Chronic Pain Management Guideline Team

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Managing Chronic Non-Terminal Pain in Adults
Including Prescribing Controlled Substances

Objective: To provide a systematic framework for providers to evaluate and manage patients with chronic, non-terminal pain with special attention to specific principles of opioid management.

Key Aspects & Recommendations

Diagnosis. Chronic pain is different from acute pain. It requires comprehensive physical, functional, behavioral and psychosocial assessment.

- **History.** Pain history should include a detailed description of symptoms, initiating injury or event, detailed treatment history, pain-related disability, psychiatric comorbidity, social stressors and barriers to care (e.g., insurance, education, pharmacy access, support systems). *[1D]**
- **Exam and laboratory findings**. Physical exam findings and radiographic studies may identify opportunities for procedural interventions or surgery, but these findings often do not correlate with symptom severity, degree of disability or appropriate intensity of treatment. *[IID]**
- **Opioids and addiction risk**. If opioid analgesics have been used or are being considered, dependence and addiction risk should be assessed through careful personal and family history, review of outside records and assessment of illicit or prescription medication misuse. Check your State's prescription monitoring program (PMP) and perform a urine screen by combination of enzyme immunolinked assay (EIA) and gas chromatography/mass spectroscopy (GCMS) prior to prescribing and at least yearly for patients given chronic opioid therapy. *[ID]**

Treatment. Treatment must be multi-dimensional, not only pharmacological. Effective therapy should control chronic pain in order to improve function at work, home, socially and in pleasurable pursuits. Complete analgesia is not possible for many patients.

- **Expectations.** Patient and provider expectations should be articulated clearly at the beginning of treatment and reviewed regularly. A written controlled substance treatment agreement is appropriate for most patients treated with ongoing daily opioid therapy. *[1D]**
- **Non-pharmacologic therapies.** Begin with these therapies (e.g., exercise, heat, sleep hygiene).
- **Medical treatment.** Choose drugs based on presumed pain type and the patient's comorbidities.
  - NSAIDs and/or acetaminophen can be effective for chronic musculoskeletal or arthritis pain. In older adults, NSAIDs and COX-2 inhibitors should be used rarely and with caution, monitoring for GI and renal toxicity, hypertension, and heart failure. *[1D]**
  - Adjuvant medications. Tricyclics (TCAs), SNRIs (duloxetine) and second generation anticonvulsant medications are effective for specific neuropathic pain states. *[1A]** For centralized pain/fibromyalgia, TCAs, SNRIs, gabapentin and pregabalin are effective. *[1A]**
  - Opioid analgesics can be safe and effective for *some* patients with chronic non-terminal pain *[I1B]**, but require careful patient selection, titration and monitoring. Scheduled, long-acting opioids, (morphine ER, or methadone, buprenorphine) are preferred for continuous treatment *[ID]**. *OxyContin* has a higher risk for misuse or diversion. Avoid long-term, daily treatment with short-acting opioids and opioid combinations (e.g., *Vicodin, Norco, Percocet*). For "as needed" (PRN) dosing, prescribe small amounts expecting monthly (not daily) use.

Follow-up. Reassessment should center on achieving shared treatment goals and improved function.

- **Frequency.** Patients should be seen frequently (weekly to monthly) during initial evaluation and treatment, and at least quarterly thereafter. *[1D]**
- **Assessment.** Reassess physical, psychological and social domains regularly, particularly progress toward improved *function. [1D]**
- **Ineffective treatments.** Stop ineffective treatment modalities (e.g., NSAIDs, **opioids**). *[1D]**
- **Opioids and problem use.** Monitor patients receiving opioid analgesics for misuse with checks of State registries (PMP) for prescription fills (e.g., in Michigan called MAPS) and random urine comprehensive drug screens by EIA-GCMS. *[1ID]**
- **Referral.** Referral to pain management specialist should be considered for failure to achieve treatment goals, intolerance of therapies, need for interventional management, need for multidisciplinary treatment, need for excessive opioid doses, suspicion of addiction, or opioid misuse. *[1B]**

*** Strength of recommendation:**
I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Levels of evidence reflect the best available literature in support of an intervention or test:
A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

Table 1. Evaluation and Management Checklist for Patients with Chronic Pain

Initial Visit (See outline in Appendix A)

Assessment

Detailed pain history: quality, location, radiating patterns, exacerbating factors, associated injuries/events at original onset

Pain treatment history: consultants seen, interventions or surgeries performed, medications tried and their perceived effectiveness, rehabilitation therapy completed, reasons for leaving previous providers

Complete psychosocial history: psychiatric evaluations and/or diagnoses, family status and living arrangements, social support, employment history (including workers compensation claims), educational level, financial resources and stressors, history of physical or sexual abuse

Substance history: alcohol, illicit drugs, smoking, heavy caffeine use

Legal issues: DUI or substance-related violations, pending litigation related to pain (employer, car accident, disability, etc.)

Family history: chronic pain syndromes, psychiatric illness, disability, substance abuse, alcoholism

Verification: review available local and outside documentation to assess consistency of history provided

Functional status: capacity and disability in work, family and recreational domains

Physical examination and diagnostic testing: as appropriate

For patients being considered for, or already receiving, chronic daily opioid therapy: check comprehensive drug screen = EIA + GCMS (at UM = DRUG COMP = Drug6 (i.e. EIA) + GCMS) and search State prescription monitoring programs (PMP) for opioid prescriptions (e.g., MAPS search in Michigan [https://milogintp.michigan.gov/eai/tplogin/authenticate?URL=/], OARRS in Ohio [www.ohiopmp.gov]).

Management Plan

Goals: establish with patient realistic treatment goals for functional improvement or maintenance, not analgesia alone

Lifestyle interventions: exercise, weight management, smoking cessation, sleep hygiene.

Psychiatric co-morbidities: manage (treat or refer), e.g., depression, anxiety, molestation, substance abuse, personality disorders, schizophrenia, PTSD

Physical modalities: consider physical therapy, massage, acupuncture, transcutaneous electric nerve stimulation (TENS) units

Medications: select based upon presumed pain type (Table 3):

Somatic (nociceptive) pain: Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs – caution in older adults) and opioids (long-acting preferred); trial of adjuvants (see Table 3) for refractory symptoms.

Neuropathic pain: Serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anticonvulsants, lidocaine patch, tramadol and opioids. *(SSRIs and NSAIDs often ineffective.)*

Centralized pain/Fibromyalgia: TCAs (amitriptyiline, cyclobenzaprine), SNRIs (duloxetine) and alpha-2-delta ligands (pregabalin and gabapentin) are effective for conditions such as fibromyalgia. Serotonin-selective reuptake inhibitors (SSRIs) can also be useful. *(Opioids are **not** indicated.)*

If initiating opioid therapy:

Assess risk for addiction (see Table 4)

Present opioids as a tool to help reach functional improvement goals; be clear that opioids will be continued *only* if they contribute to functional improvement or maintenance

Establish prescribing practices: one prescriber/one pharmacy, no after-hours refills, no early refills without appointment, compliance with adjuvant therapies, no Emergency Department visits for pain medications, random urine drug screens, required follow-up at scheduled intervals. See model "Controlled Substance Treatment Agreement" in Appendix B.

Referral: consider interventional pain evaluation for refractory or geographically distinct syndromes (e.g., complex regional pain syndrome [CRPS], persisting radicular pain, chronic spasticity, localized post-traumatic neuralgia).

Follow-up Visits (weekly to quarterly) (See outline in Appendix A)

Adherence: determine level of adherence to management plan (medications, physical therapy, lifestyle interventions, etc.)

Progress: document progress toward functional goals, and pain response

Adverse effects: evaluate for adverse effects of medications (NSAIDs, adjuvants, opioids)

For patients receiving opioids, assess addiction behavior: monitor 'red flag' drug-taking behavior (Table 4). Consider written pain management agreement for patients at risk (see Appendix B), repeat checks of the state PMP periodically, random urine screening with EIA + GCMS.

Review management plan: refine functional goals, titrate effective medications, stop ineffective medications (including NSAIDs and opioids), modify non-interventional modalities, review expectations

Therapeutic relationship: evaluate for appropriate boundaries

Referral: consider referral to appropriate specialist(s) (e.g., Comprehensive Pain Management Center) if evidence of addiction behavior, failure to reach functional goals despite adherence to plan, rapidly escalating or very high dose opioid need, poor psychological adjustment to symptoms.

Table 2. PEG Scale Assessing Pain Intensity and Interference (Pain, Enjoyment, General Activity)

1. What number best describes your pain on average in the past week?

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Computing the PEG Score.

Add the responses to the three questions, then divide by three to get a mean score (out of 10) on overall impact of points.

Using the PEG Score.

The score is best used to track an individual's changes over time. The initiation of therapy should result in the individual's score decreasing over time.

Source.

Krebs, E. E., Lorenz, K. A., Bair, M. J., Damush, T. M., Wu, J., Sutherland, J. M., Asch S, Kroenke, K. (2009). Development and Initial Validation of the PEG, a Three-item Scale Assessing Pain Intensity and Interference. Journal of General Internal Medicine, 24(6), 733–738. http://doi.org/10.1007/s11606-009-0981-1

Table 3. Selected Medications for Chronic Pain

Generic Name	Brand Name	Effective Dose	30 Day Cost * Generic/Brand	Indications	Comments
Acetaminophen	Tylenol	325 mg Q 4-6 hours OR 500 mg Q 6 hours Typical: 500 mg Q4 hours Q 6 hours Max: 10 tablets of regular strength (325 mg) or 6 tablets of extra strength (500 mg) /day	$10 / $30	Osteoarthritis *[IA]* Other musculoskeletal pain *[IIB]*	Effectiveness improves with scheduled (vs. prn) dosing. Very useful with other adjuvants, as well as opioids
Non-Steroidal Anti-inflammatories (NSAIDs)					
Ibuprofen	Advil, Motrin	Initial: 200 or 400 mg TID Typical: 600 mg TID Max: 2400 mg in divided doses	$13 / $50	Osteoarthritis and musculoskeletal pain *[IA]*	Long-term use associated with GI and renal toxicity; ongoing NSAID therapy should be re-evaluated regularly and stopped if ineffective. Extreme caution needed for older adults; use PPI with NSAID or with COX-2/aspirin . NSAID use in patients with heart disease or its risk factors increases overall risk of heart attack or stroke.
Naproxen	Aleve	Initial: 225 – 550 mg BID Typical: 375 mg BID Max: 500 mg BID	$13 / $13		NSAID use in patients with heart disease or its risk factors increases overall risk of heart attack or stroke.
Opioids (listed in order of increasing potency) [1]					
Tramadol [Schedule 4]	Ultram	Initial: 25 or 50 mg QID, titrate slowly Typical within 50–100 mg QID Max: 400 mg daily divided BID to QID	$250 / $320	Neuropathic pain *[IA]* Fibromyalgia *[IA]* Somatic pain *[1A]*	Tramadol is a structurally atypical opioid; acts principally on opioid receptors. Dependence and withdrawal can occur. Overdose can cause respiratory depression / seizures / coma.
Codeine/Acetaminophen [Schedule 3]	Tylenol #3: 30/300 mg Tylenol #4: 60/300 mg	Initial: 1 or 2 Q4 hours PRN short-term or breakthrough pain. Typical: 1 Q 6 hours	$48 / $240- $60 / $420	Somatic and neuropathic pain *[IIB]* *Not for chronic daily use* as a primary opioid. Should be used PRN only, with adjuvants and non-medication therapies *[IIB]*. *Should not be used as "rescue" for high potency opioids below.*	Avoid total acetaminophen doses over 3000 mg/day. Codeine products are less euphoric and may have lower abuse risk than hydrocodone, with a lower street value if diverted. Codeine is detected more readily than hydrocodone on routine follow-up urine drug screens. Codeine is occasionally less well-tolerated.

