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The authors declare no conflicts of interest.

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GUIDE FOCUS

The American College of Occupational and Environmental Medicine (ACOEM) Opioids Guideline is designed to provide health care providers who are the primary target users of this guideline with evidence-based guidance on the use of opioids for treatment in the specific settings of acute (up to 1 month’ duration), subacute (1 to 3 months’ duration), chronic (>3 months’ duration), and postoperative pain. This report summarizes findings from the 220-page ACOEM Opioids Guideline (960 references) and addresses the following questions developed by the Evidence-based Practice Opioids Panel:

- What evidence supports the need for a history and physical examination before prescribing opioids?
- Are opioids superior to other medications or other treatments for pain relief and functional improvement?
- Is screening for risk factors effective for reducing adverse effects of treatment from opioids?
- What is the dose–response relationship between morphine-equivalent dose and overdose, fatalities, and other adverse effects?
- What evidence addresses the balance of risk and benefits of opioid use for acute, subacute, chronic, and postoperative pain?
- Are opioids efficacious for treatment of acute, subacute, chronic, and postoperative nonmalignant pain?
- Are opioid treatment agreements (opioid contract, doctor/patient agreement, or informed consent) effective?
- What is the prevalence of aberrant urine drug screening results among patients using opioids for treatment of chronic pain?
- What evidence supports the use of intrathecal drug delivery systems for treatment of chronic, nonmalignant pain?
- What tapering regimens are effective for weaning off opioids?

TARGET POPULATION

The primary target population is working-age adults, although the literature searches included articles addressing all

ACOEM Practice Guidelines: Opioids for Treatment of Acute, Subacute, Chronic, and Postoperative Pain

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Description: The American College of Occupational and Environmental Medicine’s guidelines have been updated to develop more detailed guidance for treatment of acute, subacute, chronic, and postoperative pain with opioids. Methods: Literature searches were performed using PubMed, EBSCO, Cochrane Review, and Google Scholar without publication date limits. Of 264,617 articles’ titles screened and abstracts reviewed, 263 articles met inclusion criteria. Of these, a total of 157 were of high and moderate quality addressing pain treatment. Comprehensive literature reviews were accomplished with article abstraction, critiquing, grading, evidence table compilation, and guideline finalization by a multidisciplinary expert panel to develop evidence-based guidance. Recommendations: No quality evidence directly supports histories, physical examinations, and opioid treatment agreements, although they are thought to be important. No quality trials were identified showing superiority of opioids, compared with nonsteroidal anti-inflammatory and other medications for treatment of chronic, noncancer pain. The use of opioid-sparing treatments associated with lower doses of postoperative opioids is also associated with better long-term functional outcomes. Selective use of opioids is recommended for patients with acute and postoperative pain. Consensus recommendations also include consideration of carefully conducted trials of chronic opioid treatment for highly select patients with subacute and chronic pain and to maintenance opioid prescriptions only if documented objective functional gain(s) results. A strong and reproducible dose–response relationship identifies a recommended morphine equivalent dose limit of no more than 50 mg/day. Higher doses should be prescribed only with documented commensurately greater functional benefit(s), comprehensive monitoring for adverse effects, informed consent, and careful consideration of risk versus benefit of such treatment. Chronic opioid use should be accompanied by informed consent, a treatment agreement, tracking of functional benefits, drug screening, and attempts at tapering.

In contrast to prior efforts to limit opioid use since the early 1900s, Portenoy and Foley reported a case series of 38 patients in 1986 and opined that long-acting opioids for chronic, noncancer pain (CNCP) were safe and effective and referenced other data supporting a less than 1% risk of addiction. Pharmaceutical companies then performed trials generally not more than 3 months, claimed long-term safety and efficacy of opioids for chronic pain treatment, and marketed opioids to physicians and potential patients. Recognition of undertreatment of pain in many populations, legislative, regulatory, and health care accreditation-related activities further contributed to lowering barriers to, and rapid increases in opioid prescriptions, primarily for CNCP.

In 2009, there were 201.9 million Schedule II through IV (including strong and weak) opioid prescriptions paid in the United States. It is estimated that 4.9% of US adults used opioids in the prior week and 2.0% used them regularly. Along with increased use of opioids, emergency department visits for nonmedical use of opioids increased 111% from 2004 to 2008.17

Opioid use and deaths associated with opioids have also risen closely together. Deaths related to opioids quadrupled from 1999 through 2010, increasing from 4000 to 16,000 deaths in 2010, occurring in both urban and rural areas.25,36 Opioids have surpassed motor vehicle crashes as the cause of death in several states.19,27,31-34

There have been an increasingly large number of policies and guidelines that have been developed to address opioids. Recent reviews of these opioid guidelines found widely varying quality. There was no guideline identified meeting current guidelines quality standards and addressing up-to-date and detailed opioid use guidance for nonmalignant pain management.
adults. Thus, it is recognized that the principles may apply more broadly.

**GUIDELINE DEVELOPMENT PROCESS**

A detailed methodology document specifies evidence selection, scoring, incorporation of cost considerations, and formulation of recommendations. Briefly, the aim is to identify the highest-quality evidence on any given topic. The only noteworthy additions regarding this guideline are inclusion of large epidemiological studies for evidence of harms used for guidance and a change in the databases searched.

