricylics and anticonvulsants should be tried first.

In most cases, analgesic treatment should begin with acetaminophen, aspirin, and NSAIDs. While maximum efficacy is modest, they may reduce pain sufficiently to permit adequate function. When these drugs do not satisfactorily reduce pain, opioids for moderate to moderately severe pain may be added to (not substituted for) the less efficacious drugs.

Consultation or referral to a pain specialist should be considered when the pain persists but the underlying tissue pathology is minimal or absent and correlation between the original injury and the severity of impairment is not clear. Consider consultation if suffering and pain behaviors are present and the patient continues to request medication, or when standard treatment measures have not been successful or are not indicated.

1. **General Indications** – There must be a clear understanding that opioids are to be used for a limited term in the first instance (see trial indications below), that their use is contingent upon certain obligations or goals being met by the patient, e.g., return-to-work, and the patient understands that there may be drug screening to ensure compliance.
2. **Therapeutic Trial Indications** – A therapeutic trial of opioids should not be employed unless the patient has begun or completed a full rehabilitation program. Once this criterion has been met, opioids would be indicated when a patient meets the following:
   A) The failure of pain management alternatives, including active therapies, cognitive behavioral therapy, pain self-management techniques, and other appropriate medical techniques.
   B) Physical and psychosocial assessment, performed by two specialists including the authorized treating physician and a specialist with expertise in chronic pain.
   C) Informed, written, witnessed consent by the patient.
   In addition, there should be documentation of sustained improvement of pain control and/or functional status, including return-to-work, with use of opioids. Frequent follow-up at least every 2 to 4 weeks may be necessary to titrate dosage and assess clinical efficacy.
3. **On-Going, Long-Term Management** – Actions should include:
   A) Prescriptions from a single practitioner,
   B) Ongoing review and documentation of pain relief, functional status, appropriate medication use, and side effects,
   C) Ongoing effort to gain improvement of social and physical function as a result of pain relief,

D) Contract detailing reasons for termination of supply, with appropriate tapering of dose,
E) Use of annual random drug screening and additional screening as deemed appropriate by the prescribing physician,
F) Use of more than two opioids: a long acting opioid for maintenance of pain relief and a short acting opioid for limited rescue use when pain exceeds the routine level. If more than two opioids are prescribed for long-term use, a second opinion from specialist who is Board Certified in Neurology, Physical Medicine and Rehabilitation, or Anesthesiology with recognized training and/or certification in pharmacological pain management is strongly recommended. G) Use of acetaminophen-containing medications in patients with liver disease should be limited; and
H) Continuing review of overall situation with regard to nonopioid means of pain control.
I) Inpatient treatment in complex cases. Refer to Section F.6, Interdisciplinary Rehabilitation Programs for detailed information on in-patient criteria.

4. **Relative Contraindications** – Extreme caution should be used in prescribing controlled substances for workers with one or more "relative contraindications":
A) History of alcohol or other substance abuse, or a history of chronic, high-dose benzodiazepine use;
B) Off work for more than six months;
C) Severe personality disorder

5. **General Contraindications** –
A) Active alcohol or other substance abuse.
B) Untreated mood or psychotic disorders (e.g., depression).
C) Decreased physical or mental function with continued opioid use.
D) Addictive behaviors. Warning signs include:
1. Preoccupation with drugs;
2. Refusal to participate in medication taper;
3. Reporting that nothing but a specific opioid works;
4. Strong preference for short-acting over long-acting opioids;
5. Use of multiple prescribers and pharmacies;
6. Use of street drugs or other patients drugs;
7. Not taking medications as prescribed;
8. Loss of medications more than once; and/or
9. Criminal behaviors to obtain drugs, i.e., forged prescriptions.

6. **Dosing and Time to Therapeutic Effect** – Oral route is the preferred route of analgesic administration because it is the most convenient and cost-effective method of administration. When patients cannot take medications orally, rectal and transdermal routes should be considered because they are also relatively noninvasive.