[1] The FDA provides safety warnings on the entire class of opioids:

- Opioids can interact with antidepressants and migraine medicines to cause serotonin syndrome. Patients taking an opioid along with a serotonergic medicine should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea
- Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of cortisol. Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure.
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility

Table 3. Selected Medications for Chronic Pain, continued

Generic Name	Brand Name	Effective Dose	30 Day Cost * Generic/Brand	Indications	Comments
Opioids, continued (listed in order of increasing potency)					
Hydrocodone/ acetaminophen [Schedule 2]	Norco or Lortab: 5/325, 7.5/325, 10/325 mg Vicodin: 5/300, 7.5/300, 10/300 mg	Initial: 1 or 2 Q4 hours PRN short-term or breakthrough pain. Typical: 1 Q 6 hours	$45 / $525-800 $45 / $125-180		The recommended dose of acetaminophen is 325 mg / dose, with a daily limit of 3000 mg per 24 hours * These products should be avoided
Morphine Sulfate [Schedule 2]	Tablets: 10, 15, 30 mg Liquid: various concentrations	Initial: 10 – 15 mg Q4 hours PRN Typical breakthrough dose: 10% of total daily morphine equivalent, available Q4 h PRN	$23 / $840	Somatic and neuropathic pain. *Not for chronic daily use* as a primary opioid. Should be used either PRN with adjuvants, or as "rescue" for long acting morphine	Useful for patients requiring stronger opioid therapy, those with acetaminophen or hydrocodone intolerance or swallowing difficulties.
Morphine ER [Schedule 2]	MS Contin: dosed BID or TID. Kadian: dosed Q12-24H	Initial: 15 mg BID or 30 mg QD Typical: 30 or 60 mg total per day Max: ≤ 100 total mg per day	$270 / $690	Somatic and neuropathic pain [IIB]	Long-acting, available generically and covered by all insurances.
Oxycodone [Schedule 2]	5, 10, 15, 30 mg	Initial: 5-10 mg Q4 hours PRN Typical breakthrough dose: 10% of total daily long-acting opioid equivalent, available Q4 h PRN	$50 / $650	Somatic and neuropathic pain. Not for chronic daily use as primary opioid. Should be used either PRN with adjuvants, or as "rescue" for long acting oxycodone.	Alternative for patients intolerant to hydrocodone and morphine, may have higher abuse potential. Will not be detected on many standard urine toxicology screens without separate testing
Oxycodone / acetaminophen [Schedule 2]	Percocet: 2.5/325, 5/325, 7.5/325, 7.5/325, 10/325, 10/325 mg	2.5-10mg Q6 hours	$75 / $1823		
Oxycodone ER [Schedule 2]	Oxycontin: 10, 15, 20, 30, 40, 60, 80 mg	Initial: 10 mg BID Typical: 20 mg PO BID Max: ≤ 60 total mg/day	$270 / $410	Somatic and neuropathic pain [IIB]	Alternative for patients intolerant to morphine. Duration of action varies, has high diversion value.
Oxymorphone [Schedule 2]	Opana: 5, 10 mg	Initial: 5 mg every 4 hours, titrate to effect	$480 / $1200	Somatic and neuropathic pain [IIB] Alternative for patients intolerant to morphine	Not recommended – nothing unique about it, expensive, highly sought for diversion

Table 3. Selected Medications for Chronic Pain, continued

Generic Name	Brand Name	Effective Dose	30 Day Cost * Generic/Brand	Indications	Comments
Opioids, continued (listed in order of increasing potency)					
Oxymorphone ER [Schedule 2]	Opana ER: 5, 7.5, 15, 10, 20, 30, 40 mg	Initial: 5 mg every 4 hours, titrate to effect	NA / $508	Somatic and neuropathic pain *[IIB]* *Alternative for patients intolerant to morphine*	Not recommended as above
Hydromorphone [Schedule 2]	Dilaudid	Initial: 1-2 mg Q4 hours PRN Usual: 2-4 mg Q4 hours PRN Max: <6 mg Q4 hours PRN	$30 / $635	Somatic and neuropathic pain. *[IIB]* *Not for chronic daily use* as a primary opioid. Should be used either PRN with adjuvants, or as "rescue" with transdermal fentanyl or methadone, when morphine and oxycodone are not tolerated or contraindicated.	Very potent opioid, with higher abuse potential than other opioids. Expensive, has high diversion value—should be used only when other opioids are not tolerated or are contraindicated such as morphine in CKD. Long-acting versions not recommended – very expensive.
Methadone [Schedule 2]	Dolophine	Initial: Dosing requires experience as conversion from other opioids is highly variable. Usual starting dose for patients without high tolerance, 2.5 or 5 mg BID or TID Typical: 15 or 30 mg divided into BID or TID Max: ≤ 20 mg/day divided into Q12H or Q8H dosing (per CDC)	$28 / $40	Somatic and neuropathic pain *[IIB]*	Long-acting, effective, dose escalation less likely with chronic use, relatively inexpensive, covered by most insurances. Prolonged QTc possible at higher doses (usually >100 mg/d), and with drug interactions (complete list at www.qtdrugs.org).
Fentanyl Patch [Schedule 2]	Duragesic	Initial: 12 or 25 mcg/hr Max: ≤ 50 mcg/hr *Breakthrough opioid should be available as morphine sulfate (or hydromorphone or oxycodone, if morphine allergic). Consult conversion table for proper dosing.	$50 / $430	Somatic and neuropathic pain *[IIB]* Not indicated for initial therapy, particularly in older adults.	Useful when PO route not available. Is lipophilic, requires some subcutaneous fat for proper absorption. Limited as dose escalation often occurs due to rapid tolerance, very expensive, insurance coverage varies
Buprenorphine [Schedule 3]	Suboxone Subutex Zubsolv Belbuca (FDA approved for pain) Butrans (transdermal) – also approved for pain	Varies; specialist prescribing only, for initiation of SL Typical: 2/0.5 mg tablet TID Butrans start 5-10 mcg weekly patch	$150 / $400 $1060	Somatic and neuropathic pain [IIB]	Effective, safe, low misuse potential, highly useful in setting of chronic pain, addiction, or hyperalgesia, Very expensive, generic tablets less expensive, off label use may not be covered by insurance for "pain" indication.

Table 3. Selected Medications for Chronic Pain, continued

Generic Name	Brand Name	Effective Dose	30 Day Cost * Generic/Brand	Indications	Comments
Antidepressants					
Amitryptiline Nortriptyline Desipramine Doxepin	Elavil Pamelor Sinequan Norpramin	Initial: 10 or 25 mg at HS; may titrate by 10 or 25 mg every 5-7 days. Typical: 50 mg nightly Max: < 150 mg.	$8 / $643	Neuropathic pain *[IA]* Fibromyalgia *[IA]* Other pain syndromes *[IIB]*	Amitriptyline is strongly anti-cholinergic—should NOT be prescribed for elders. Doxepin and nortriptyline are recommended alternatives.
Duloxetine	Cymbalta	Initial: 20 or 30 mg QAM Typical: 30 or 60 mg QAM or divided BID Max: 60 mg BID	$15 / $240	Neuropathic pain *[IA]* Fibromyalgia *[IA]*	Less effective than TCAs, but fewer side effects. Not covered by all insurances for pain indications. Side effects include nausea, sedation, dry mouth and dizziness. BID dosing often requires payor prior authorization. Duloxetine is best studied SNRI; venlafaxine more limited. Very little data on milnacipran.
Venlafaxine	Effexor	Initial: 37.5 to 75 mg BID or once daily (extended release) Typical: 150 mg daily Max: 225 mg daily	$180 / $417	Neuropathic pain *[IA]*	Effectiveness not as well supported in the literature
Milnacipran	Savella	Initial: 12.5 mg QD Typical: 50 mg BID Max: 100 mg BID	NA / $172-344	Fibromyalgia [IA]	
Fluoxetine	Prozac	Initial: 10 or 20 mg dose daily Typical: 20-40 mg daily Max: 80 mg daily (titrate Q4-6 weeks)	$5-9 / $448-896	Fibromyalgia *[IA]* Neuropathic pain *[IIIA]*	Indicated for fibromyalgia and centralized pain syndromes only; fluoxetine and other SSRIs are *not* effective for peripheral neuropathic pain.

Table 3. Selected Medications for Chronic Pain, continued

Generic Name	Brand Name	Effective Dose	30 Day Cost * Generic/Brand	Indications	Comments
Anticonvulsants					
Gabapentin	Neurontin	Initial: 300 mg at HS, titrate over two days to 300 mg TID increasing to effect or side effects. Typical: 300 or 600 mg TID.	$11-17 / $480-900	Neuropathic pain *[IA]* Fibromyalgia [IA]	Dosing regimens are complex, need careful instruction and follow-up. Common side effects include fatigue, dizziness, nausea and sedation
Pregabalin	Lyrica	Initial: 75 mg daily Typical: titrate to 150 mg PO QHS for peripheral neuropathy, 225 mg PO BID for fibromyalgia, 300 mg PO BID for post-herpetic neuralgia	NA / $446	Neuropathic pain *[IIB]* Fibromyalgia *[IA]*	Common side effects: fatigue, dizziness, drowsiness, nausea, weight gain. Very expensive.
Carbamazepine	Tegretol	Initial: 200 mg daily Typical: titrate weekly to 400 mg TID	$60 / $214	Trigeminal neuralgia *[IA]* Neuropathic pain *[IIB]*	Rarely used. May cause diplopia, nausea dizziness. Requires periodic CBC to monitor for aplastic anemia.
Lamotrigine	Lamictal	Initial: 25 mg daily, titrate slowly Typical: within 100–150 mg daily Max: 400 mg daily	$7 / $470	Trigeminal neuralgia *[IB]* Neuropathic pain *[IIC]*	Second-line treatment for trigeminal neuralgia, not indicated for other pain states. Can cause nausea, dizziness, constipation. Rare severe rash possible.
Other Options					
Transdermal lidocaine patch	Lidoderm	Initial: 1 patch daily Typical: 1 patch daily Max: 3 patches to affected area, applied for 12 hours per day	NA / $405	Post-herpetic neuralgia *[IA]* Other neuropathic pain *[IIB]*	Ideal for discrete pain syndromes (post-herpetic neuralgia, proximal radicular pain, post-traumatic neuropathy).
Capsaicin cream	Zostrix	Initial: 0.025% applied three to five times daily to affected area Max: 0.075% applied three to five times daily affected	$7 / $12	Post-herpetic neuralgia *[IA]* Musculoskeletal pain *[IC]*	Few to no systemic side effects, but local burning and irritation often limit frequency and/or strength of application

*Cost is listed for the underlined dose and frequency in the "Effective Dose" column. If a range of doses/frequencies is underlined, the corresponding range of costs is presented. If more than one brand is listed in the "Brand Name" column, costs are presented for each brand at the indicated dose/frequency.

Cost = Average Wholesale Price minus 10%. AWP from Red Book Online 5/17. For generic drugs, Maximum Allowable Cost plus $3 from BCBS of Michigan MAC List, 5/17.

Table 4. Considerations for Initiation or Continuing Chronic Opioid Therapy

Indications	Cautions	"Red Flag" Behaviors	Contraindications
Somatic or neuropathic pain Malignant origin of pain Non-malignant pain causing dysfunction including cessation of usual activities or employment Failure of non-opiate treatments including adjuvant medications Non-interventional treatments (lifestyle alteration, physical therapy, complementary medicine therapies) unsuccessful Interventional treatments not an option or unsuccessful Records reviewed verify the patient's history	Non-malignant origin of pain Patient refuses to attempt non-opioid approaches to therapy; "red flag" behaviors Untreated psychological comorbidity Addiction risk: Active alcohol or illicit substance use; family history of chronic pain, alcohol or substance abuse. (See Opioid Risk Tool, Appendix A.3) MAPS or urine comprehensive drug screening results positive for non-prescribed or illicit substances, or the *absence* of a prescribed medication	Overwhelming focus on opiates during visits rather than the underlying disease process, unwilling to consider non-opioid therapy Three or more requests for early refills Multiple office contacts about opiates Reports of lost, spilled or stolen opiates Multiple sources of opiates Concurrent alcohol or substance abuse (See text for detail)	Centralized pain syndrome – opioid not indicated Forgery of prescriptions, evidence of diversion of controlled substances, illegal activities with prescriptions

Table 5. Sample State (Michigan) Guidelines for the Use of Controlled Substances for the Treatment of Pain

Evaluation of the Patient. Complete medical history and physical examination

Treatment Plan. Clear objectives that will be used to determine treatment success; plan for further testing

Written treatment agreement. Should be strongly considered for patients receiving chronic daily opioid therapy, and include:

- Risks/benefits of therapy
- One physician and one pharmacy shall be utilized
- Urine/serum monitoring specimens are given upon request
- Timing of prescription refills
- Reasons for which drug therapy may be discontinued, including violations of the agreement

Periodic Review. At reasonable intervals, there should be:

- A review of course of treatment
- Any new information about the etiology of the pain
- Determination of progress toward the stated treatment objectives
- Monitoring of patient compliance.

Content of Medical Records. Accurate and complete medical records must include

- Medical history and physical examination
- Diagnostic, therapeutic and laboratory, consultation results
- Treatment objectives
- Discussion of risks and benefits
- Treatments and medications (including dates, type, dosage and quantity prescribed)
- Instructions and agreements
- Periodic reviews

Clinical Background

Clinical Problem and Current Dilemma

Pain is the most common reason for which individuals seek health care. Effective pain management is a core responsibility of all clinicians, and is a growing priority among providers, patients and regulators. Despite increased attention, many patients' pain remains under-treated or incorrectly treated.

The prevalence of chronic pain in the US is difficult to estimate, but its impact is profound. Fifty to eighty million Americans suffer daily pain symptoms at a cost of approximately $90 billion annually, and chronic pain is the leading cause of long-term disability in the US. These numbers will only increase as our population ages, amplifying the need for effective, accessible interventions to manage chronic pain and preserve function.

While multidisciplinary subspecialty pain services are increasingly available, primary care providers will continue to manage the majority of patients with chronic pain. This care can be challenging and resource-intensive, and many clinicians feel reluctant or ill-equipped to provide it. This guideline is intended to support clinicians in evaluating and managing patients with chronic pain and, if controlled substance therapy is appropriate for a patient, offer specific guidance and tools for managing these patients in a safe and effective fashion.

Rationale for Recommendations

General Approach

Acute and chronic pain are fundamentally different processes. Acute pain is a protective response to tissue injury and is usually nociceptive, or signaled to the brain via normally functioning afferent neural pathways. Common anti-inflammatory and opioid medications work at different levels in this signal chain to relieve acute pain. Effective acute pain management has been shown to improve both patient satisfaction and treatment outcomes and reduce the risk of developing chronic pain**.**

Chronic pain is not merely acute pain that does not resolve. In chronic pain patients, abnormal peripheral or central neural function is present. For example, repeated nociceptive stimulation or direct nerve injury can result in neuropathic pain, which is characterized by dysfunctional nerve signaling, increased neural irritability, hyperalgesia (decreased pain threshold), allodynia (heightened pain response to usually non-painful stimuli), and decreased responsiveness to many common pain medications.[3, 4] As a result, simply extending acute pain treatments – rest, anti-inflammatory medications, short acting acetaminophen-opioid combinations, etc. – often does not effectively manage chronic pain and, in the case of the use of opioids, may worsen pain for some patients.