Guidance was drafted using tables of evidence that abstracted the epidemiological evidence. Draft text and tables were forwarded to the multidisciplinary Evidence-based Practice Opioids Panel (Michael S. Weiss, Kirk Bowden, Fernando Branco, Kimberly DuBruler, Charl Els, Steven Mandel, David W. McKinney, Rafael Miguel, Kathryn L. Mueller, Robert J. Nadig, Michael I. Schaffer, Larry Stuty, James B. Talmage, Russell L. Travis, and Thomas Winters). The Panel reviewed the evidence and finalized the text and recommendations. This guideline achieved 100% Panel agreement for all developed guidance.

**EVIDENCE REVIEW AND GRADING**

All evidence related to opioids in prior ACOEM Practice Guidelines, after searching seven databases was included in this guideline (MEDLINE, EBM Online, Cochrane, TRIP, CINAHL, EMBASE, and PEDro). Comprehensive searches for epidemiological evidence were performed with both PubMed and Google Scholar through October 2013 to help ensure complete study capture. There was no limit on the year of publication. Search terms for this report are available at: http://www.acoem.org/PubMedSearchDetails.aspx. Reference lists of included articles were reviewed for inclusion. All included studies were scored for quality. Articles scoring moderate or high quality were included.

The search strategies identified a total of 264,617 article titles, which were screened, with all potentially appropriate study abstracts reviewed and evaluated against specified inclusion and exclusion criteria. A total of 263 studies were included in these analyses. Articles reporting the studies were critically appraised and scored, and a total of 157 were of high and moderate quality addressing pain treatment.

**COMMENTS AND MODIFICATION**

Guidance was developed with sufficient detail to facilitate assessment of compliance (Institute of Medicine [IOM]) and auditing/monitoring (Appraisal of Guidelines for Research and Evaluation [AGREE]). Alternative options to manage conditions are provided in other ACOEM guidelines when comparative trials are available.

The only AGREE and IOM criterion not adhered to is incorporation of the views of the target population. Patients taking opioids, those with current or past opioid dependence or addiction, or other affected patient groups were not involved on the Panel or external review process, nor were advocates for or against the use of opioids. In accordance with the IOM’s Trustworthy Guidelines, this guideline underwent external peer review by 27 external reviewers, and subsequent revisions to the guidance, and detailed records of the peer review processes are kept, including responses to external peer reviewers.

The Evidence-based Practice Opioids Panel and the Research Team have complete editorial independence from ACOEM and Reed Group, which have not influenced the guideline. The literature is routinely monitored and formally searched at least annually for evidence that would materially affect this guideline. This guideline is planned to be updated at least every 3 years or more frequently should evidence require it.

A separate report on this guideline’s findings concerning the utility of opioids for safety sensitive work is available elsewhere. All treatment recommendations are guidance based on synthesis of the evidence plus expert consensus. These are recommendations for practitioners, and decisions to adopt a particular course of action must be made by trained practitioners on the basis of available resources and the particular circumstances presented by the individual patient.

**CLINICAL RECOMMENDATIONS**

**Comprehensive History and Physical Examination**

No quality studies assess the utility of a history and physical examination. Nevertheless, the Panel’s consensus recommendation is that a careful history and physical examination are highly important for appropriate pain management and consideration of opioid prescriptions regardless of pain acuity (Table 1). The Panel recommended to evaluate current and prior pharmacological and nonpharmacological methods for safe and effective control of pain, associated symptoms, and function. This comprehensive evaluation and documentation include a history, prior treatment, vocation, avocational activities, current functional level, medical history, family history, social history including substance(s) use (tobacco, alcohol, and illicit substances), review of systems, laboratory testing, and imaging studies as appropriate. In many cases of chronic pain, the most accurate “diagnosis” may be a symptom rather than a pathophysiological diagnosis, for example, chronic low back pain (LBP). An evidence-based treatment plan should focus on addressing the diagnosis or symptoms. Obstacles for treatment and rehabilitation should be identified and addressed.

**Acute Pain**

There were four quality trials of acute pain patients treated with opioids compared with placebo, with a small overall magnitude of benefit, whereas the adverse effects profile was high. Among trials for treatment of acute pain, ibuprofen was reportedly superior to codeine or acetaminophen for acute injuries including fractures. Diflunisal was equivalent to codeine for sprains, strains, and mild to moderate LBP. Valdecoxib was better tolerated and trended toward greater pain relief than tramadol for ankle sprains. Valdecoxib was equivalent to oxycodeone as assessed by pain ratings, but trended toward less rescue medication use and had fewer adverse effects among patients with spine and extremity pain. Global ratings for LBP showed that carisoprodol was superior to propoxyphene and has fewer adverse effects. Ketorolac was equivalent for pain relief, but superior to meperidine regarding adverse effects for treating severe LBP. Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments. Diflunisal was superior to codeine/APAP for LBP. One trial suggests that transcutaneous electrical stimulation was equivalent to codeine/acetaminophen for acute trauma. There are many emergency department trials of up to a few hours of treatment and no follow-up, with minimal if any differences, and thus of somewhat unclear utility for guidance. No quality trials suggest superiority of opioids to other active treatments. Prolonged use of opioids after an acute event has been associated with worse functional outcomes. Quality evidence indicates that safety profiles are considerably worse for opioids.