7. **Major Side Effects** – There is great individual variation in susceptibility to opioid-induced side effects and clinicians should monitor for these potential side effects. Common initial side effects include nausea, vomiting, drowsiness, unsteadiness, and confusion. Occasional side effects include dry mouth, sweating, pruritus, hallucinations, and myoclonus. Rare side effects include respiratory depression and psychological dependence. Constipation and nausea/vomiting are common problems associated with long-term opioid administration and should be anticipated, treated prophylactically, and monitored constantly.

8. **Drug Interactions** – Patients receiving opioid agonists should not be given a mixed agonist-antagonist (pentazocine [Talwin], butorphanol [Stadol]) because doing so may precipitate a withdrawal syndrome and increase pain.

9. **Recommended Laboratory Monitoring** – Primary laboratory monitoring is recommended for acetaminophen/aspirin/NSAIDs combinations (renal and liver function, blood dyscrasias).

10. **Patient Physician Contracts** – All patients on chronic opioids should have an informed, written, witnessed consent. The contract should discuss side effects of opioids, results of use in pregnancy, inability to refill lost or missing medication, withdrawal symptoms, requirement for drug testing, and necessity of tapering.

11. **Potentiating Agents** – Some medications appear to potentiate the analgesic effects of opioids. Dextromethorphan is available as a nonopioid non-prescription antitussive agent in numerous cough and cold remedies. It antagonizes N-methyl-D-aspartate receptors involved in central sensitization of pain pathways. It may exert some morphine sparing effects in patients taking morphine, but its activity as an analgesic in neuropathic pain is likely to be weak. It is well tolerated in most patients. Because the patient profiles that might predict response to dextromethorphan are undefined, its use in chronic pain must be empirically tried on an individual basis. Diphenhydramine and hydroxyzine (Atarax, Vistaril) are antihistamines, which act at H1 receptors to alleviate allergic symptoms and produce somnolence. Diphenhydramine is a component of some non-prescription sleeping preparations. Their use in potentiating the effects of analgesic drugs is not clearly defined, but it may be used empirically for this purpose.

F.7.g Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are useful for pain and inflammation. In mild cases, they may be the only drugs required for analgesia. There are several classes of NSAIDs and the response of the individual injured worker to a specific medication is unpredictable. For this reason a range of NSAIDs may be tried in each case with the most effective preparation being continued. Patients should be closely monitored for adverse reactions. The US Food and Drug Administration advises all NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Naproxen sodium does not appear to be associated with increased risk of vascular events. Administration of proton pump inhibitors, histamine 2 blockers, or prostaglandin analog misoprostol along with these NSAIDs may reduce the risk of duodenal and gastric ulceration but do not impact possible cardiovascular complications. Due to the cross-reactivity between aspirin and NSAIDs, NSAIDs should not be used in aspirin-sensitive patients, and should be used with caution in all asthma patients. NSAIDs are associated with abnormal renal function, including renal failure, as well as, abnormal liver function. Certain NSAIDs may have interactions with various other medications. Individuals may have adverse events not listed above. Intervals for metabolic screening are dependent upon the patient's age, general health status and should be within parameters listed for each specific medication. Complete blood count (CBC), liver and renal function should be monitored at least every six months in patients on chronic NSAIDs and initially when indicated.

Non-selective Nonsteroidal Anti-Inflammatory Drugs

Includes NSAIDs and acetylsalicylic acid (aspirin). Serious GI toxicity, such as bleeding, perforation, and ulceration can occur at any time, with or without warning symptoms in patients treated with traditional NSAIDs. Physicians should inform patients about the signs and/or symptoms of serious gastrointestinal toxicity and what steps to take if they occur. Anaphylactoid reactions may occur in patients taking NSAIDs. NSAIDs may interfere with platelet function. Fluid retention and edema have been observed in some patients taking NSAIDs.

- Optimal duration: 1 week
- Maximum duration: 1 year. Use of these substances long-term (3 days per week or greater) is associated with rebound pain upon cessation.

Selective Cyclo-oxygenase-2 (COX-2) Inhibitors

COX-2 inhibitors are more recent NSAIDs and differ in adverse side effect profiles from the traditional NSAIDs. The major advantages of selective COX-2 inhibitors over traditional NSAIDs are that they have less gastrointestinal toxicity and no platelet effects. COX-2 inhibitors can worsen renal function in patients with renal insufficiency; thus, renal function may need monitoring.