Perhaps more importantly, chronic pain also has significant cognitive, affective and interpersonal components. Patients with chronic pain are more likely to report depression, anxiety, poor quality-of-life and financial stress, and are five times more likely to use health care resources than patients without chronic pain. Many patients' chronic pain is also unlikely to resolve, challenging providers to create long-term management strategies to maximize function and limit disability.

Effective chronic pain management thus requires attention to each patient's physical, psychological, behavioral and social needs. Key components include:

- Detailed symptom history and physical exam
- Identifying and treating sources of pain, if possible
- Functional assessment and documentation
- Screens for important co-morbidities (psychiatric diagnoses, smoking, addiction risk, history of disability/legal action, etc.)
- Setting patient-centered treatment goals for improved or maintained function, not analgesia alone.
- Treatment strategies that combine one or more of the following: medications, physical/occupational therapy modalities, behavioral techniques, interventional procedures, and mental health treatment.
- Clear expectations for patient's involvement in a comprehensive plan, including pain management agreements, or 'contracts', as appropriate (Appendix B) and the patient's acceptance of self-management strategies for pain control
- Careful and systematic follow-up to monitor treatment safety and progress toward functional goals
- Identifying pain medication problems (diversion for illicit use or sale, addiction, lack of therapeutic effect), and prompt action to resolve them
- Compliance with state and federal laws regarding prescribing pain medications

Table 1 presents an overview of topics for evaluation and management. Appendix A presents more detailed outlines of topics to be addressed in the initial evaluation of chronic pain and in follow-up/monitoring visits.

The multidimensional nature of chronic pain and variations in pain syndromes based on patient demographic factors (e.g., race, gender, age) render its assessment and management challenging. Several patient populations are particularly vulnerable to inadequate pain assessment and limited access to quality pain care. Structural barriers (e.g., insurance, pharmacy location) affect access. Less attention may be paid to the pain reports of women, children, minorities, older adults, cognitively impaired patients, low socio-economic status individuals, and other patients with difficulty communicating. Difficulties in accessing quality pain care, poor pain assessment, and ultimately poor pain management have direct implications on overall health and well-being (i.e., physical, emotional, and social health).

Chronic Pain Assessment

Acute pain and chronic pain are fundamentally different processes and must be evaluated differently. Acute pain assessment seeks to identify its underlying injury or disease and treat it, thereby eliminating both the pain and the need for pain management. Pain *intensity*, *quality* and *location* are core to acute pain assessment, and reduction of pain intensity is the primary outcome measure of acute pain interventions.

In contrast, chronic pain is the disease itself, and, in many cases will not resolve. Chronic pain evaluation thus focuses on assessing **function** and co-morbidities**,** rather than merely intensity, quality and location. *Pain disability* refers to the impact of chronic pain on function, and should be assessed as a basis for setting treatment goals. *Pain beliefs* are important to evaluate as well, particularly for patients who have had difficulty adjusting to living and with chronic pain. Additionally, a detailed *pain and treatment history* is necessary to identify potential problems and opportunities for success in ongoing management.

Pain intensity and functional impact. Pain scores, though useful in assessing and treating acute pain, have a *limited role* in treating chronic pain. While chronic pain intensity is important to assess, patients should understand that reducing pain intensity will not be the sole focus of evaluation or management. This requires both a shift in expectations for many patients accustomed to an acute pain management model, as well as a direct, consistent approach from providers.

Pain scales commonly used to assess acute pain are not adequate for assessing chronic pain. Ten-point pain scales that assess only pain severity/intensity (various single item written or visual scales) do not adequately assess broader functional effects of chronic pain.

For chronic pain, the 3-item PEG Scale (see Table 2) is commonly used to assess intensity and functional impact. It provides a simple, multidimensional measure of Pain intensity, Enjoyment of life, and interference with General activity. The PEG score is best used to track an individual's changes over time. The initiation of therapy should result in the individual's score decreasing over time. Scores for specific individuals are not directly comparable since individuals will vary on which aspect (pain, enjoyment, general activities) is the most important problem.

Complete analgesia (i.e. achieving a pain assessment score of 'zero') is not possible for most patients with chronic pain. The score should be used **in conjunction** with functional assessment to set treatment goals and monitor treatment effectiveness. Analgesia without improved function is not a legitimate treatment goal.

Pain quality. Eliciting descriptions of pain quality may help identify potential types/sources of pain. Musculoskeletal or myofascial pain is often described as "aching", "throbbing" or 'tight'. Primarily neuropathic pain can be described as 'shooting'. burning or 'electric". Visceral pain may be

'gnawing', 'deep' and difficult to localize. Such associations are not absolute and many patients will report more than one type of pain, but pain quality assessment is often helpful in context of the broader evaluation.

Pain location. Pain drawings are frequently included as part of a thorough pain evaluation. A drawing on an anatomical outline can provide a quick impression of the breadth and character of the presenting pain complaint. However, the statistical association between quantitative ratings of pain drawings and other aspects of pain disability are inconsistent, so clinical conclusions (e.g., contribution of psychological causation for pain and disability) should be avoided.

Pain beliefs and response to pain. A number of cognitive variables or 'pain beliefs' have been identified that influence the intensity, distress and dysfunction of chronic pain experience. In many studies, these factors have been found to be better predictors for pain intensity, mood disturbance, and self-reported disability among cohorts of chronic pain sufferers than medical and demographic indices. Relevant pain beliefs include:

- Perceived control over pain
- Knowledge of diagnosis
- Causal attributions regarding the etiology of pain
- Treatment expectations
- Fear of movement and (re)/injury (often related to a belief that the pain stimulus reflects progressive physiologic harm and damage)
- Pain "catastrophizing" (belief that pain experience overwhelms capacity to function)
- Perceived capacity to function with pain,
- Who is responsible for pain control/relief (provider vs. patient)
- Availability of a medical cure for pain

Formal pain belief inventories are available and typically administered in a referral setting. For patients who display concerning pain beliefs, consider pain psychology evaluation.

Risk for poor adjustment to pain. Pain-related anxiety and fear is a key determinant of poor adjustment to chronic pain. Fear of pain generates avoidance of physical activity due to concerns that movement will increase pain and cause further physical harm or impairment. In fact, fear-avoidance beliefs hold a stronger relation to disability and poor pain rehabilitation outcomes than does pain intensity. A number of scales assess fear-avoidance beliefs and associated pain anxiety and all demonstrate adequate reliability and validity. The Tampa Scale for Kinesiophobia is easy to administer for the interested clinician and is available at www.tac.vic.gov.au/upload/tampa_scale_kinesiophobia.pdf.

Use of either the SOPA assessments or Tampa Scale may not be practical in a routine office schedule, and is likely to be most useful for subsets of primary care patients with significant functional distress. Consultation or co-management with a pain psychologist or experienced mental health provider should be strongly considered in these situations.

Pain and treatment history. Many patients with chronic pain have long and sometimes complex treatment histories. These histories should be elicited in full, including:

- Details of treatment success or failure ("What has worked best to manage your pain?", "What has not worked?");
- Relevant surgeries and hospitalizations (particularly for pain control);
- Perceived origin of pain (work injury, car accident, trauma) and any associated disability or legal actions; and
- Personal or family history psychiatric, substance abuse, or other significant medical problems.

These details should be verified by reviewing internal records, obtaining outside documentation, and contacting other treating providers as necessary. For patients receiving (or being considered for) opioid analgesics, addiction risk should be further evaluated (Table 4). Consider formal use of the Opioid Risk Tool (see Appendix A.3). Illicit and prescription substance use assessment should also be screened for through comprehensive urine drug testing and a check of your State's controlled prescription monitoring program, looking for evidence of medication non-adherence, misuse, or diversion.

Non-Pharmacologic Treatment

Physical therapy. Physical therapy involves the use of modalities, manual techniques, therapeutic exercise and patient education in the treatment of a wide variety of musculoskeletal disorders. Modalities, such as hot packs, ice, ultrasound, transcutaneous electrical stimulation (TENS), iontophoresis and traction are useful in decreasing pain and increasing tissue extensibility, thereby facilitating stretching and mobilization. Manual therapy is useful in optimizing proper mobility, alignment and joint biomechanics. Therapeutic exercise, consisting of stretching, strengthening, conditioning and muscle re-education is useful in restoring joint range of motion, muscle strength, endurance and to correct muscle imbalances. When treatment goals have been met or progress plateaus, formal therapy is discontinued and the patient continues with an independent daily home exercise program.

Psychological intervention for chronic pain. Current psychological interventions for chronic pain are based on recent advances in our understanding of the complexity of pain perception. Pain is influenced by a wide range of psychosocial factors, such as emotions, sociocultural context, and pain-related beliefs, attitudes and expectations. Chronic pain that persists for months or years often initiates a progressive loss of control over numerous aspects of one's psychological and behavioral function. A biopsychosocial model is now the prevailing paradigm for interventional strategies designed to treat chronic pain and this model places particular emphasis on addressing cognitive-behavioral factors pertinent to pain experience.

The strong evidence for the contribution of psychosocial factors in pain experience, particularly in explaining disability attributed to pain, has led to the development of mulitidisciplinary pain rehabilitation programs (MPRPs) that simultaneously address physical, psychological and functional aspects of chronic pain disorders. For some patients, referral for individual behavioral and psychological intervention may be all that is required.

Pharmacologic Treatment

Several classes of medications can be part of effective chronic pain management, including acetaminophen, non-steroidal anti-inflammatory medications (NSAIDs), and opioid derivatives. In addition, 'adjuvant' medications, such as certain anti-depressants and anticonvulsants, may augment other analgesics or may be used alone for selected patients. Many successful regimens combine different types of pain medications to increase effectiveness and limit risk of toxicity.

Acetaminophen. Acetaminophen is among the most well-known analgesics, yet its mechanism of action remains unclear. It is roughly equivalent in potency to aspirin, and should be considered a first-line agent to treat mild to moderate chronic musculoskeletal pain (e.g., osteoarthritis). While 'prn' dosing is appropriate for acute or periodic symptoms, patients with chronic pain should take acetaminophen at regular intervals (every 6 hours) throughout the day. Total acetaminophen doses for healthy adults in excess of 3 grams/day are not advised.

Although acetaminophen is generally safe and well tolerated by most patients, excessive doses can cause severe or even fatal hepatic injury. Older adults and patients with active liver disease or increased risk (e.g. concurrent carbamazepine, zidovudine, isoniazid or high-dose phenytoin administration; heavy alcohol use; cachexia, etc.) should be monitored closely while taking acetaminophen regularly. Such patients should be limited to a total of 3 grams daily.

Non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are the most widely used medications in the US. Their efficacy in treating mild to moderate acute pain is well-established, though no specific agent has been shown to be more effective than any other. Long-term NSAID therapy for chronic pain may benefit some patients, particularly those with defined musculoskeletal problems who are at low risk for complications.

However, chronic NSAID use also poses significant risks for gastrointestinal bleeding, renal insufficiency and platelet dysfunction. Hazards are magnified for patients with known peptic ulcer disease, renal insufficiency, bleeding dyscrasias, heart disease or risk of heart disease, congestive heart failure and concurrent corticosteroid therapy, among others. Age is a particular risk: older adults receiving daily NSAIDs for six months or more face a 6 to 9 percent risk for GI bleeding requiring hospitalization. NSAIDs also increase risk for exacerbations of hypertension, heart failure and renal dysfunction. NSAID use in patients with heart disease or its risk factors increases overall risk of heart attack or stroke.

Chronic NSAID therapy should be considered only for patients without significant risk for adverse events. They should be used only rarely and with extreme caution in older patients.[19] Patients receiving ongoing NSAIDs should be monitored regularly for GI and renal toxicity, exacerbation of hypertension and heart failure, and to ensure continued efficacy. Ineffective therapy should be stopped.

High risk patients for whom NSAIDs have proven the only effective treatment should be considered for GI prophylaxis with proton-pump inhibitors. Older adults receiving chronic NSAID therapy should also be prescribed a proton pump inhibitor. Additionally, providers should have a low threshold for investigating symptoms suggesting NSAID complications in any patient. It may be reasonable to rotate among different NSAIDs to maximize effectiveness and tolerability for an individual, but these trials should be structured and monitored carefully for effectiveness and safety. Patients who have a significant adverse event (GI bleeding or renal failure) with one NSAID should not receive others.

Cyclooxygenase-2 (COX-2) Selective NSAIDs. COX-2 selective NSAIDs, such as celecoxib (Celebrex), were developed to inhibit presumptively pathologic COX-2 activity while allowing physiologic COX-1 activity to continue normally. While COX-2 inhibitors demonstrated lower GI risk compared to traditional NSAIDs, subsequent studies have shown increased cardiovascular risk with ongoing COX-2 use. Subsequently, manufacturers of COX-2 selective NSAIDs have either significantly modified labeling for these medications or withdrawn them altogether. Older patients treated with COX-2 inhibitors and aspirin together should be given gastrointestinal protection with a proton pump inhibitor.

Opioids. In recent years, the use of opioid analgesics in the management of chronic non-malignant, or chronic pain has greatly increased as physicians have been encouraged to be more aggressive with pain control. While opioids can be effective in treating chronic pain, care should be taken in patient selection, monitoring and follow-up to ensure that chronic opioid therapy is effective and safe over time. For example, with prolonged use in some patients, opioids can become ineffective and, at more than minimal doses, can *lower* pain threshold and induce hyperalgesia.