Routine use of opioids for treatment of acute pain is strongly not recommended and the recommendation for select use of opioids based purely on the evidence is downgraded from “A” to “C” (Table 1). Although there are a few trials of patients with acute pain treated with opioids compared with placebo, the overall magnitude of benefit is small while the adverse effects profile is sufficiently high that this resulted from...
TABLE 1. Summary of Panel Recommendations for Use of Opioids (Evidence-Rating; Confidence Level Rating).

<table>
<thead>
<tr>
<th>Pain Type</th>
<th>Recommended</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Pain (up to 4 weeks)</strong></td>
<td>Comprehensive history and physical (I; High Confidence)</td>
<td>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; moderate confidence)</td>
</tr>
<tr>
<td></td>
<td>Opioids for treatment of acute, severe pain (eg, crush injuries, large burns, severe fractures, injury with significant tissue damage) uncontrolled by other agents and/or with functional deficits caused by pain. They also may be indicated at the initial visit for a brief course for anticipated pain accompanying severe injuries (ie, failure of other treatment is not mandatory). A Schedule IV opioid may be indicated if there is true allergy to NSAIDs and acetaminophen, other contraindication to an alternative medication, or insufficient pain relief with an alternative. Recommend to taper off opioid use in 1 to 2 weeks. (C; High Confidence)</td>
<td>Routine opioid use for treatment of nonsevere acute pain (eg, LBP, sprains, or minor injury without signs of tissue damage) (A; High Confidence)</td>
</tr>
<tr>
<td></td>
<td>Initial screening of patients with more detailed screening for (i) requiring continuation of opioids beyond 2 weeks for those with an acute severe injury and (ii) at consideration of initiation for severe pain but no objective evidence. (I; High Confidence)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>The maximum daily oral dose recommended for opioid-naive, acute pain patients based on risk of overdose/death is 50-mg MED (see Fig. 1). Only the dosage required should be dispensed (C; Moderate Confidence)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinuation of opioids for patients with acute pain who have reached meaningful functional recovery. Patients treated for acute pain who are opioid-naive should generally require no tapering. Patients with acute pain treated with continuous opioids over 50-mg MED for longer than 3 weeks’ duration may benefit from brief tapering over 3 to 7 days. Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated. (I; High Confidence)</td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative pain (up to 4 weeks)</strong></td>
<td>Comprehensive history and physical (I; High Confidence)</td>
<td>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence)</td>
</tr>
<tr>
<td></td>
<td>Limited use of opioids as adjunctive therapy to more effective treatments (C; High Confidence)</td>
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<tr>
<td></td>
<td>Screening of patients for those requiring continuation of opioids beyond the second postoperative week (I; High Confidence)</td>
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<tr>
<td></td>
<td>Maximum daily oral dose recommended for opioid-naive, acute pain patients based on risk of overdose/death is 50-mg MED (see Fig. 1) (I; Moderate Confidence)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Discontinuation of opioids for postoperative patients who have reached meaningful functional recovery. Patients treated for acute pain who are opioid-naive should generally require no tapering. Patients with acute pain treated with continuous opioids over 50-mg MED for longer than 3 weeks’ duration may benefit from brief tapering over 3 to 7 days. Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is/are generally indicated. (I; High Confidence)</td>
<td></td>
</tr>
<tr>
<td><strong>Subacute (1–3 months) and Chronic Pain (&gt;3 months)</strong></td>
<td>Comprehensive history and physical (I; High Confidence)</td>
<td>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence)</td>
</tr>
<tr>
<td></td>
<td>Screening of patients prior to consideration of initiating a trial of opioids (I; High Confidence)</td>
<td>Opioid use for treatment of subacute and chronic nonmalignant pain. When indicated, opioid prescriptions should be patient-specific and limited to cases in which other treatments are insufficient and criteria for opioid use are met. (B; High Confidence)</td>
</tr>
<tr>
<td></td>
<td>Use of an opioid trial if other evidence-based approaches for functional restorative pain therapy have been used with inadequate improvement in function. Opioids are then recommended for treatment of function impaired by subacute or chronic severe pain (eg, inability to work because of any of the following: chronic severe radiculopathy, chronic severe peripheral neuropathies, complex regional pain syndrome, and severe arthroses). (I; Low Confidence)</td>
<td>Opioids for routine treatment of breakthrough superimposed on chronic pain in the absence of overt trauma or acute nociceptive pathology (eg, fracture, myocardial infarction, tooth abscess) (I; Moderate Confidence)</td>
</tr>
<tr>
<td></td>
<td>Maximum daily oral dose recommended based on risk of overdose/death is 50-mg MED (Fig. 1) (C; High Confidence)</td>
<td>Intrathecal drug delivery systems for chronic nonmalignant pain conditions (I; High Confidence)</td>
</tr>
<tr>
<td></td>
<td>Use of an opioid treatment agreement (opioid contract, doctor–patient agreement, or informed consent) to document patient understanding, acknowledgment of potential adverse effects, and agreement with the expectations of opioid use. If consent obtained, it is recommended that appropriate family members be involved in this agreement. (I; Moderate Confidence)</td>
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<tr>
<td></td>
<td>Baseline and random urine drug screening, qualitative and quantitative, for patients prescribed opioids for the treatment of subacute or chronic pain to evaluate presence or absence of the drug, its metabolites and other substance(s) use. In certain situations, other screenings (eg, hair particularly for information regarding remote use or blood) (for acute toxicity) may be appropriate. (C; High Confidence)</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
in the recommendation being downgraded. When needed, the lowest effective dose of a short-acting opioid is recommended for those with acute, severe pain uncontrolled by other agents such as nonsteroidal anti-inflammatory drugs (NSAIDs). Based on expert opinion, NSAIDs or acetaminophen should generally accompany an opioid prescription. Lower potency opioids are recommended when sufficient for pain relief. As-needed dosing rather than scheduled is generally indicated. Dispensing quantities should be only what is needed to treat the pain. Long-acting opioids are recommended for treatment of acute pain. Long-acting opioids are not recommended. If parenteral administration is required, ketorolac has demonstrated superior efficacy compared with opioids for acute severe pain. The maximum daily oral dose recommended based on risk of overdose/death is 50-mg morphine equivalent dose (MED) (Fig. 1). Exceeding that dose should be based on documented need, and incremental functional gain increased surveillance for adverse effects and frequent reconsideration of benefit versus risk. Lower doses are also indicated in the elderly, women, and those of low body weight. Prescribed drug monitoring program databases are recommended to be checked. Considerable caution is recommended among those receiving other CNS-depressing medications such as benzodiazepines or depressive medications, and patients with concomitant psychiatric disorders or other risk factors for adverse effects, overdose, and death (Table 2). Because of risk of impairment and lost time from work due to medication effects, opioids should be prescribed at night or while not working when possible. The Panel recommends tapering the opioid in 1 to 2 weeks. Potential benefits of prescribing opioids are improved short-term pain control and accelerated functional recovery, whereas potential harms are numerous (Table 2).