COX-2 inhibitors should not be first-line for low risk patients who will be using an NSAID short term but are indicated in select patients for whom traditional NSAIDs are not tolerated. Serious upper GI adverse events

can occur even in asymptomatic patients. Patients at high risk for GI bleed include those who use alcohol, smoke, are older than 65, take corticosteroids or anti-coagulants, or have a longer duration of therapy. Celecoxib is contraindicated in sulfonamide allergic patients.

- Optimal duration: 7 to 10 days
- Maximum duration: Chronic use is appropriate in individual cases. Use of these substances long-term (3 days per week or greater) is associated with rebound pain upon cessation.

F.7.h Acetaminophen

1. Description -- Acetaminophen and paracetamol are sometimes considered nonspecific NSAIDs, although their effects on cyclooxygenase activity are minimal and they are not anti-inflammatory agents. Acetaminophen blocks the activation of COX by another enzyme, peroxidase. Acetaminophen has very weak anti-inflammatory activity and essentially no platelet inhibition because of the absence of peripheral COX activity, but it selectively inhibits brain prostaglandin synthesis where peroxide concentrations are low. That is why tissues with high levels of peroxidase (platelets and immune cells) are "resistant" to acetaminophen, but tissues with low levels of peroxidase (i.e., nerve and endothelial cells that participate in pain and fever) are "sensitive" to acetaminophen.
2. Indications -- Acetaminophen is somewhat recommended for treatment of chronic persistent pain and radicular pain syndromes, particularly in patients with contraindications for NSAIDs.
3. Major Side Effects -- Acetaminophen is hepatotoxic in high doses (>4g a day chronically or a single dose >7g) and may cause liver failure requiring transplantation. Risk is increased with ethanol consumption and malnutrition. Although it has a more benign adverse effect profile than NSAIDs, in the U.S. alone, acetaminophen misuse accounts for more than 100,000 calls to poison control centers, more than 56,000 emergency department visits and 2,600 hospitalizations.

F.7.i NMDA Receptor Antagonists

1. Description – Numerous new compounds that specifically target mechanisms mediating neuropathic pain such as the N-methyl-D-aspartate (NMDA) receptor complex are currently in clinical trials. These compounds include dextromethorphan, amantadine, and memantine. Methadone is a mu agonist that also has affinity for the NMDA receptor. NMDA inhibitors purportedly help to prevent acute pain from progressing to chronic pain. These agents theoretically act by blocking receptors of neurotransmitters that are essential to long-term memories. They also are thought to potentially help reduce opioid tolerance and may enhance opioid analgesia.
2. Indications – Dextromethorphan for treatment of select patients (e.g., those who have failed NSAIDs, TCAs, and anti-convulsant agents) with peripheral diabetic neuropathy and, by inference, other peripheral neuropathies.
3. Dosing and Time to Therapeutic Effect – Doses used have ranged widely. In the successful trial, an average daily dose of 400mg was utilized. Dextromethorphan is recommended in doses that are on average at least 3 times higher than the antitussive dose, and carefully titrated to therapeutic effect. Duration of use for patients with chronic neuropathic pain should generally be limited to 2 or 3 months as there is not evidence of long-term safety, although longer periods of use may be reasonable.
4. Major Side Effects – The utility of these agents has been limited by their significant adverse-effect profile, which includes lightheadedness, dizziness, tiredness, headache, nervous floating sensation, bad dreams, and sensory changes. Dextromethorphan, amantadine, and memantine are better tolerated with lower CNS adverse effects than ketamine possibly due to a lower affinity for the NMDA receptor which plays a role in both normal physiological functions as well as pathological pain processing.