Concerns about the use of opioids are many and are shared by providers and patients alike. These are drugs with potentially serious adverse effects and complications including drug abuse, addiction and diversion for sale. Unscrupulous and/or poorly supervised use of these medications can lead patients down a path to inappropriate use, often does not lead to desired outcomes, and creates ethical dilemmas and legal risks for providers. However, excessive fear of and reluctance to use these medications can lead to their under use, preventing effective therapy of chronic pain. In the right circumstances, opioids are

effective in providing pain relief and improving physical and psychosocial function.

Some patients with complex conditions, coexisting addictive disorders, or psychiatric/psychological syndromes that complicate therapy are better managed by a multi-disciplinary program.

Adjuvant medications. Adjuvant pain medications may be used to augment other analgesics, or as monotherapy in certain circumstances. Several classes of antidepressants and anticonvulsant medications have proven to be effective, though their tolerability, ease of dosing, side effect profiles, and cost vary significantly.

Antidepressants. The analgesic effect of anti-depressants has been attributed in large part to their ability to inhibit reuptake of norepinephrine and serotonin, both of which act on descending pain pathways. Tricyclic antidepressants (amitriptyline [Elavil], nortriptyline [Pamelor], doxepin [Sinequan] and desipramine [Norpramin]) and two serotonin-norepinephrine reuptake-inhibitors (venlafaxine [Effexor], and duloxetine [Cymbalta]) share this pair of actions, and each has established efficacy for chronic and neuropathic pain syndromes (NNT for both classes 3.5 to 4).

Serotonin-selective medications (fluoxetine [Prozac], paroxetine [Paxil], citalopram [Celexa] and others) demonstrate little or no effect on neuropathic pain.

While depression and chronic pain are frequently comorbid, the analgesic efficacy of antidepressants appears to be independent of their effect on depression. Tricyclic medications often provide analgesia at lower doses than those used to treat depression, while newer agents may require titration to or above anti-depressant doses to treat chronic pain syndromes. Tricyclic medications can also assist disrupted sleep associated with chronic pain.

Anticonvulsants. The analgesic mechanisms of anticonvulsants for neuropathic pain are not entirely known, though they likely involve calcium and sodium ion channel blockade, N-methyl D-aspartate (NMDA) and glutamate receptor antagonism, and/or enhancement of gamma-aminobutyric acid (GABA) activity to inhibit neural activity. While the first-generation anticonvulsants phenytoin (Dilantin) and carbamazepine (Tegretol) have shown some efficacy for neuropathic pain, they are associated with frequent side effects, drug-drug interactions and potentially severe adverse reactions. Second generation agents such as gabapentin (Neurontin) topiramate [Topamax] and pregabalin (Lyrica) are also effective in treating neuropathic pain and generally better-tolerated, though they can be significantly more expensive, more complex to dose, and still pose significant adverse risk. Additionally, caution is advised with the use of Topiramate in reproductive-aged women due to increased risk of cleft lip/cleft palate in newborns. Pregabalin is additionally indicated for treatment of fibromyalgia. Table 3 summarizes adjuvant medication options, prescribing considerations and evidence appraisal.

Special Treatment for Common Conditions

Low back pain. Chronic low back pain (LBP) is an extraordinarily common cause of chronic pain and disability. A recent review of "failed back syndrome" (persistent back pain in patients with previous surgery) does not mention opioid therapy among the treatment options.[22] Prior to initiating maintenance opioid therapy, referral to a back pain specialist is recommended to seek treatable sources of pain or to determine if an interventional therapy may be appropriate.[23] Therapeutic exercise (mobilization, stretching and strengthening) and aerobic exercise have been shown to improve pain and function in patients with chronic LBP. Activity modification and patient education are important measures in the management chronic LBP. Physical modalities, such as ultrasound, TENS, phonophoresis and diathermy have not been shown to have any lasting benefit. Persons disabled by LBP for >3 months have been shown to benefit from a multidisciplinary pain program. These programs usually include physical therapy, occupational therapy, psychology, social work, exercise physiology, interventional therapy, and medication management.

Other musculoskeletal pain. Chronic painful conditions involving the shoulder, knee, hip and foot may result as a sequela of acute macrotrauma (e.g. fracture, dislocation) or from repetitive microtrauma. Activity modification, therapeutic exercise programs and patient education are important measures in the management of these disorders. Many patients benefit from formal physical therapy for stretching, strengthening, correction of underlying biomechanical dysfunction and muscle imbalance and instruction in an independent home exercise program. An ergonomic work site evaluation and consultation with an occupational medicine specialist should be considered in patients who are disabled from work. Patients with continued pain and disability should be referred to a musculoskeletal specialist (e.g., orthopedic surgeon, rheumatologist, physiatrist, sports medicine specialist).

Osteoarthritis. Optimal medical management of osteoarthritis consists of non-pharmacologic measures and pharmacologic treatment. Non-pharmacologic treatment includes patient education, weight loss, self-management programs, physical and occupational therapy. Stretching, strengthening and low impact aerobic exercises are beneficial in improving pain and function in patients with osteoarthritis of the hip and knee. The use of braces, splints, orthotics and assistive devices are helpful in many patients. Acetaminophen, NSAIDs and topical analgesics, heat or cold are effective in persons with mild to moderate pain. There are insufficient data to recommend glucosamine and chondroitin sulfate for generalized OA, though some studies suggest that knee OA symptoms may improve with long-term (>6 months), daily use. Aspiration and intra-articular glucocorticoid injections are beneficial in patients with joint effusion or signs of inflammation. Opioids should be considered in patients with severe pain and in those unresponsive or intolerant of other treatments. In patients with moderate to severe osteoarthritis, opioids have been shown to improve function, sleep and enjoyment of life.

Patients with severe pain despite maximal medical management and impaired activities of daily living should be referred to an orthopedic surgeon for evaluation.

Fibromyalgia. The prevalence of fibromyalgia in the general population is estimated to be 2-6%, and is four to seven times more common in women. The chronic pain associated with fibromyalgia is felt to result from augmented processing of pain and sensory information, rather than due to increased nociceptive input from peripheral tissues. Biochemical abnormalities have been demonstrated in fibromyalgia patients, including increased pronociceptive neuropeptides and excitatory amino acids in the CSF (e.g. Substance P, glutamate) and decreased concentrations and activity of antinociceptive substances (e.g. serotonin, norepinephrine). In light of this, one could conclude that chronic opioid therapy may be *contraindicated* in these patients.

Treatment for fibromyalgia consists of patient education, exercise, cognitive behavioral therapy, and medications *not* including opioids. Tricyclic antidepressants (especially amitriptyline), SNRIs (duloxetine, milnacipran) and alpha-2-delta ligands (pregabalin, gabapentin) have shown benefit. TCAs and SNRIs work equally well in fibromyalgia patients with and without depression. NSAIDs and opioids have little efficacy in decreasing pain in these patients.[5,6] Exercise programs should be introduced gradually with a goal of daily activity/exercise. The efficacy of physical modalities such as massage and heat have not been proven, however may be of benefit to some patients. Referral to a rheumatologist or physiatrist is recommended in patients with severe disabling pain. Multidisciplinary treatment may be helpful in these individuals.

Neuropathic pain (e.g., diabetic peripheral neuropathy [DPN], post herpetic neuralgia [PHN]). First-line pharmacologic agents in the treatment of neuropathic pain include tricyclic antidepressants (TCAs),[21] SNRIs, anticonvulsants, tramadol[20] and topical lidocaine. Three agents, duloxetine, milnacipran and pregabalin, have received FDA approval for the treatment of diabetic peripheral neuropathic pain. High dose (225 mg/d) venlafaxine has been shown to be an effective therapy.[7] Combination therapies may be synergistic.[8] Phenytoin and carbamazepine are effective as second-line agents; however, their side effect profile and need for serum monitoring may limit their use. Carbamazepine may be particularly effective for trigeminal neuralgia. There is insufficient evidence to recommend the newer antiepileptic drugs levetiracetam, topiramate, tiagabine and zonisamide. Equally effective as TCA and gabapentin in the treatment of neuropathic pain, opioids are considered a second line therapy.[8]

Patients with peripheral neuropathy often have underlying comorbid musculoskeletal sources of pain, e.g. plantar fasciitis, pes planus, Achilles tendinosis, hallux valgus, thus referral to a musculoskeletal specialist may be of benefit to evaluate and treat these disorders. Multidisciplinary treatment, including physical therapy, pain psychology, occupational therapy and vocational rehabilitation may be helpful in those persons with chronic disability and impaired function. Referral to a foot specialist is recommended for severe deformities and insensate (Charcot) foot. Patients with suspected CRPS should be referred to an interventional pain specialist as soon as possible so that interventions can be provided to optimize the patient's ability to participate in physical therapy.[1] When more conservative therapy has not resulted in improvement a spinal cord stimulator may be an effective treatment option.

Psychiatric Comorbidities

The dilemma confronting the clinician assessing a chronic pain patient is to discern the relative relation between psychological dysfunction and the presenting pain complaint. Mood and personality disorders can be a prime cause of pain, may be solely the result of living with pain and pain-related disability, or contribute to the maintenance and/or exacerbation of pain through both physiological and psychological processes. Psychological impairment is a strong predictor in the transition from acute pain to chronic pain and disability. Factors associated with lack of recovery from an acute pain episode include maladaptive pain beliefs, lack of social support, heightened emotional reactivity, job dissatisfaction, substance abuse, compensation status, psychiatric diagnosis and severe pain behaviors.

Depressive disorders. Patients with chronic pain have rates of depression three to four times greater than that reported in the general population – as high as 50% or more. Major depressive disorder is present in about 1/3 of chronic pain patients. For cases of medically unexplained pain, the prevalence rate of major depression increases to 2/3.

As pain is a common feature of depressive disorders, with 60-70% of depressed patients reporting pain symptoms, there is a tendency to infer depression as a cause of pain for patients presenting with comorbid depression and pain. However, in the majority of cases, depressive symptoms have their onset following the initiation of a pain problem, sometimes not appearing until years after the onset of pain. In these cases, depression generally resolves to normal levels with eradication of the pain problem. However, for some specific pain disorders, for example fibromyalgia, premorbid depression may be relevant as an etiologic source.

Initial treatment for depression in patients with chronic pain may be influenced by their specific pain syndrome (see Table 3—adjuvants), though providers should also be familiar with standard guidelines regarding depression management (see University of Michigan Health System [UMHS] Depression Guideline). Patients not responding to therapy should be referred to pain psychology for further evaluation.

Anxiety disorders. Published prevalence estimates for specific anxiety disorders are highly variable, ranging from 26% to 59% for any type of anxiety problem. Anxiety is more likely in a chronic pain patient if a comorbid depression is present.

Generalized anxiety disorder can be rooted in chronic worry and ruminations about present and future pain experience. Panic disorder, particularly if accompanied by agoraphobia, can create numerous pain symptoms (e.g., chest pain) and profound disability superimposed on the primary pain problem, and is frequently a consequence of accident-related pain.

Anxiety has multiple potential deleterious effects on pain, including increasing muscle tension, inducing patient expectations for future pain suffering, enhancing vigilance to pain stimuli, and fostering avoidance behavioral patterns that may interfere with functional restoration of pain-related disability. Like depression, anxiety is a negative prognostic factor for pain treatment outcome.

Post-traumatic stress disorder (PTSD) is an under-appreciated, but important part of the assessment of every chronic pain patient whose pain onset is associated with an accident or trauma, regardless of the severity of the inciting event. Nearly 30% of patients involved in a motor vehicle accident suffer PTSD when medical attention is required due to the accident. Patients who suffer an accident-induced pain problem, who meet criteria for PTSD, report more severe pain and higher levels of affective disturbance than accident-induced pain without PTSD. Pain associated with a traumatic accident is associated, in general, with greater disability, greater perceived severity of symptoms, and is more refractory to intervention, than non-accident-related pain. An individual who has sustained a work-related injury may resist return-to-work efforts due to PTSD rather than secondary gain or other factors.

Anxiety in patients with chronic pain may respond to usual therapy (e.g., SSRIs, cognitive behavior therapy), though more complex or refractory symptoms should be referred to appropriate psychiatric or psychological care. Benzodiazepines should not be routinely prescribed for patients with chronic pain, as they carry independent and complicating risks for tolerance, misuse and addiction.

Personality disorders. The presence of a comorbid personality disorder can be an especially poor prognostic sign for the treatment of a chronic pain patient. While personality disorders are not as prevalent as mood and anxiety disorders among chronic pain populations, they are more difficult to treat given the absence of reliably effective pharmacologic options for treatment and the enduring and entrenched nature of personality traits.

A wide range of personality disorders exist and each can pose a unique challenge for the clinician. For example, pain patients with borderline personality disorder may make repeated and urgent demands for immediate pain relief and specialized care, and become hostile when their unrealistic expectations are not met. Individuals with dependent personality disorders frequently present with a pervasive sense of helplessness regarding their pain, and exhibit non-adherence to treatment protocols and failure to accept responsibility for self-management of their pain.

Patients displaying characteristics of multiaxial psychiatric disorders should be referred to appropriate psychiatric or psychological specialist for evaluation.

The Rational Use of Opioids

Definitions. The terms addiction, physical dependence and drug tolerance must be accurately defined and used in the context of opioid therapy for chronic pain. Patients, family members, and medical providers and staff frequently misuse or misinterpret these terms. The presence of tolerance or physical dependence are *not* synonymous with addiction. The definitions below reflect the consensus of the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine:

Tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects (either therapeutic or adverse effect) over time. Tolerance is predictable in long-term opioid therapy, and may be addressed by careful titration or adjuvant use. Tolerance may be aggravated by short-acting use, and minimized by preferred long-acting preparation.