**Postoperative Pain**

Findings and recommendations for postoperative pain management with opioids are mostly comparable with those treating acute pain (Table 1). Nevertheless, studies also include at least one trial showing modestly improved long-term knee range of motion and fewer venous thromboses after continuous femoral nerve catheter analgesia instead of solely using oral narcotics. Ketorolac appeared superior as a primary pain treatment supplemented with opioids compared with opioids alone for spine and joint procedures. Data also suggest that patient-controlled analgesia may not be superior to intramuscular opioids. Thus, opioids may have deleterious postoperative effects if not used solely as adjunctive medications. Preoperative consultation with anesthesiology and/or pain management specialists may be needed for those taking chronic opioids preoperatively. Additional differences from the acute pain recommendations above include administration of NSAIDs at the time of surgery without undue complications, although these studies would likely be underpowered for rare complications. For major surgeries, scheduled opioid medication is frequently required. Opioids sufficient to participate in therapeutic exercise (eg, progressive ambulation) and allow sleep may be needed. It is recommended to dispense only what is needed to avoid either overmedication and/or

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**TABLE 1. (Continued)**

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation for subacute and chronic pain patients who (i) used opioids on a chronic basis and (ii) (any one of) no demonstrated functional gain, noncompliance, aberrant drug screening results and/or diversion, adverse effects (eg, cognitive impairment, falls, poor judgment, untreated sleep apnea, psychological disorders, and concurrent use of depressant medications such as benzodiazepines and diphenhydramine). Tapering is recommended if the opioid was used at a moderate or high level (eg, above 50–100 mg of morphine equivalent dose) on a long-term basis. Consultation with an addiction specialist or psychiatrist is recommended for complex patients (eg, high-dose patients, prior withdrawal problems, complex psychosocial confounders). Transitioning to only an NSAID or acetaminophen or complete cessation of analgesics is generally indicated. (I; High Confidence)</td>
<td>---</td>
</tr>
</tbody>
</table>

*The Evidence-based Practice Opioids Panel has 100% agreement on these recommendations. Recommendations are based on critically appraised higher-quality research evidence and on expert consensus observing First Principles when higher-quality evidence was unavailable or inconsistent. It is recommended to utilize the more detailed indications, specific appropriate diagnoses, temporal sequencing, prior testing or treatment, and contraindications that are elaborated in more detail in the body of the guideline in using these recommendations in clinical practice or medical management. These recommendations are not simple “yes/no” criteria, and the evidence supporting the recommendations is in nearly all circumstances developed from typical patients, not unusual situations or exceptions.

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**FIGURE 1.** Death rate (hazard ratio) vs morphine equivalent dosage (mg/d). Statistical significance present for acute and chronic pain at and above 50 mg/day of oral morphine equivalent dose. Adapted from Dunn and Bohnert.110

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placebo-controlled clinical trials addressing
Chronic Noncancer Pain
use recommendations given later apply.
beyond 1 month, the subacute/chronic opioid
opioid use. For those requiring opioid use
expected and require high doses or ongoing
considered for those who do not improve as
and/or mental health consultation should be
programs should be checked. Psychiatric
matters with recommendations summarized
as adjunctive therapy to more effective treat-
management is recommended for limited use
may somewhat moderate the cautions about
the recommended MED limit of 50 mg and overdoses (Fig. 1). Nevertheless, the
evidence that early ambulation is critical to
functional recovery is strong. Therefore,
oversedation that interferes with function is
a concern. For patients on chronic opioids
preoperatively, especially moderate to high
doses, consultation with a physician expe-
rienced in managing these complex cases
may be necessary. Thus, thoughtful use of
medications or treatments should be used prior to
consideration of an opioid prescription for
subacute/subacute pain patients.263
Tramadol is a synthetic opioid and is a
controlled substance in some US states. Tra-
madol is associated with potential abuse264
and has a similar adverse effect profile
as other opioids. Nevertheless, death risks,
while elevated, seem to be somewhat lower
than other opioids. Tramadol seems to be a
better initial option than more potent opi-
oids. Nevertheless, with the long-term use,
especially higher dose, it may be considered
equivalent to other opioids for purposes of
this guideline. It has also been associated
with motor vehicle crashes.76