F.7.j Topical Drug Delivery

1. Description – Topical medications may be an alternative treatment for localized musculoskeletal disorders and is an acceptable form of treatment in selected patients although there is no scientific evidence to support its use in chronic pain.
2. Indications – Generalized musculoskeletal or joint pain. Patient selection must be rigorous to select those patients with the highest probability of compliance.
3. Dosing and Time to Therapeutic Effect – It is necessary that all topical agents be used with strict instructions for application as well as maximum number of applications per day to obtain the desired benefit and avoid potential toxicity.
4. Side Effects – Localized skin reactions may occur, depending on drug.

F.7.k Herbal/Dietary Supplements Botanical preparations have been used for centuries to remedy human illnesses, but only recently have been subjected to systematic study. Many medications currently manufactured by pharmaceutical firms are derivatives of compounds originally isolated from plants.

Clinical trials of folk remedies have been few in number, and often flawed by methodological problems. The lack of reliable data on the clinical and biological effects of herbal remedies often leads to inappropriate use. Patients commonly use non-standard remedies without discussing them with their physicians; when pharmacological interactions exist between herbs and prescription drugs, adverse effects may follow. Quality control varies between manufacturers, and because herbs are classified as dietary supplements, they are exempt from regulations governing standardization of ingredients. Physicians should ask all patients about their use of herbal medications and dietary supplements.

1. **Description** – The following herbs may be appropriate for patients who prefer herbs as an alterative to prescription analgesics or NSAIDs:
   A) White Willow Bark – There is some evidence of the effectiveness of Salix (willow) bark extract in chronic low back pain. A principal ingredient is salicin, with salicylic acid as the principal metabolite. In doses of 240 mg of salicin daily, willow bark extract is more effective than placebo in alleviating pain and improving scores of physical impairment. This dose is approximately equivalent to 50 mg of acetylsalicylate, which cannot alone account for its analgesic effect. It is well tolerated, with gastrointestinal complaints occurring no more frequently than with placebo. In patients at risk for GI problems from NSAID drugs, willow bark may be an appropriate option.
   B) Devil's Claw Root – Extract of Hapagophytum procumbens, with the common name of devil's claw root, have been used in parts of Europe for conditions of the musculoskeletal system, including osteoarthritis and low back pain. There is some evidence that it may relieve back pain more effectively than placebo, but functional improvement has not yet been shown. The doses used in clinical trials have consisted of 50 to 100 mg of harpagoside daily. Mild gastrointestinal upset has been reported at higher doses.
   C) Phytodolor – A standardized extract of Populus tremula (aspen), Fraxinus excelsior (European ash), and Solidago virgaurea (goldenrod), Phytodolor may have anti-inflammatory properties through inhibition of cyclooxygenase pathways. In doses of up to 180 drops per day in 3 divided doses, it has shown superiority to placebo in osteoarthritis and epicondylitis when pain and grip strength were evaluated. Adverse effects were not reported to exceed those of placebo.
   D) St. John's Wort – An herbal extract of the flowering plant Hypericum perforatum commonly used in the treatment of mild to moderate depression, St. John's Wort has been tested for effectiveness in neuropathic pain. There is some evidence that it lacks effectiveness on pain in polyneuropathy. The Department does not recommend its use as an alternative analgesic in chronic pain conditions. There is also some evidence that it is no more effective than placebo in the treatment of major depression. It should not be considered an antidepressant agent in patients requiring medical treatment of depression.
2. **Specific Drug Interactions** – Current regulations prohibit herb manufacturers from claiming that their products treat or prevent disease, but allow them to make claims about the product's effect on

body function. Because herbal products are biologically active, they may interact with prescription drugs and with one another. Much of what is known concerning drug interactions is based on case reports or case series, which commonly lack crucial documentation of concomitant medication use or positive identification of herbs involved.

A) Physicians should be aware that patients on warfarin should have international normalized ratio (INR) measured a week after starting to take any herbal preparation.

B) Ginkgo, ginseng, and garlic are commonly used for reasons unrelated to relief of pain; they interfere with platelet function, and patients who take them should have bleeding times monitored.

C) St. John's Wort should not be combined with an SSRI, since a serotonin syndrome may result. St. John's Wort induces the CYP3A4 hepatic enzyme, lowering levels of drugs metabolized by this system; these drugs include anticonvulsants, oral contraceptives, antiretroviral, and calcium channel blockers.