Physical Dependence: A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Addiction: A primary, chronic, neurobiologic disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: loss of control over drug use, compulsive use, continued use despite harm, craving, and large amounts of time spent obtaining prescriptions.

Pseudo-addiction: A pattern of behavior that may occur when pain is undertreated, leading the patient to be focused on obtaining medications, and engaging in behavior that appears to resemble drug addiction. Pseudo-addiction can be distinguished from addiction in that these behaviors resolve when pain is effectively treated. Inadequate evaluation and ineffective treatment of pain, including suboptimal medication doses or intervals, as well as failure to address psychological co-morbidities often leads to patient behavior that seems disparate, and unfortunately often leads to patients being mislabeled as "addicts" or "drug abusers", when in reality the patients are suffering from chronic pain.

Opioid-induced hyperalgesia: Increased sensitivity to pain caused by chronic high dose opioid exposure that may be mistaken for progression of disease or opioid tolerance and thought to be a reason for increased patient pain complaints. The central mechanism for this phenomenon is well-described.

Narcotic: This is a poor choice of word to refer to opioid analgesic therapy. The word 'narcotic" has acquired negative connotations, and its use is discouraged. It can

stigmatize a patient who is using opioid analgesic therapy responsibly and effectively to manage severe pain.

Opioid therapy for chronic pain: Prescription opioid use in the US has risen dramatically over the past 15 years, in part due to heightened awareness of pain management. Unfortunately, along with increased prescribing has come increased prevalence of misuse, diversion, addiction and overdose. Physicians must exercise care and diligence when considering opioid therapy, to maximize functional benefit while minimizing risk.

All new opioid prescriptions should be considered as a trial of therapy, and following a "universal precautions" approach is essential. Because one cannot accurately predict in advance which patients are at risk for misuse of their medication or manifesting aberrant behaviors, it is advisable to apply a uniform, minimum approach to the screening and follow-up of *all* opioid treated patients.[12] By doing so, the risks to both patients and physicians may be diminished, bias avoided and conflict minimized.

Four recent reviews and guidelines[13, 14, 18, 24] advise similar approaches to the use of opioids for chronic pain. What we add here is specifically what, how and when to prescribe and follow up these patients with tools to assist in that process.

The process of prescribing controlled medications can be grouped into three phases:

1. Decision phase: Patient selection, counseling and contracting
    a. Assessment. Pain should be moderate to severe that is causing dysfunction, such as missing work, not sleeping, contributing to mood disorder, cessation of usual activities. Consideration of other therapeutic modalities, and further diagnostic testing to determine etiology of pain, if unknown, must continue, even after opioids are started. Consider psychological assessment for treating comorbid conditions or for pain coping psychotherapy.
    b. Other treatment failure. The patient should have had a well-documented failure to non-opioid analgesics and adjuvant medications. Opioid analgesics are only rarely first line medications for chronic non-malignant pain and should be avoided in centralized pain states.
    c. Addiction risk. Active addiction with alcohol, or other illicit drug use, raises the risk of opioid addiction. Opioid use in these situations should be avoided, and if used, requires intensive patient counseling and monitoring. If the provider is unable to do so, referral to pain / addiction specialist is warranted.
    d. Review goals. Providers must review the goals of therapy with the patient: a reduction, not elimination, of pain to a level that allows return of function. It is important to define with each individual what a successful return to function will be, and use these goals as indicators of success or failure of therapy.
    e. Review expectations. Providers must review potential adverse effects with patient, address concerns of patient, review all the terms of a provider/patient treatment agreement, and obtain patient's agreement to abide by the terms of the contract. A signed agreement may be preferred. A recommended sample agreement is provided in this guideline (see Appendix B). Both patient and provider should be focused on functional improvement rather than mere reduction in pain score.
    f. Do not prescribe benzodiazepines together with opioids given the high risk of respiratory suppression.
    g. Patients who are already on high dose opioid (> 90 mg/day morphine equivalent), not functioning well in life or who have evidence of aberrant medication use must be tapered.
    h. High risk patients (history of intoxication, co-treatment with benzodiazepines, morphine equivalent dose of opioid ≥ 90 mg/day, or medical illness such as sleep apnea) should have their opioid tapered or discontinued. Further, naloxone should be prescribed for patients to use for rescue in case of overdose and to impress upon patients their risky situation.

2. Initiation and titration phase
    a. Drug. Physician selects initial drug and dose. See Table 3 for recommended medications and dosing considerations. In general, if more than a weak opioid is required, morphine should be the default choice. The rationale for this includes the fact that all opioids are essentially similar regarding effects and side effects. True allergy to any one of them is very rare. Morphine and codeine may be slightly less well-tolerated, but should still be used initially unless side effects become intolerable.

        Advantages of morphine:
        - Useful and may be prescribed by all routes (unlike oxycodone).
        - Easiest to calculate doses, as all calculations utilize whole numbers (unlike hydromorphone)
        - Promotes safety as it has the most predictable analgesic interchange and has predictable conversion between parenteral and oral dosing
        - Exists in truly long-acting preparations (unlike oxycodone, hydrocodone)

        Cost in all oral forms is relatively low and the long-acting form is covered by all insurances, particularly Medicaid. Specific disadvantages exist for other medications.
        - OxyContin® is an often problematic choice for chronic pain patients inasmuch as nearly 40% of a dose has a half-life of 37 minutes while the slow phase half-life is approximately only 6 hours.[11] A short duration of activity combined with high cost, high abuse potential (crushing and snorting) and street value for diversion lead us not to recommend oxycodone preparations.

- While at least one study has suggested that transdermal fentanyl may be preferred in non-cancer pain patients over extended release morphine,[9] it has disadvantages including unpredictable dosing when converting from other opioids, it is slow and difficult to titrate, and requires a different opioid for "breakthrough" therapy. Patches often present problems with adherence to the skin, variable absorption, and have abuse potential when cut open and ingested.

Previously treated patients, especially those on multiple opioids, should be converted to a single opioid when possible rather than mixing two or more different ones of varying receptor affinities and potencies. Patients treated with short-acting medications should have those medications converted to or added to long-acting medication using the equianalgesic dosing and conversion information in Appendix C. In general, patients should not be treated with continuous, short-acting medications.

b. Action time. Newly treated patients should be prescribed only short acting opioids at a dose of ≤ 50 mg/day morphine equivalent. If pain persists beyond a few weeks, if opioid is thought to be beneficial, and continuation is required, the opioid may be converted to a long-acting preparation. During dose titration, short acting medication may be provided for "breakthrough pain," but should soon be discontinued. Again, use the short and long acting versions of the same medication, such as instant release morphine and long-acting morphine.

c. Limit short-acting use over time. In general, when long-acting opioid preparations are prescribed, "rescue" dosing with short-acting medication should be a *few times per month*, not multiple daily doses, except during the first few days of titration when the long-acting medication is being adjusted to a proper steady state dose over 3-5 half-lives of the medication.

d. Frequent assessments. Physician should see the patient frequently initially (every 1-4 weeks) to assess response to drug, monitor for adverse effects, assure compliance and assess for any inappropriate use or behavior. Reminders of the terms of the treatment agreement are useful in this stage.

e. Reassess plan in as soon as 2–6 weeks. The titration phase should be relatively short. If after 2-6 weeks, the patient has not achieved satisfactory pain control with a stable dose of medication, the patient should be referred to a pain management specialist. Opioids do not effectively treat all patients and discontinuation of opioids may be considered at this point, assuming that adequate dosing was done.

3. Maintenance phase of opioid management

a. Periodic visits (≤ 3 months). Once the patient has reached a stable dose and pain is under control, the patient should be seen by his/her provider at regular intervals—in most cases no less often than every 3 months. Requests for increases in medication should prompt a full reassessment of any pain generators and changes in psychosocial state. Additionally, check the state PMP (MAPS in Michigan) and consider repeat urine drug testing. Doses should not be repeatedly increased when above 50 mg / day morphine equivalent.

b. Assessment. At *each* follow up visit, the provider should assess average level of pain, functional status, adverse effects, and compliance with the evaluation treatment plan including physical and psychological therapies. Any behavior or actions that suggest inappropriate use, addiction or diversion must be addressed.

c. Treatment of all conditions. Other pharmacologic and non-pharmacologic therapies should continue. Chronic pain treatment must include assessment and treatment of underlying psychological issues, social stressors, and addiction if necessary. Failure to comply with diagnostic testing or other therapy is suspicious – consider addiction and misuse.

d. Urine drug testing. Urine drug testing is important for verifying the actual use of rather than diversion for sale of the prescribed medication. It is also a safety matter to assure through testing that other sedating substances or medications are not also in use. The interpretation of testing requires knowledge and care because of large numbers of possible false positive or negative results.[2] Testing should be conducted randomly at least once yearly and more often if the patient is at additional risk for misuse or diversion for sale. Testing should utilize a combination of an enzyme immunolinked screening assay (EIA) for abused illicit substances and gas chromatography/mass spectroscopy (GCMS), for maximum specificity in detecting prescribed or illegally purchased medications that are typically missed by simple screening tests. Three types of results should raise concern:

1) Presence of non-prescribed controlled substances
2) Absence of prescribed medications (opioids or adjuvants)
3) Presence of illicit drugs of abuse

Response to these results may include counseling, shortened follow-up intervals and urine testing, referral for substance abuse treatment, or discontinuation of opioid therapy. See Appendix C for a guide to the ordering and interpretation of urine drug testing.

e. Other prescription sources. Regularly check state-wide prescribing registries (prescription monitoring programs) for other prescription sources. These can quickly provide details regarding prescriptions filled by the patient for all controlled substances. As of Fall, 2009, only 10 states do not have a functioning prescription monitoring program.

Methadone use in chronic pain. Methadone has unique qualities that make it particularly useful in the management

of chronic pain when long-term opioid therapy is appropriate. It has a prolonged duration of activity, has a lower incidence of constipation than other opioids, is not particularly euphoric at low doses used for pain and is available at relatively low cost. Because of its low tendency to require increasingly large doses over time (tolerance), methadone may be useful for the treatment of patients who require opioid therapy for several months or longer. However, its safe use requires knowledge of its particular pharmacologic properties. Because methadone is often associated with opioid addiction therapy, patients may need additional counseling that methadone is an effective analgesic, not merely a treatment for opioid addiction.

Methadone has a prolonged half-life so the degree of analgesia and side effects increases over several days after an initial dose or a change of dosage. The duration of methadone analgesia upon first initiation may be only 6-8 hours. With repeated use, daily to TID dosing are effective.

Be cautious when converting from another opioid to methadone (see Appendix C).[15,16] As the daily morphine equivalent dose rises, the methadone/morphine conversion ratio *declines* until methadone is approximately *twenty times* as potent as oral morphine (daily doses of morphine above 500 mg). Patients requiring high dose conversions to or from methadone should be referred to a specialist in pain management who has experience with methadone dosing.

During the titration phase of methadone, supplemental short acting opioids may be used to manage inadequate analgesia. Educate the patient about the delayed response of both therapeutic and adverse effects, especially if benzodiazepines or other sedatives are in use. For opioid-naïve patients, methadone should be initiated at very low doses (<10 mg/day) in divided doses. For opioid-tolerant patients, methadone should be initiated using proper rotation ratios (see Appendix C), and starting doses should generally not exceed 30 mg/daily. Higher dose conversions may be indicated for some patients, but should prompt consultation with a pain management specialist. Regardless of starting dose, methadone should be titrated by small increments (max 10-15% of total daily dose) not more often than once every 7 days.

Methadone can prolong QT interval, especially at higher doses (>100 mg/day) or when used in combination with other medications that prolong QT, including several classes of common antibiotics (macrolides and quinolones). Periodic EKG monitoring should be performed in patients on higher doses of methadone, or those being considered for therapy with other QT-prolonging medications (full list available www.qtdrugs.org).

Methadone, like other opioid analgesics, is associated with a substantial risk for diversion. Mere confirmation of its presence on GCMS testing may not be adequate. Prescribers should have a low threshold for periodic testing of serum levels. Specimens should be drawn with the variables of patient weight (kg), time since last dose taken (h) and the total daily methadone dose (mg) known. Also, be aware of drug interactions that may affect an individual's methadone clearance. Calculate the expected serum trough level: 263 x total daily dose divided by the weight. Methadone peaks approximately two hours after dosing and fades over 5-6 hrs. A peak level would be approximately double a trough level.

Buprenorphine. Buprenorphine has been increasingly utilized in pain management, particularly for long-term opioid-treated patients with or without a component of opioid use disorder. As a partial agonist that is potent and long-acting, it may be a safer alternative to full agonist opioids. Advantages of buprenorphine include effectiveness, ease of prescribing a Schedule III drug and lack of development of tolerance to it. Disadvantages include occasional problems with rash at the patch site and great expense.

Ttransdermal buprenorphine (Butrans) may be a good alternative for patients who have developed tolerance to other opioids and are taking less than or equal to 80 mg/day morphine equivalent. Start with a 5 or 10 mcg weekly patch and discontinue other opioids.

While sublingual buprenorphine may be prescribed off label "for pain" with a regular DEA, the initiation of sublingual buprenorphine may provoke acute opioid withdrawal. Therefore, we recommend that sublingual buprenorphine be initiated only by prescribers trained in its use and in possession of an XDEA. Once a patient is on it and stable, primary prescribers may perform chronic management.

Adverse effects of opioid analgesics. Mild to moderate side effects to opioids are as common as 50% to 66%. The most common adverse effects are sedation, nausea, headache, pruritus, and constipation. Other effects can be confusion, hallucinations, nightmares, urinary retention, dizziness and headache. Tolerance and regression of most side effects often occur quickly. Constipation and urinary retention (smooth muscle inhibitory effects) are more persistent.