For subacute and chronic pain, an
opioid trial, preceded by full informed
consent and a trial agreement, is recom-
mended if other evidence-based approaches
for functional restorative pain therapy have
been implemented, with documented ad-
herence, and with inadequate improvement in
function63,81 (Tables 1 and 3). Pain or
diversion. Weaning should begin as soon as
function is recovering and pain is subsiding.
Also, closely monitored inpatient settings
may somewhat moderate the cautions about
the recommended MED limit of 50 mg and overdoses (Fig. 1). Nevertheless, the
evidence that early ambulation is critical to
functional recovery is strong. Therefore,
oversedation that interferes with function is
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been implemented, with documented ad-
herence, and with inadequate improvement in
function63,81 (Tables 1 and 3). Pain or

Of these, 52% lasted up to 1 month, 12%
were 1 to 2 months, and 34% were 3 months
in duration. Only one trial was longer than
3 months at 16 weeks.251 There is only one
quality trial that targeted subacute pain, find-
ing flupirtine equivalent to tramadol for sub-
acute LBP.252 As tolerance develops quickly,
guidance for subacute and chronic pain are
combined.

For treatment of subacute and chronic
pain, there is quality evidence that other
medications and treatments are at least equi-
vivalent if not superior for subacute or chronic
pain (eg, NSAIDs,253–256 nortriptyline,257
clonidine,258 and flupirtine.252) No quality
trials suggest superiority of opioids to other
medications or treatments. One trial suggests
that morphine is superior to benztrptine for
pain, but not function.259 Among trials for

treatment of subacute or chronic pain, one
trial failed to find superiority of morphine
to nortriptyline for treatment of chronic
lumbar radiculopathy.257 Another found
neither morphine nor mexiletine superior to
placebo.260 Another found celecoxib superior
to tramadol for chronic LBP253 Diclofenac
was superior to dextropropoxyphene/APAP
for treatment of hip or knee osteoarthritis.254
Diclofenac was approximately equivalent
to tramadol in another trial.256 Naproxen
was equivalent to oxyndode for treatment
of chronic LBP.255 There are no trials
documenting improved objective functional
outcomes, with more than 100 studies doc-
umenting many adverse effects.261 There is
quality evidence that opioids are associated
with reduced pain thresholds.262 Thus, there
is considerable evidence that other medica-
tions and treatments should be used prior to
consideration of an opioid prescription for
subacute/subacute pain patients.263


<table>
<thead>
<tr>
<th>Medications/Substances</th>
<th>Psychiatric Disorders</th>
<th>Sleep</th>
<th>Cardiovascular</th>
<th>Social Support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines (F)</td>
<td>Depression (F)</td>
<td>Sleep disorders (F)</td>
<td>Coronary artery disease (F)</td>
<td>Unemployment (F)</td>
</tr>
<tr>
<td>H1 Antihistamines (F)</td>
<td>Anxiety (F)</td>
<td>Insomnia</td>
<td>Dysrhythmia (F)</td>
<td>Less than high school education (F)</td>
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<tr>
<td>Illicit substances (including marijuana) (F)</td>
<td>Personality disorder (F)</td>
<td>Respiratory disorders</td>
<td>Cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>Tobacco (F)</td>
<td>Thought disorders (F)</td>
<td>Chronic obstructive pulmonary disease</td>
<td>Orthostatic hypotension</td>
<td>Lack of regular church attendance (F)</td>
</tr>
<tr>
<td>Alcohol (F)</td>
<td>Attention-deficit/hyperactivity disorder (F)</td>
<td>Asthma</td>
<td>Metabolic/renal</td>
<td>Legal problems (F)</td>
</tr>
<tr>
<td>Psychotropic medication use (F)</td>
<td>Posttraumatic stress disorder (F)</td>
<td>Recurrent pneumonia</td>
<td>Severe obesity</td>
<td>Family dysfunction (F)</td>
</tr>
<tr>
<td>Substance abuse history (F)</td>
<td>Impulse control problems (F)</td>
<td>Gastrointestinal</td>
<td>Thermoregulatory problems</td>
<td>White race (F)</td>
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<tr>
<td>Aberrant medication taking behaviors (F)</td>
<td>Thought disorders (F)</td>
<td>Abdominal pain</td>
<td>Water retention</td>
<td>Reproductive</td>
</tr>
<tr>
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<td>Suicidal risk (F)</td>
<td>Gastroparesis</td>
<td>Renal failure</td>
<td>Testosterone deficiency</td>
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<tr>
<td>Dementia</td>
<td></td>
<td>Constipation</td>
<td>Osteopenia</td>
<td>Erectile dysfunction</td>
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<tr>
<td>Cognitive dysfunction</td>
<td>Pain-related</td>
<td>Hepatitis (F)</td>
<td>Osteoporosis</td>
<td>Testosterone deficiency</td>
</tr>
<tr>
<td>Gait problem</td>
<td>Allodynia</td>
<td>Cirrhosis (F)</td>
<td>Genotype(s)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Tremor</td>
<td>Hyperalgesia</td>
<td>Nausea, emesis</td>
<td></td>
<td>Amenororhea</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>Advanced age†</td>
<td>Infectious Diseases</td>
<td>Family History</td>
<td>Infertility</td>
</tr>
<tr>
<td>Coordination problems</td>
<td>Middle ages (teens to ~50s) (F)</td>
<td>Human immunodeficiency virus</td>
<td>Substance use disorder</td>
<td>Ineffective birth control</td>
</tr>
<tr>
<td>Slow reaction time</td>
<td>Male</td>
<td></td>
<td></td>
<td>Prostatic hypertrophy</td>
</tr>
</tbody>
</table>