D) Kava, often used to alleviate anxiety, may potentiate benzodiazepine anxiolytics and produce excess sedation.

E) Herbal preparation usage during the perioperative period should be discouraged.

F.7.l Other Agents **Tramadol (Ultram)**

A) Description – An opioid partial agonist that is generally well tolerated, does not cause GI ulceration, or exacerbate hypertension or congestive heart failure.

B) Indications – Mild to moderate pain relief. This drug has been shown to provide pain relief equivalent to that of commonly prescribed NSAIDs.

C) Contraindications – Use cautiously in patients who have a history of seizures or who are taking medication that may lower the seizure threshold, such as MAO inhibitors, SSRIs, and TCAs. Not recommended in those with prior opioid addiction.

D) Side Effects – May cause impaired alertness or nausea. This medication has physically addictive properties and withdrawal may follow abrupt discontinuation.

E) Drug Interactions – Narcotics, sedating medications.

F) Recommended Laboratory Monitoring – Renal and hepatic function.

Baclofen (Lioresal)

A) Description – May be effective due to stimulation of Gamma Aminobutyric Acid (GABA) receptors.

B) Indications – Pain from muscle rigidity.

C) Side Effects – Development of ovarian cysts, exacerbation of psychotic disorders, may precipitate seizures in epileptics, dry mouth, sexual dysfunction.

D) Recommended Laboratory Monitoring – Renal function.

Mexilitene (Mexitil)

A) Description – An antiarrhythmic drug, which, like some anticonvulsive agents, may act on ion channels in neuronal tissue and reduce its pathological activity to a more stable level. Low concentrations may suffice to abolish impulses in damaged nerves, and mexilitene has been used successfully to treat neuropathic pain.

B) Indications – Neuropathic pain.

C) Major Contraindications – Heart disease (may depress ventricular function).

D) Dosing and Time to Therapeutic Effect – Titrate to therapeutic effect.

E) Major Side Effects – Tremor, light-headedness, coordination difficulties, and nausea are common dose-related adverse effects that may be reduced by taking with food.

F) Drug Interactions – Lidocaine.

G) Recommended Laboratory Monitoring – Hepatic function, CBC. Plasma levels may also be necessary.

Tumor Necrosis Factor-Alpha Blockers

A) Description – A variety of tumor necrosis factor (TNF) alpha blockers, including infliximab (a chimeric monoclonal anti- body directed against TNF-alpha), etanercept (a recombinant molecule comprising part of

the TNF receptor plus the constant region of human immunoglobulin G1 that binds to TNF-alpha), and adalimumab (an IgG1 monoclonal antibody that binds to TNF-alpha) are in widespread use for rheumatologic and other inflammatory disorders. The mechanism of action involves neutralizing the biological activity of TNF-alpha by binding to it and blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF alpha inhibitors are thought to have a role in the treatment of disorders such as inflammatory arthropathies which are non-occupational.

B) Indications – not indicated for treatment of occupational chronic pain conditions. TNF-alpha blockers are not recommended for treatment of radicular pain syndromes.

C) Major Side Effects – increased risk of severe (and potentially fatal) infections, demyelinating disease, lupus-like syndromes [associated with the production of anti-nuclear antibody (ANA) and antibodies to double-stranded DNA (dsDNA)], congestive heart failure, malignancies and cytopenias, rash, headaches, nausea, abdominal pain and pain at the injection site. Rare, aggressive and often fatal cases of T-call lymphomas have been reported in adolescent and young adult patients with Crohn's disease on infliximab concomitantly prescribed azathioprine or 6-mercaptopurine.

D) Drug Interactions – It is recommended that patients using them avoid vaccinations. Use in combination with NSAIDs may increase risk of thrombocytopenia.

DISCLAIMER

The State of Montana provides this segment of guidelines for practitioners and notes that decisions to adopt particular courses of actions must be made by trained practitioners on the basis of the available resources and the particular circumstances presented by the individual patient. Accordingly, the State of Montana disclaims responsibility for any injury or damage resulting from actions taken by practitioners after considering these guidelines.