Nausea may be a bit more common with codeine while constipation may be a bit worse with oxycodone and rash may be more common with morphine. Otherwise, most opioids are very similar.

Respiratory depression may occur with high dose administration to opioid naïve patients. It is the most serious potential adverse effect, and is accompanied by symptoms of sedation and confusion. Opioids, at therapeutic doses, depress respiratory rate and tidal volume. As CO_2 rises, central chemoreceptors cause a compensatory increase in respiratory rate. Patients with impaired ventilatory reserve (COPD, asthma) are therefore at greater risk of clinically significant respiratory depression. Tolerance to respiratory depression develops within just a few days.

Cognitive function, including the ability to drive, is preserved when on stable, moderate doses of opioids. Cognitive impairment may occur temporarily after an increase in dose. Tolerance to cognitive effects usually develops quickly.

Though not FDA approved for the management of chronic pain, sublingual buprenorphine has an evolving role, particularly in patients treated with high dose opioid therapy or where addiction issues complicate the patient's situation. A partial agonist, buprenorphine has many characteristics that make it an excellent choice including high potency (about 30 times that of oral morphine), being truly long-acting with less abuse potential or tendency to dose escalation and a high safety profile.[10] High cost and lack of physician knowledge of its proper use have so far limited its use as a pain treatment.

The long term use of opioids, particularly in doses above those typically prescribed for pain, may be associated with the development of an increased sensitivity to pain (opioid-induced hyperalgesia). This may be one mechanism of "apparent opioid tolerance" along with true pharmacologic tolerance, and disease progression. Fortunately, tolerance to the analgesic effect, when it does occur, develops much more slowly than tolerance to these adverse effects.

Patients with continued uncontrolled pain on high doses of opioids will likely require detoxification, often via buprenorphine (Suboxone®). This drug may be prescribed only by physicians and certified pain specialists experienced in its use.

Substance use disorders in chronic pain. The prevalence of addictive disorder among patients with chronic pain has primarily been studied in the practices of pain management specialist practices. Between 3% and 19% of chronic pain patients have evidence for an addictive disorder including alcoholism. This is similar to the lifetime prevalence rates of addictive disease in the general population of 6%-17%.

Among pain patients receiving opioids, a study found that 28% demonstrated evidence of abuse and that a pre-pain history of substance abuse did not predict misuse of prescribed opiates. Other studies have reported a positive association between familial and personal histories for chemical dependency and opioid misuse in chronic pain patients.

The use of opioids in a chronic pain patient with a past or current history of addictive disease is controversial. Clinicians vary in their comfort level and expertise in dealing with this selected portion of chronic pain patients. A pain patient with a distant, non-active history of drug dependence or abuse can reasonably be considered for opioid therapy with careful attention to early signs of aberrant drug behavior.

Assessing potential problems with opioid therapy. Criteria have been established to evaluate the presence of opioid abuse among chronic pain patients receiving long-term opioid therapy.[17] The authors determined that misuse of opioids was defined by meeting 3 or more of the following criteria:

1. Focus on opiates. The patient displays an overwhelming focus on opiate issues during pain clinic visits that occupy a significant proportion of the pain clinic visit and impedes progress with other issues regarding the patient's pain. This behavior must persist beyond the third clinic treatment session.
2. Early refills. The patient has a pattern of early refills (3 or more) or escalating drug use in the absence of an acute change in his or her medical condition.
3. Multiple contacts about opiates. The patient generates multiple telephone calls or visits to the administrative office to request more opiates, early refills, or problems associated with the opiate prescription. A patient may qualify with less visits if he or she creates a disturbance with the office staff.
4. Prescription problems. There is a pattern of prescription problems for a variety of reasons that may include lost medications, spilled medications, or stolen medications.
5. Multiple sources of opiates. The patient has supplemental sources of opiates obtained from multiple providers, emergency rooms, or illegal sources.
6. Other substance abuse. Concurrent alcohol or illicit substance use.

The authors reported that 34% of chronic pain patients on opiates met at least one criterion, 27% met 3 or more. Other 'red-flags' for opioid misuse are presented in Table 4. The Opioid Risk Tool is a validated tool that may be used to assess a patient's risk for aberrant behavior (see Appendix A.3). Of patients categorized as "high risk", 91% demonstrated aberrant behavior.

The risk of developing an addictive disorder to chronic opioid therapy appears similar to the general population for patients with no history of substance abuse/addiction, who exhibit no suspicious behavior, and who follow other diagnostic and treatment recommendations.

Response to suspicion for opioid misuse or possible diversion or sale. Suspicion of these behaviors requires a diligent response from the provider. Hints of this may be found by MAPS checks or by urine comprehensive drug screening, with the presence of non-prescribed medications or illicit substances, or by the *absence* of prescribed controlled substance medications. Thorough assessment and consideration of the differential diagnosis may identify a reason other than addiction. Appropriate intervention with the patient can result in cessation of suspicious behavior.

If the diagnosis of suspicious behavior is active or suspected addiction, the patient should be referred to an addiction management or chronic pain specialist. The management of chronic pain in the context of addiction is controversial, difficult, requires close monitoring and ongoing assessment and treatment of addiction, and is generally best managed by a multidisciplinary program.

Addiction is a serious disorder that has significant morbidity and can even threaten life. The failure to address suspected addiction is a disservice to the patient and will prevent achievement of the intended outcomes of therapy for the patient's chronic pain. A provider who knowingly prescribes

under these circumstances may be subject to legal action by the State Licensing Board with punishment up to and including jail.

Treatment of opioid addiction. Treatment of pain patients who exhibit evidence of opioid addiction may require discontinuation of opioid therapy, and referral to formal addiction treatment with or without medication assistance (methadone, buprenorphine, naltrexone). Do not continue to prescribe opioids for patients who exhibit loss of control over proper medication use or who use illicit substances. Successful treatment depends on the physician making the diagnosis of addiction, informing the patient, offering referral to addiction treatment specialist, and the agreement by the patient to seek therapy. A patient need not feel abandoned by his/her provider, just because a diagnosis of addiction is made, and opioid therapy is withdrawn. Further discussion of management of addiction is beyond the scope of this guideline.

Indications for referral to pain / addiction specialist. Any one of the following is sufficient to refer.

1. Failure to achieve the outcomes of therapy (adequate pain relief to achieve functional improvement goals) after *6 weeks* of opioid analgesic dose titration.
2. Non-compliance with the terms of the signed treatment agreement between patient and provider.
3. Persistent behavior suspicious for addiction or diversion.
4. Ongoing adverse effects of opioid therapy.
   The patient requires unexpectedly large doses of opioids, doses beyond what the primary care provider is comfortable prescribing, or doses beyond what are considered typically adequate for most pain management meaning individual medications or combinations of opioids that exceed a total daily dose of greater than 90 mg of morphine equivalents. Individually, daily doses greater than morphine or hydrocodone 90 mg, oxycodone 60 mg, fentanyl 50 mcg/hr, hydromorphone 16 mg or methadone 30 mg per day or a calculation that converts and sums combination of opioids to morphine equivalents (see Appendix C) should prompt referral to a pain specialist. Also, referral may be appropriate if a patient is requiring more than a few times *per month* "rescue" dosing.
5. Opioid-induced hyperalgesia
6. Desire for detoxification/conversion to buprenorphine (Suboxone®)
7. Desire for multidisciplinary management

Discontinuing prescribing of opioids. Opioids may be discontinued or converted for a variety of reasons, including lack of benefit, excessive dosing, hospitalization, non-compliance, and diversion. Appendix E presents actions (immediate discontinuation, rapid taper, slower taper, buprenorphine conversion) along with associated reasons and recommended processes to perform the respective action.

When discontinuation of opioid therapy need not be immediate (see next paragraph and Appendix E), prevention of opioid withdrawal is desired. This can be accomplished with a relatively quick taper of medications. Although the amount of opioid necessary to prevent withdrawal is only 20% of the previous days' dose (from rapid detoxification studies), a taper of 25-50% per week over 2-4 weeks is commonly practiced.

Opioid therapy should be immediately discontinued when diversion or prescription forgery is discovered. DEA regulations require reporting diversion and prescription fraud. If diversion for sale or fraud is suspected, local law enforcement agencies should be notified. Immediate discontinuation of opioids should also occur upon dangerous behaviors such as motor vehicle accident or arrest due to opioid or illicit drug or alcohol intoxication, intentional overdose or suicide attempt. Aggressive and threatening behavior in the clinic can also be grounds for immediate discontinuation of therapy. Inpatient detoxification can be offered to treat withdrawal when immediate discontinuation of opioid therapy is necessary.

Legal issues with opioids. Providers must be aware of the requirements in their individual states for prescribing opioids and other controlled substances. A sample set of state regulations has been provided in Table 5 and includes:

1. Evaluation of the patient. A complete evaluation of the patient's history, exam, prior treatments, nature and intensity of pain, physical and psychological functional assessment, substance abuse history, and the indication for the use of a controlled substance, must be in the medical record.
2. Treatment Plan, including the objectives that will be used to determine treatment success, and subsequent documentation of the response to therapy must be in the medical record.
3. Informed Consent and Agreement for Treatment. Documentation of the counseling and contracting with the patient, regarding risks and benefits of therapy, prescription management requirements (e.g., Appendix B). Written contracts are not a legal requirement, but are suggested, especially for patients at increased risk of substance abuse or addiction.
4. Periodic Review of Therapy "at reasonable intervals based on the individual circumstances of the patient", assessing pain intensity, physical and psychosocial functioning, and whether treatment goals are being reached. All prescriptions, including date, type, dosage and quantity prescribed should be entered in the medical record.

Occasionally, providers may be asked, or are tempted to prescribe opioid analgesics as therapy for opioid (illicit or prescription) addiction. This is *illegal* – special licensing is required to prescribe methadone, buprenorphine or other scheduled substances for the purpose of treating addiction. For patients with opioid addiction who also have well substantiated moderate to severe pain, opioid analgesics have been used, but should be used with extreme caution, and

under close supervision. Consultation or referral to a pain/addiction management specialist is advised in this situation.

Opioid prescription management. Providers must be familiar with their state's and federal regulations regarding controlled substances prescriptions. Key features of Michigan law are:

- Class II controlled substance prescriptions shall be dated the date written, shall be for a one-month supply, cannot be phoned in, cannot have authorized refills and are valid for up to 60 days. A provider may write a prescription dated today, but with instructions that the prescription not be filled for 30 or 60 days.
- Class III, IV, V controlled substances may be called in, with up to 6 months of refills.
- All prescriptions, including date prepared, the desired fill date, dose, and quantity, should be created and recorded in the medical record and should be readily retrievable.

A clinic policy regarding patients on long-term controlled substances will support appropriate use of these substances, care coordination within the practice, and coordination between providers and patients. Appendix F presents an example of a clinic policy. Individual clinics may customize provisions to meet local circumstances.

One source of both provider and patient dissatisfaction relates to the dispensing of prescriptions. Prescriptions should not be called in at night or on weekends by covering providers. For most patients, it is recommended that prescriptions are picked up in person every one to 3 months.

Involvement of clinic personnel to monitor prescription dispensing can relieve some of the burden on the physician. Every prescription should be clearly documented in the medical record. With proper organization, the provider may see patients on a stable opioid regimen every 3 months, write the prescriptions, and nursing staff can see the patient monthly to give him/her the monthly prescription. Walk-in and phone requests for refills will then be greatly reduced, and any inappropriate use or behavior will be readily identified.

Strategy for Literature Search

Preliminary evidence was identified using literature considered relevant in the VA/DOD clinical practice guideline for the management of opioid therapy. That report utilized literature searches from six earlier documents supplemented by a systematic literature search of publications from 1998 through July 2002.