F = Adverse effect includes reported fatality risk.
†Especially with mentation issues, fall risk, and debility.
TABLE 3. Opioids for Treatment of Chronic Pain With Factors to Consider an Opioid Trial, Trial Parameters, and Opioid Maintenance Continuation

Consider an opioid trial if:
- A severe disorder warranting potential opioid treatment is present (eg, complex regional pain syndrome, severe radiculopathy, severe degenerative joint disease).82
- Other evidence-based approaches for functional restorative pain therapy have been used with inadequate improvement in function.63, 81
- Other approaches that should have been first utilized include physical restorative approaches, behavioral interventions, self-applied modalities, nonopioid medications (including nonsteroidal anti-inflammatory drugs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain) and functional restoration. For patients with low back pain, this also includes* fear avoidance belief training and ongoing progressive aerobic exercise, and strengthening exercises. For CRPS patients, this includes progressive strengthening exercise. For degenerative joint disease, this includes nonsteroidal anti-inflammatory drugs, weight loss, aerobic and strengthening exercises.
- Function is impaired by subacute or chronic severe pain (eg, inability to work or participate in aerobic or strengthening exercises).266
- Pain or pain scales alone are insufficient reasons.82, 113, 265–275
- Prescription drug monitoring program database should be checked, if available, with a finding of neither opioid prescriptions from other providers nor evidence of misreporting.
- There are few or no risks for adverse effects and deaths from opioids. Because of more than 10-fold elevated risk of death, caution is particularly warranted among those taking benzodiazepines, illicit substances (eg, marijuana), H1-anti-histamines, and among those unemployed.30, 112–114 There are many additional risks (Table 2).
- Should not receive opioids if they use illicit substances unless there is objective evidence of significant trauma or moderate to severe injuries.

Parameters of the opioid trial:
- Functional target defined.
- Ongoing active exercise program is prescribed and complied with.
- Nonopioid prescriptions (eg, nonsteroidal anti-inflammatory drugs, acetaminophen) absent a contraindication should nearly always be the primary pain medication and accompany an opioid prescription. Other medications to consider include topical agents, norepinephrine adrenergic reuptake blocking antidepressants, or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).
- Informed consent and treatment agreement is signed (available at: http://go.reedgroup.com/opioid-treatment-agreement.html).
- Lowest effective dose should be used.109
- Weaker opioids should be used whenever possible.134, 135 Meperidine is not recommended for chronic pain due to bioaccumulation and adverse effects.
- Only one opioid prescribed.
- Prescribed on a regular basis, not as needed, considering at night or when not at work.
- Dispensing only what is needed to treat the pain.†
- Frequent, eg, weekly follow-up to track progress toward functional goal, adverse effects, compliances, and surreptitious medication use.
- Discontinuation of the opioid if there is no functional gain, resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects.
- Nonopioid medications (including nonsteroidal anti-inflammatory drugs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants, or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).
- Ongoing active exercise program is prescribed and complied with.
- Functional target defined.
- Discontinuation of the opioid if there is no functional gain, resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects.
- Frequent, eg, weekly follow-up to track progress toward functional goal, adverse effects, compliances, and surreptitious medication use.
- Lowest effective dose should be used.109
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- Dispensing only what is needed to treat the pain.†
- Frequent, eg, weekly follow-up to track progress toward functional goal, adverse effects, compliances, and surreptitious medication use.
- Discontinuation of the opioid if there is no functional gain, resolution of pain, improvement to the point of not requiring opioids, intolerance or adverse effects.
- Nonopioid medications (including nonsteroidal anti-inflammatory drugs, acetaminophen, topical agents, norepinephrine adrenergic reuptake blocking antidepressants, or dual reuptake inhibitors; also antiepileptic medications particularly for neuropathic pain).

Maintenance of the opioid (same as the opioid trial parameters above plus):
- Less frequent follow-up, eg, every 3 to 6 months is sufficient for many clinically stable patients.
- Consider conversion to, and maintenance on extended-release/long-acting opioids used on a scheduled basis, rather than as needed.82
- As-needed opioids should generally be avoided for treatment of chronic pain, although limited use for an acute painful event (eg, fracture, sprain) is reasonable.
- Sublingual fentanyl is not recommended for treatment of subacute or chronic pain. Caution is warranted with fentanyl patches due to unpredictable absorption.
- Prescription drug-monitoring program databases should be checked, if available, for opioid prescriptions from other providers or evidence of misreporting.
- Ongoing compliance with the opioid consent and agreement.

* A previous trial of a muscle relaxant is generally recommended. Nevertheless, if an opioid trial is contemplated, cessation of all depressant medications, including muscle relaxants, is advisable.
† Generally, this should be sufficient to cover 1 week of treatment at a time during the trial phase. If a trial is successful at improving function, prescriptions for up to 90-day supplies are recommended.

TREATMENT AGREEMENTS AND INFORMED CONSENT

Although there are no quality studies to document efficacy of opioid consent forms and/or opioid treatment agreement contracts, they are commonly used to monitor patients on opioids.39, 41, 62, 63, 277, 278 These agreements usually include provision for urine drug testing for assessing compliance for use of that particular opioid, as well as ascertaining other illicit substances use.62, 63, 279–282 This guideline developed a combined Opioid Consent Form and Opioid Treatment Agreement into one form that is recommended for subacute and chronic pain patients (available at:}
Urine Drug Screening

Most evidence documents aberrant drug screen prevalence rates of 32% to 45%.277,280,281,283-286 Drug screening may identify both aberrant use and other substance use outside a treatment agreement.280,281 Urine drug screening, qualitative and quantitative, is recommended at baseline, randomly at least two to four times a year and at termination for patients prescribed opioids for the treatment of subacute or chronic pain; these tests are to evaluate presence or absence of the drug, its metabolites, and other substance(s) use.63 Higher frequencies of drug screening are recommended among those consuming more than 50 mg of MED (Fig. 1). It is recommended to be performed in a federally certified laboratory with a two-step process including confirmatory gas chromatography–mass spectrometry. In certain situations, other screenings (eg, hair particularly for information regarding remote use287–295) or blood (for acute toxicity) may be appropriate. Standard urine drug/toxicology screening processes are recommended among those consuming more than 50 mg of MED (Fig. 1). It is recommended to be performed in a federally certified laboratory with a two-step process including confirmatory gas chromatography–mass spectrometry. In certain situations, other screenings (eg, hair particularly for information regarding remote use287–295) or blood (for acute toxicity) may be appropriate.

Tapering Opioids

Many studies have described widely varying rates of tapering opioids, mostly ranging from 10% per week to 50% per day.40,56,303,304 Nevertheless, there are no high- or moderate-quality studies among the desired target population to define the best methods. The clinical approach is, therefore, largely empirical.

“Breakthrough Pain”

Non–cancer-related breakthrough pain (BTP) has been treated with opioids.205–308 There are cases in which BTP may indicate hyperalgesia, or potentially, insufficient treatment of pain. Nevertheless, in treating BTP, functional gain is recommended to be documented; otherwise, the total dose should revert to the prior dose level. The treatment of BTP with opioids is likely a common means of dose escalation.309 Thus, treatment of nonmalignant BTP in the absence of overt trauma is not recommended.

Intrathecal Opioids

No quality studies document efficacy of intrathecal opioid delivery systems for treatment of chronic nonmalignant pain. Intrathecal opioid delivery systems are invasive and costly, with possible significant adverse effects, including potential long-term sequelae from both implantation/retention of the devices, including granuloma formation, and those associated with the concurrent use of intrathecal opioids.137,138,310–313 Thus, with a lack of documented efficacy, invasiveness, serious adverse effects, and marked costs, these devices are not recommended. For new patients, there are fewer barriers for implementing this guideline, whereas for existing patients, this guideline should not be interpreted as requiring device removal.

Adverse Effects

Opioids have been associated with numerous adverse effects, which differ somewhat on the basis of the specific drug and route of administration. In aggregate, these effects include (see also Table 2) opioid-induced hyperalgesia,199,200 lower pain thresholds (hyperalgesia), nausea, vomiting, delayed gastric emptying, constipation, pruritus, drowsiness, sedation, respiratory depression,54,141–178 clouding of consciousness or “mental fog,” dysphoria, decreased concentration, lack of coordination, myoclonus, muscle rigidity, dizziness, euphoria, sexual dysfunction, bladder dysfunction, immune system effects, hair loss, anaphylaxis, sleep disturbance,62,138,179–192 motor vehicle crashes,136,193–196 lower return to work status,197 injuries and other adverse accidents,132 disability,197,198 and drug tolerance.199 Deaths from unintentional and intentional overdoses, misuse, and therapeutic misadventures occur, although they are infrequent relative to the adverse events listed previously.

There is no quality literature to identify which patients can be safely prescribed opioids without escalation of dose or other adverse risks. This caused a downgrading of the level of evidence from “C” to “I” especially when combined with evidence of adverse effects (see Table 2) in addition to concerns regarding the inability to control escalating doses.309 Prescribing opioids may initiate the path to opioid dependency, addiction, and other adverse effects. Tolerance is a common occurrence, although generally not significantly problematic. Addiction and drug-seeking behaviors are less common.259,314–315 Yet, approximately 80% of patients experience some adverse effects from opioids and approximately 33% to 80% do not finish a clinical trial with opioids due primarily to these adverse effects (the large range in estimates is in part due to trial design such as whether a washout phase was included, length of treatment, and severity of pain).319–321

Although the clinical interview remains an important method to identify risk for aberrant drug-related behaviors,52,323 it is neither systematic nor efficient. Thus, there are many screening/monitoring methods that have been developed.41,322–342 The three tools with the largest volume of research seem to be the Screener and Opioid Assessment for Patients with Pain (SOAPP) and its revised version (SOAPP-R), the Pain Medication Questionnaire, and the Current Opioid Misuse Measure. All three of these tools have undergone partial validations, although none of them has been fully validated to document prevention of opioid misuse/abuse.200,262,271,273,322,323,325–328,331,340,341,343–354 The Pain Disability Index is also widely used; it is also wholly subjective and has somewhat fewer supportive data.355,356