A search of more recent literature was conducted on Medline prospectively using the major keywords of: *chronic pain non-malignant, human, English language, clinical trials, guidelines,* and *published from 1/1/00 through 1/15/2010*. For some specific topics (noted below) the timeframe was extended to include publications *from 1/1/95 through 4/15/05*. Terms used for specific topic searches within the major key words included: *pain assessment, opioids (since 1995), other drugs (e.g., NSAIDS, acetaminophen, muscle relaxants, tricyclics, gabapentin; since 1995), physical therapy (since 1995), psychological interventions (since 1995), multidisciplinary treatment (since 1995), other non-pharmacologic treatment (since 1995), pain reassessment and monitoring, psychiatric comorbidities (e.g. personality disorders, history of substance abuse; since 1995), vulnerable populations (e.g., elderly, poor, minorities, pediatrics, disabled, psychiatric; since 1995), legal issues with opioids, prevention of opioid abuse, monitoring opioid use, opioid abusing patients, discontinuing prescribing opioids and discharging patients.* Detailed search terms and strategy available upon request.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with recent information available to expert members of the panel, including abstracts from recent meetings and results of clinical trials. Negative trials were specifically sought. The search was a single cycle. Conclusions were based on prospective randomized controlled trials if available, to the exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Disclosures

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

Team Member / Consultant	Relationships	Company
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References

1. Rho RH. Brewer RP, Lamer TJ, Wilson PR. Complex regional pain syndrome. *Mayo Clin Proc* 2002; 77:174-80.
2. Moeller KE, Lee KC, Kissack, JC. Urine drug screening: practical guide for clinicians. *Mayo Clin Proc* 2008; 83:66-76.
3. Brookoff D. Chronic pain: a new disease? Hospital Practice 2000; 35:45-59.
4. Woolf C. Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Ann Intern Med* 2004; 140:441-51.
5. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. *Ann Intern Med* 2007; 146:726-34.
6. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *Journal of Pain* 2009; 10:777-91.
7. Argoff, CE, Backonia M, Belgrade M, Bennett GJ, et al. Consensus guidelines: treatment planning and options. *Mayo Clin Proc* 2006; 81 (4, Suppl):S12-S25.
8. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. *Amer J Med* 2009; 122:S22-S32
9. Allan L, Hays H, Jenson N, Le Polain de Waroux B, Bolt M, Donald R, Kalso E. Randomised croxxover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; 322:1-7.
10. Heit HA, Gourlay DL. Buprenorphine: new tricks with an old molecule for pain management. *Clin J Pain* 2008; 24:93-7.
11. Davis MP, Varga J, Dickerson D, Walsh D, LeGrand SB, Lagman R. Normal-release and controlled-release oxycodone: pharmacokinetics, pharmacodynamics, and controversy. *Supporyt Care Cancer* 2003; 11:84-92.
12. Gourlay DL, Heit HA, Aimahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Medicine* 2005; 6:107-12.
13. Ballantyne JC and Mao J. Opioid therapy for chronic pain. *NEJM, 2004, 349(20):1943-53.*
14. Veterans Health Administration, Department of Defense. VA/Dod clinical practice guideline for the management of opioid therapy for chronic pain. Washington (DC): Veterans Health Administration, Department of Defense; 2003 March.
15. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? *J Clin Oncol* 1998; 16:3216-3221.
16. Galvagno SM, Correll DJ, Narang S. Safe oral equianalgesic opioid dosing for patients with moderate-to severe pain. *Resident and Staff Physician* 2007; 53 (4) Published Online: May 17, 2007 - 11:48:22 PM
17. Chabal C. Erjavec MK. Jacobson L. Mariano A. Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clinic Journal of Pain 1997; 13:150-55*.
18. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain 2009;* 10:113-30.
19. Fine PG, Herr KA. Pharmacologic management of persistent pain in older persons. *Clinical Geriatrics* 2009; 17:25-32.
20. Hollingshead J. Duhmke RM. Cornblath DR. Tramadol for neuropathic pain Cochrane Database of Systematic Reviews. 3:CD003726.2006.
21. Saarto T. Wiffen PJ. Antidepressants for neuropathic pain *Cochrane Database of Systematic Reviews. (4):CD005454, 2007.*
22. Ragab A, deShazo RD. Management of back pain in patients with previous back surgery. *Amer J Med* 2008; 121:272-78.
23. Chou R, Atlas SJ, Stanos SP, Rosenquist, RW. Nonsurgical interventional therapies for low back pain - a review of the evidence for an American Pain Society clinical practice guideline. *Spine* 2009; 34:1078–93.
24. Andrea M. Trescot AM, Helm S, Hansen H, BenyaminR, Glaser SE, Adlaka R, Patel S, Manchikanti L. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. Pain Physician 2008; Opioids Special Issue: 11:S5-S62.
25. Krebs, E. E., Lorenz, K. A., Bair, M. J., Damush, T. M., Wu, J., Sutherland, J. M., Asch S, Kroenke, K. (2009). Development and Initial Validation of the PEG, a Three-item Scale Assessing Pain Intensity and Interference. Journal of General Internal Medicine, 24(6), 733–738. http://doi.org/10.1007/s11606-009-0981-1
26. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. Recommendations and Reports, 3/18/2016, 65(1);1-49. https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

Appendices

Title	Page
A. Outline for:	
1. Initial Evaluation of Chronic Pain	25
2. Follow-Up Evaluation of Chronic Pain Patients on Controlled Substances	26
3. Opioid Risk Tool	27
B. Patient-Provider Agreement for Ongoing Use of Controlled Medication	30
C. Oral Opioid Dosing Equivalents and Conversions	32
D. Ordering and Interpreting Urine Drug Tests	33
E Discontinuing Opioids	34
F. Example Clinic Policy Regarding Patients on Long-term Controlled Substances	35

Appendix A.1: Outline for Initial Evaluation of Chronic Pain

Current pain details (PQRST: provokes, quality, radiates, severity, time)

Medications
(Include adjuvants [e.g., SSRI/SNRI, TCAs, anticonvulsants] and opioids)
Previous

Current

Allergies and intolerances

What has worked/what hasn't worked (?)

Non-invasive treatments
(e.g., physical therapy, TENS, acupuncture, chiropractic)

Invasive diagnostic/therapeutic procedures
(e.g., nerve blocks, stimulation trials, epidural injections, surgery)

Patient's goals

Past medical history

Family history
(include alcohol, drug use, psych, chronic pain)

Psychosocial history
Living arrangements

Work history/status

Insurance

Legal matters (e.g., disability, law suits, DUI)

Family or personal history of violence, sexual abuse

Psychiatric history (e.g., depression, anxiety/panic, hallucinations, suicide attempt, hospitalized?), specific diagnosis/therapy

Substance abuse
Alcohol history (ever a problem? DUI?)

Tobacco

Illicit drugs

Caffeine

Review of systems

Physical exam

Imaging, electromyogram, laboratory tests

Urine comprehensive drug screening (EIA + GCMS; at UM = DRUG COMP)

Check opioid registry (e.g., MAPS)

Assessment/Problems

Plan **(Shared goals for functional improvement: work/home/social interpersonal/recreation)**
Medical management

Psychiatric management

Lifestyle interventions

Physical modalities

Family involvement

Follow-up

Appendix A.2: Outline for Follow-up Evaluation of Chronic Pain Patients on Controlled Substances

Current pain details (PQRST: provokes, quality, radiates, severity, time)

Progress toward patient's goals (work/home/social interpersonal/recreation, improvement of pain and functional status)

Level of adherence to pain evaluation and management plan (including psych, therapy, lifestyle)

Medications

Current include adjuvants, movement to long-acting opioids, progress with taper, avoidance of benzodiazepines

Adverse effects

Assessment for "red flag" drug-taking behavior, see written treatment agreement

Physical exam

Updated imaging, other tests

Urine comprehensive drug screening (EIA + GCMS; at UM = DRUG COMP)
once every six months (absence of illicit or non-prescribed medications; presence of and compliance with prescribed medications)

Check opioid registry (e.g., MAPS)

Assessment

Plan (Refine shared goals for functional improvement: work/home/social interpersonal/recreation)

Medical management (adjust medications, stop ineffective meds including opioids)

Psychiatric management

Lifestyle interventions

Physical modalities

Family involvement

Follow-up

Treatment agreement (contract)

Placed in medical record

Item placed in Problem List

Consider referral for comprehensive chronic pain management if:

- **evidence of addiction behavior**
- **failure to progress toward goals**
- **escalating or excessive opioid needs**
- **poor psychological adjustment**
- **buprenorphine (Suboxone®) management**

Appendix A.3: Opioid Risk Tool

Item	Mark Each Box That Applies	Item Score if: Female	Male
1. Family history of substance abuse:			
Alcohol	☐	1	3
Illegal drugs	☐	2	3
Prescription drugs	☐	4	4
2. Personal history of substance abuse:			
Alcohol	☐	3	3
Illegal drugs	☐	4	4
Prescription drugs	☐	5	5
3. Age (mark box if 16-45 years old)	☐	1	1
4. History of preadolescent sexual abuse	☐	3	0
5. Psychological disease:			
Attention deficit disorder, obsessive-compulsive disorder, bipolar, schizophrenia	☐	2	2
Depression	☐	1	1
Total score		____	____

Total score risk category

Low risk:	0 – 3
Moderate risk:	4 – 7
High risk:	≥ 8

For further information, see Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. Pain Medicine, 2006; 6(6):432-442.

Appendix B.

Patient-Provider Agreement for Ongoing Use of Controlled Medication

BIRTHDATE
NAME

The use of the following medicine(s)_____
(*list medicine names*)

Is only one part of my treatment for_____.

Primary Prescribing Doctor: _____

What should I know about this medication?

This controlled medication may help me.

Opioid pain medications often have side effects, which may include but are not limited to:

- Itching
- Rash
- Severe constipation
- Trouble urinating or passing stool
- Depression getting worse
- Problems thinking clearly

Anxiety & Sleep medicine(s) can cause:

- Dizziness
- Memory problems

Combining drugs can cause:

- Overdose
- Trouble breathing
- Death

Stimulant medicines (such as for ADHD) can cause:

- High blood pressure
- Fast or irregular heart beats

I could become addicted to this medicine.

If I must stop this medicine for any reason, I need to stop it slowly. Stopping it slowly will help me avoid feeling sick from withdrawal symptoms. If I decide to stop my medication, I will contact my doctor.

If I or anyone in my family has ever had drug or alcohol problems, I have a higher chance of getting addicted to this medicine.

If I take this medicine and drink alcohol, use illegal drugs or use drugs prescribed by other providers:

- I may not be able to think clearly
- I could risk hurting myself (such as a car crash)
- I could become ill or even die

My doctor can only prescribe this medicine if I do not use illegal drugs.

If I do not use this medication exactly as prescribed, I risk hurting myself and others.

I will not increase my medicine dose without being told to do so by my doctor.

This medicine will not be refilled early.

I am in charge of my medicine.

- I know my medicine will not be replaced if it is stolen or lost.
- I will not share or give this medicine to other people.

What can I do to help?

BIRTHDATE NAME

Bring my pill bottles with any pills that are left to each clinic visit.

When asked, I will give a urine and/or blood sample to help monitor my treatment. I understand that clinic policy requires regular testing.

Go to appointments and tests set up by my doctor. These may include physical therapy, x-rays, labs, mental health, etc.

If I miss my appointments, it may not be safe for me to stay on this medicine. If I miss appointments, my doctor may want an office visit before giving refills.

Be on time for appointments. If I arrive late to an appointment for prescription refills, my appointment may be re-scheduled. I may not be given my prescription until I am seen by my doctor.

Give my doctor permission to talk to my pharmacy. My doctor will check my prescription fill history by State Pharmacy registries and may call my pharmacy.

If my doctor decides that the risks outweigh the benefits of this medicine, my medicine will be stopped in a safe manner.

How can I get my prescriptions?

I can only get this prescription from my primary prescribing doctor's office.

I will not get controlled medications from other providers (including dentists, the Emergency Room, specialists or other providers), without checking with my primary prescribing doctor.

Controlled-substance prescriptions are monitored. These prescriptions often need a paper-prescription signed by my doctor that cannot be mailed, faxed, or called to pharmacy. This type of prescription takes 24 hours before it will be ready for pick-up from clinic.

I will only use one pharmacy to fill these prescriptions.

Refills will be given only during normal office hours.

Clinic policy prevents on-call doctors from giving controlled-substance prescriptions.

I know that unless my doctor tells me otherwise, I need a scheduled appointment to get prescription refills.

If my doctor decides it is safe for me to get a refill without an appointment, only I or someone I choose can pick up a prescription from the clinic. This person may be asked to show ID.

What are reasons for ending the agreement?

I may not be able to obtain controlled prescriptions from the University of Michigan Health System (UMHS) if I take more medication than is prescribed, if I fail to give requested urine or blood for testing, if those tests fail to contain the proper amounts of my prescribed medication, if non-prescribed medications (from friends, other prescribers, the ED, street purchases) are present, or if illegal drugs, including marijuana, are present.

I may not be able to be seen in this or any University of Michigan clinic if I am disruptive or threatening towards staff.

I understand that under State of Michigan law, the non-medical use of controlled substances (lying to get medications, giving or selling these medicines to others) is a crime is a crime and will result in termination of controlled substance treatment by UMHS.

ATTESTATION:

Today, this treatment agreement has been reviewed with the patient and the implications explained. All questions were answered. After electronically signing, this agreement will be posted automatically to the medical record and a copy of this agreement will be printed and given to the patient for his/her own records.

Date_____

Appendix C. Oral Opioid Dosing Equivalents and Conversions

Typical Oral Q4H doses of short-acting opioids shown as equivalents to morphine:

Morphine	60 mg
Hydrocodone (Vicodin, Norco, Lorcet)	60 mg (equal to morphine potency)
Oxycodone	40 mg (1.5 x morphine potency)
Hydromorphone (Dilaudid)	12 mg (5 x morphine potency)
Oxymorphone (Opana) *use generally not recommended*	15 mg (4 x morphine potency)
Codeine (Tylenol #3 or #4)	360 mg (one-sixth morphine potency)

Dosing Principles

For patients requiring daily opioid therapy for longer than a few days to a few weeks, consider switching from short-acting opioids to long-acting oral therapy. Fentanyl patches are another option, but are expensive and difficult to titrate. Conversion to methadone is appropriate for opioid use greater than several months, assuming opioids *are effective* for the patient. Buprenorphine (Suboxone®) is an option if opioid abuse, misuse or extreme opioid tolerance is a risk.

First, convert any opioid in use to its equivalent amount of morphine in mg/day. Then, divide into BID (or, occasionally TID) Morphine ER doses. Methadone and fentanyl conversions follow.

Morphine to Methadone Conversion

Typical pain doses of methadone are 15-40 mg/day, given in divided doses. As the degree of addiction increases in a patient, doses may reach those used for heroin-addicted patients in the range of 80-120 mg/day. Due to its function through NMDA receptors in addition to *mu*-receptors as well as its accumulation and excretion into the circulation from the liver, the relative potency of methadone to morphine increases *considerably* as morphine doses increase. Approximate equivalencies:

Morphine PO	Methadone PO
30-90 mg	One fourth the morphine dose
90-300 mg	One eighth (200 mg/day morphine = 25 mg methadone)
300-500 mg	One twelfth the morphine dose
> 500 mg	One twentieth the morphine dose

Morphine to Fentanyl Patch Conversion

Each 2 mg PO morphine approximately equivalent to 1 mcg/hr fentanyl patch (e.g., morphine 100 mg/day → 50 mcg/hr patch applied q3days). Caution should be used in older adults or patients with cachexia—fentanyl is lipid soluble and requires subcutaneous fat for proper absorption.

Opioid Taper

Typical taper. Taper every week by 10% of original dose until 20% remains. Then taper the remaining 20% by 5% of original dose each week until off or at goal.

Rapid taper. Reduce by 25% every 3–7 days, depending upon short vs. longer drug half life.

Appendix D. Ordering and Interpreting Urine Drug Tests

When initiating or monitoring opioid therapy, two tests are required. The **t**wo complimentary tests are the enzyme linked immunoassay (EIA) kit and gas chromatography/ mass spectrometry (GCMS). [At UM the combined order is DRUG COMP.] They provide different information.

- Illicit drugs: EIA
- Confirm taking prescribed meds (specify meds when order test): GCMS. (EIA will provide this information if your laboratory runs the test for each med. However, laboratories usually do not. *Ask!*)
- Use of non-prescribed medication: GCMS
- Testing for heroin: GCMS. Check for one of its specific metabolites, e.g., 6 monoacetyl morphine (6-AM) duration 2-4 hrs only is positive as morphine in 2-3 days

Enzyme linked immunoassay – EIA.

- Screening test for illicit substances amphetamine/ methamphetamine, marijuana, PCP, cocaine, "opiates" (e.g., morphine/codeine)
- Inexpensive, fast, point of care or lab
- Detects class of substance, not specific medication
- Will be negative for hydrocodone, hydromorphone, oxycodone, methadone, buprenorphine, benzodiazepines (particularly clonazepam) unless specific test kit for those meds is in use. *Ask your lab!*
- High false positive rates caused by numerous prescribed or OTC meds

Gas chromatography/mass spectrometry – GCMS. You must tell the laboratory the drugs you are seeking (patient is taking).

- More expensive, labor intensive
- Confirming test identifies specific meds and their metabolites. Use to confirm patient is taking prescribed meds and not taking non-prescribed meds
- High sensitivity
- False positives still occur

Results and Possible Causes

Results may be due to several possible causes.

- Illicit substance present: Use by patient; false result related to prescribed or OTC med exposure
- Non-prescribed medication present: Illicit use by patient; false positive testing – cross-reaction or possible known metabolite (morphine or codeine may → hydromorphone)
- Prescribed medication absent: diversion or binging and running out early; false negative (incorrect use of EIA rather than GCMS testing); urine adulterated

False positives. Are the results due to illicit use, a false positive on the screen, or a known metabolite of a prescribed medication? In considering prescribed medications, false positives on EIA (and GCMS where specified) may result from:

- Amphetamines/methamphetamine: bupropion, tricyclic antidepressants, phenothiazines, propranolol, labetalol, OTC cold rx, ranitidine, trazodone. Vicks Nasal Spray can test positive even on GCMS.
- Barbiturates: phenytoin
- Benzodiazepines: sertraline
- LSD: amitriptyline, doxepin, sertraline, fluoxetine, metoclopramide, haloperidol, risperidone, verapamil
- Opiates
  - EIA testing: quinolones, dextromethorphan, diphenhydramine (Benadryl), verapamil, poppy seeds
  - GCMS testing
    - Morphine: from codeine, heroin (for a few hours) and poppy seeds for 48 hrs
    - Hydromorphone: from morphine, codeine, hydrocodone, heroin
    - Oxycodone: from hydrocodone
    - Codeine: from hydrocodone
    - Fentanyl: from trazodone
    - Methadone: from quetiapine (Seroquel)
- PCP: dextromethorphan, diphenhydramine, NyQuil, tramadol, venlafaxine (Effexor), NSAIDs, imipramine
- Propoxyphene: methadone, cyclobenzaprine (Flexeril), doxylamine (Ny-Quil), diphenhydramine (Benadryl), imipramine
- Cannabinoids (on EIA not GCMS): pantoprazole (Protonix), efavirenz (Sustiva, Atripla), NSAIDs

False negatives. Are the results due to the patient running out of medication early, diversion, a tampered specimen, or a threshold issue (e.g., workplace testing using a high threshold for reporting a positive test to avoid false positives that require a job intervention)? For EIA (and GCMS where specified) false negatives may result from:

- Unless bundled *(ask your lab!)*, opiate immunoassays will miss fentanyl, meperidine, methadone, pentazocine (Talwin), oxycodone and often hydrocodone
- Morphine: GCMS may miss it unless glucuronide hydrolyzed. Can pick up with a specific test such as a specific qualitative EIA kit such as MSOPIATE. *(Ask your lab!)*
- Illnesses that cause lactic acidosis can cause false negatives
- Insensitivity of benzodiazepine screen: only 40% for lorazepam; clonazepam (Klonopin) frequently negative on both EIA and GCMS.

Appendix E. Discontinuing Opioids

Action	Reasons	Process
Discontinue Immediately	• Drug diversion or prescription forgery • Danger to the patient, e.g., work, operation of machinery, suicide attempt • Threats are made in the practice office • Patient arrested	No further prescribing.
Rapid Taper	• Non-compliance with evaluation or therapy plans (e.g., tests, appointments, consultant visits) • Medication misuse • Problem ("red flag") behaviors: focus on opioids, requests for early refills, multiple calls or visits, calls to Patient Relations, prescription problems, urine drug test results (positive or negative), illicit substance use, contract violations.	Multiple agent conversion. If multiple agents, first convert all medications to morphine equivalent (see Appendix C) and taper as morphine (morphine sulfate extended release). If methadone is in use, convert to methadone equivalents. Taper. Taper by 25% every 3-7 days (shorter interval for short half-life medications). As little as 20% of the preceding dose may be used.
Slower Taper	• Lack of benefit (opioids are given on a *trial* basis) • Opioid-induced toxicity/hyperalgesia • Excessive dosing: morphine > 180 mg/day, oxycodone > 120 mg/day, fentanyl > 75 mcg/hr, methadone > 40 mg/day	Multiple agent conversion. If multiple agents, first convert all medications to morphine equivalent (see Appendix C) and taper as morphine (morphine sulfate extended release). If methadone in use, convert to methadone equivalents. Taper. Taper every week by 10% of original dose until 20% remains. Taper remaining 20% by 5% of original dose each week until off or at goal.
Buprenorpthine Conversion with Taper (requires XDEA number and experience)	• Opioids not indicated and need for removal from them • Opioid-induced hyperalgesia related to large dose opioid therapy requiring reduction • Pain and addiction	Referral for evaluation. Refer to chronic pain service for evaluation and clinic conversion. Evaluation during hospitalization. Evaluate patients with lack of benefit of opioids or with toxicity, who may benefit from conversion to buprenorphine

Appendix F. Example Clinical Policy

Clinic Policy Regarding Patients on Long-term Controlled Substances
(opioids, benzodiazepines and stimulants)

New Patients with a History of Long–term Use of a Controlled Substance

Before a new patient with a history of long-term controlled substance prescription use receives the first prescription from a clinic physician, our clinic record must contain: the medical records, urine comprehensive drug scan, MAPS search results and, if long term use is anticipated, a completed controlled substance contract.

Medical records. These new patients must provide medical records documenting previous medical work-up regarding the complaint necessitating these prescriptions and notes from previous physicians that prescribed these medications.

Obtain relevant medical records from previous providers. The patient is responsible for having this information sent. This clinic will provide to the patient forms for release of information along with the fax number and mailing address of our clinic. The previous physician's office should send the information directly to this clinic. This clinic will also provide to the patient the clinic phone number to verify that the patient's medical records have been received and to make appointments.

The Initial clinic note should follow the suggested format outline and must be complete for elements of the Past, Family and Social histories that could put a patient at risk for medication problems. It should include a detailed prescription history (last time/date controlled substance taken).

Urine comprehensive drug screen ("DRUG COMP"). DRUG COMP is combined immunoassay screening and gas chromatography/mass spectroscopy that together detect specific synthetic opioids along with morphine/codeine, benzodiazepines and drugs of abuse such as amphetamines, THC, and cocaine. It will also detect many common prescription meds such as tramadol, cyclobenzaprine, and TCAs. (A SAMHSA Drug 5 or Drug 6 immunoassay screen is inadequate due to difficulty of interpretation and problems with false positives and negatives.)

Order a DRUG COMP screen for all new patients. To avoid false negatives, inform the lab in the test order if a specific opioid should be present (particularly methadone, fentanyl and buprenorphine).

DRUG COMP specimen is collected in the clinic. Patients should not wear coats and other outer clothing or take purses, bags, backpacks into the bathroom. The nurse or provider should confirm promptly that the specimen is appropriately warm and should send it directly to the lab, not give it to the patient to deliver.

Check consistency between screen results and patient history and that no illicit drugs are present.

Michigan Automated Prescription System (MAPS). Search the state's online database of prescription fills controlled substances (MAPS: https://milogintp.michigan.gov/eai/tplogin/authenticate?URL=/ /) for the patient's filling history. Physicians should register at https://milogintp.michigan.gov/uisecure/tpselfservice/anonymous/register .)

Controlled Substance Contract/Informed Consent – long term use. At the visit when the first prescription is provided for a controlled substance, if long term use is anticipated the provider should initiate with the patient completion of the clinic's controlled substance contract/informed consent. The completed contract is scanned to the medical record, labeled "Controlled Substance Contract," and noted on the Problem List in the PSL (Problem Summary List).

Established Patients Using a Controlled Substance

Use the attached Established Patient Visit Checklist (copy also in the UMHS Chronic Pain guideline).

New patient criteria. All established patients must meet the above criteria for new patients.

Lost prescriptions: No lost prescriptions will be replaced.

Early refills. No early refills will be given.

Pill counts with urine screen. Ask the patient to bring existing pill bottles (with remaining pills, for a pill count) and submit a urine comprehensive drug screen (DRUG COMP) in the following situations:

- Twice yearly for all chronic non-malignant pain patients receiving opioids – once during January-June and another July-December.
- Patient requesting early prescription – for example, "going on vacation, emergency trip out of state", "had to change pharmacies."
- Patient behavior concerning for intoxication by illicit drugs.
- Patient requesting refill on controlled substance we have never prescribed.
- Person other than patient requesting refill or picking up prescription.
- Patient cannot state directions as prescribed for taking medication.
- Patient not permitted to speak with physician alone (other people won't leave examining room).
- Patient's physical exam or history concerning for misuse of controlled substance or illicit drug use.
- Clinic receives information from a pharmacy or other health care provider concerning for patient obtaining controlled substances from multiple physicians.

Problem results of urine comprehensive drug screen ("DRUG COMP"). (Note: A "Drug 6 immunoassay" screen is inadequate.)

- Diversion – drug screen negative for drugs prescribed. If diversion is suspected, prescribing controlled substances is *illegal*. No prescription will be provided by any member our practice. A repeat test must be completed within 48 hrs.
- Multiple sources – drug screen positive for controlled substances not being prescribed by our practice. The patient appears to be receiving opioids from multiple physicians. Members of our practice will not continue to prescribe controlled substances for these patients.
- Illegal/illicit drugs– positive screen. Absolutely no controlled prescription will be prescribed. Controlled substances cannot be safely prescribed in patients taking illicit drugs, *including cannabis*.

Disorderly behavior in clinic. Abusive behavior toward clinic staff, or disruptive behavior interfering with the care of other patients will not be tolerated. Call a "yellow card" for any threatening behavior. The patient may be dismissed from our clinic permanently.

Terminate controlled substance prescriptions. The following patient behaviors will result in terminating these prescriptions. Note termination of controlled substances in the CareWeb PSL.

- Fails to comply with drug testing as requested, including second follow-up test in timely manner
- Fails to comply with medical evaluation of pain complaint: diagnostic tests requested (e.g., radiology tests, EMG, stress test) and referrals (e.g., neurology, neurosurgery, physical or occupational therapy, pain specialist/anesthesia, psychology or psychiatry).
- Does not report treatment with opioids/controlled substances by other physicians
- Has drug testing results not consistent with clinic physician's prescription plan:
  - Prescriptions patient reports taking daily are not detected on screen.
  - Patient tests positive for controlled substances not prescribed by clinic.
  - Patient tests positive for illicit substances, particularly cocaine – patients should be referred for drug treatment.
- Misses more than two appointments (no show) per year without proper cancellation

Visit Checklist for Established Patients on Long-term Controlled Substances

- □ Determine level of adherence to both pain and general medical management plans (medications, physical therapy, lifestyle interventions, etc.).
- □ Document progress toward functional goals and pain response.
- □ Evaluate for adverse effects of medications (NSAIDs, adjuvants, opioids)
- □ Assess for 'red flag' drug-taking behavior. Review written pain management agreement for patients at risk.
- □ Check MAPS quarterly.
- □ Order a urine comprehensive drug screen ("DRUG COMP") on all patients twice per year – once during January-June and another July-December,
- □ Review management plan: refine functional goals, titrate effective medications, stop ineffective medications (including NSAIDs and opioids), modify non-interventional modalities, review expectations.
- □ Assure that a Treatment Agreement (Contract) is scanned to the record, labeled "Controlled Substance Contract" and noted on the PSL Problem List.
- □ Evaluate for appropriate boundaries in therapeutic relationship.
- □ Consider referral to Comprehensive Pain Management Center for evidence of addiction behavior, failure to reach functional goals despite adherence to plan, rapidly escalating or very high dose opioid needs, or poor psychological adjustment to symptoms.