Opioid deaths have been associated with CYP2D6 and OPRM1 gene variations,205–361 with the CYP cytochromes (CYP 3A4/3A5, CYP2D6, CYP2C9, CYP2D9) responsible for metabolism through the cytochrome P450 system and genetic variations impairing opioid metabolism. As one example of potential clinical impacts, there is a strong tendency for those of Chinese ancestry, as well as some whites, not to metabolize codeine to morphine. Currently, screening for genetic risks prior to opioid treatment is not in widespread use.52–53 Non-Cytochrome-blocking drugs57 and cytochrome-inducing pharmaceuticals also influence efficacy and toxicity.364,366,368,369–387

Opioids are moderate to high cost, depending on the duration of treatment. Provider and organizational barriers to implement recommendations to prescribe

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nonopioid medications and therapies are low, consisting primarily of altering practice habits. Barriers regarding dose limit recommendations are similarly low, consisting primarily of altering practice habits. Barriers to dose reduction are greater for established patients, especially on higher doses. Tools are identified to assess functional progress, assessing opioid risk, and guidance to assist with tapering. Urine drug testing guidance has also been developed.

**RESEARCH RECOMMENDATIONS**

None of 28 comparative effectiveness trials reviewed reported that opioids are superior to other medications or treatments for acute, subacute, chronic, or postoperative pain. Several trials suggested that opioids are inferior to other medications, generally NSAIDs. Reported magnitudes of benefit of opioids compared with placebo are modest. As there currently is none, high-quality evidence regarding objective gains in function from treatment with opioids for chronic pain is a particularly important need.

For chronic pain, there are no placebo-controlled trials lasting more than 4 months. Thus, long-term efficacy of opioids for chronic pain is unknown. There also is no quality literature to identify which patients with chronic pain is unknown. There also is no quality literature to identify which patients are likely to tolerate opioids, even if they are potentially indicated.408, 314, 319, 388, 390–393 The vast majority of the trials of opioids either are industry-sponsored or have significant conflicts of interest. By contrast, epidemiological studies of motor vehicle crash risk associated with opioids show no significant conflicts of interest.79 Sponsored studies have been frequently reported to have better apparent results and lower complication rates than studies conducted by independent investigators.393–396 A prior review of 546 pharmaceutical trials found that 63% were primarily funded by industry, 14% by government, and 23% by nonprofit or nonfederal organizations.395 Industry sponsorship revealed in the present systematic review and guideline on opioid use was greater still especially for chronic pain. For acute pain, 42.1% of 19 trials for patients with acute pain, 60.0% of 20 perioperative and postoperative trials, and 87.1% of 93 chronic pain patient trials with sponsorship identified had partial or full industry sponsorship. When analyzing only the studies that had a minimum level of follow-up time (1, 7, and 30 days for acute, postoperative, and chronic pain, respectively), 80.0%, 80.0%, and 93.9% had partial or full industry sponsorship, respectively.

The number of comparative trials with nonopioid treatment arms compared to an opioid is fairly limited and focused on a few medications. Altogether, there are 9 acute pain, 7 peri/postoperative, and 12 chronic pain comparative trials that scored high or moderate quality. Industry sponsorship of these is similarly 73.9%. Thus, the large majority of evidence regarding efficacy of opioids is at least partially industry-sponsored or with conflicts of interest. These analyses provide additional direction for needed nonconflicted research.

Many of the studies have low sample sizes and the designs of the trials vary, especially for treatment of chronic pain. In those studies that include all patients in a randomized controlled trial, overall dropout rates (including washout phases, run-in phases, conversion phases, titration phases, trial “enrichment” phases, as well as those who drop out during the trial) and adverse effect profiles each frequently exceed 50% and several are more than 75%.261, 308, 314, 319, 388, 393 Studies that include or require prior chronic opioid use and/or have early washout and/or run-in phase(s) likely remove patients who (i) cannot tolerate the adverse effects, (ii) are unwilling to endure the adverse effects for a duration of time, (iii) recognize prior adverse impacts on function, and/or (iv) have lower psychological and substances use profiles. Consequently, the bulk of reported chronic pain trials likely have artificially lower adverse-effect profiles than treatment of the general population.394 Ergo, fewer than 50% of patients with chronic pain appear likely to tolerate opioids, even if they are potentially indicated.308, 314, 319, 388, 390–393

The evidence-based Practice Opioids Panel recognizes the considerable work of the managing editors: Marianne Dreger, MA (Production), and Julie A. Ording, MPH (Research). The Opioids Panel also much appreciates the research for this guideline that was conducted by the research team: Ulrike Ott, MSPH; Atin C. Effiong, MPH; Debra G. Passeray, MS; William G. Caughey, MS; Holly Uphold, PhD; Alzina Koric, MPP; Zac Carter, BS; Zachary C. Arnold, BS; Katherine Schweif, BS; Kylee Tokita, BS; Leslie M. Cepeda-Ech Weaver; Ninoska De Jesus; and Jeremiah L. Dortch, BS. Drs Hegmann and Thiese also conducted research for this guideline. Dr Harris served as the Opioids Panel methodologist.

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