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.

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In contrast to prior efforts to limit opioid use since the early 1900s,[1] Portenoy and Foley[2] 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 of 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.[3,4] Recognition of undertreatment of pain in many populations, legislative,[5] litigation,[6] regulatory,[7–9] and health care accreditation-related activities[10–13] further contributed to lowering barriers to, and rapid increases in opioid prescriptions, primarily for CNCP.[14]

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.[15,16] 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.[18–27] Deaths related to opioids quadrupled from 1999 through 2010, increasing from 4000 to 16,000 deaths in 2010,[28] occurring in both urban and rural areas.[29,30] 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.[35–63] Recent reviews of these opioid guidelines found widely varying quality.[64,65] There was no guideline identified meeting current guidelines quality standards[66] and addressing up-to-date and detailed opioid use guidance for nonmalignant pain management.

GUIDELINE 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 overdoses, 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

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,[67] and formulation of recommendations.[68–70] 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 DuBrueler, Charl Els, Steven Mandel, David W. McKinney, Rafael Miguel, Kathryn L. Mueller, Robert J. Nadig, Michael I. Schaffer, Larry Studt, 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*[39,71–78] 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.[68–70] Articles scoring moderate or high quality were included.[68–70]

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]).[66,67] Alternative options to manage conditions are provided in other ACOEM guidelines when comparative trials are available.[39,71–78]

The only AGREE[67] 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.[66]

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 guidance. 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 use of opioids for safety sensitive work is available elsewhere.[79] 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.[63,80–82] A 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.[62,63,80,81,83,84] This systematic approach should result in a clear diagnosis to treat as evidence indicates.[63,80,83] 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.[85] Diflunisal was equivalent to codeine for sprains, strains, and mild to moderate LBP.[86] Valdecoxib* was better tolerated and trended toward greater pain relief than tramadol for ankle sprains.[87] Valdecoxib was equivalent to oxycodone as assessed by pain ratings, but trended toward less rescue medication use and had fewer adverse effects among patients with spine and extremity pain.[88] Global ratings for LBP showed that carisoprodol was superior to propoxyphene and has fewer adverse effects.[89] Ketorolac was equivalent for pain relief, but superior to meperidine regarding adverse effects for treating severe LBP.[90] Ketorolac was also superior to codeine/acetaminophen for acute LBP treated in emergency departments.[91] Diflunisal was superior to codeine/APAP for LBP.[92] One trial suggests that transcutaneous electrical stimulation was equivalent to codeine/acetaminophen for acute trauma.†[93] 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.[94–105] 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.[106–108] 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

*Valdecoxib is currently withdrawn from the market.
†Flupirtine also has evidence of efficacy, although not currently approved in the United States.

TABLE 1. Summary of Panel Recommendations for Use of Opioids (Evidence-Rating; Confidence Level Rating).

	Recommended	Not Recommended
Acute Pain (up to 4 weeks)	Comprehensive history and physical (I; High Confidence) 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) 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) 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) 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)	Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; moderate confidence) Routine opioid use for treatment of nonsevere acute pain (eg, LBP, sprains, or minor injury without signs of tissue damage) (A; High Confidence)
Postoperative pain (up to 4 weeks)	Comprehensive history and physical (I; High Confidence) Limited use of opioids as adjunctive therapy to more effective treatments (C; High Confidence) Screening of patients for those requiring continuation of opioids beyond the second postoperative week (I; High Confidence) 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) 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)	Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence)
Subacute (1–3 months) and Chronic Pain (>3 months)	Comprehensive history and physical (I; High Confidence) Screening of patients prior to consideration of initiating a trial of opioids (I; High Confidence) 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) Maximum daily oral dose recommended based on risk of overdose/death is 50-mg MED (Fig. 1) (C; High Confidence) 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) 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)	Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence) 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) 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) Intrathecal drug delivery systems for chronic nonmalignant pain conditions (I; High Confidence)

(*Continued*)

TABLE 1. (*Continued*)

	Recommended	Not Recommended
	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/are generally indicated. (I; High Confidence)	

*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[70] 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.

Recommendations are made under the following categories[69,70]:

- Strongly Recommended, "A" Level
- Moderately Recommended, "B" Level
- Recommended, "C" Level
- Insufficient—Recommended (Consensus-based), "I" Level
- Insufficient—No Recommendation (Consensus-based), "I" Level
- Insufficient—Not Recommended (Consensus-based), "I" Level
- Not Recommended, "C" Level
- Moderately Not Recommended, "B" Level
- Strongly Not Recommended, "A" Level

Confidence in Ratings based in part on GRADE system: www.ncbi.nlm.nih.gov/pmc/articles/PMC2335261/pdf/bmj-336-7650-analysis-00924.pdf

LBP, low back pain; MED, morphine equivalent dose; NSAID, nonsteroidal anti-inflammatory drug.

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).[109] 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. Short-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.[90,91] The maximum daily oral dose recommended based on risk of overdose/death is 50-mg morphine equivalent dose (MED)[110] (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,[111] and those of low body weight. Prescription drug monitoring program databases are recommended to be checked. Considerable caution is recommended among those receiving other CNS-depressing medications such as benzodiazepines or depressant medications, and patients with concomitant psychiatric disorders or other risk factors for adverse effects, overdose, and death (Table 2).[17,29,30,32,112–133] Because of risk of impairment and lost time from work due to medication effects,[134,135] opioids should be prescribed at night or while not working when possible.[136] 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).

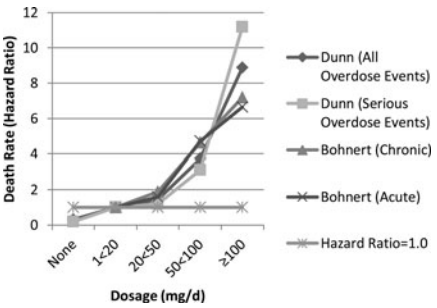

FIGURE 1. Death rate (hazard ratio) vs morphine equivalent dosage (mg/d). Statistical significance present for acute and chronic pain at and above 50 mg/day of oral morphine equivalent dose. Adapted from Dunn[201] and Bohnert.[110]

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 less opioid use with pregabalin for 14 days plus epidural and opioid management after total knee arthroplasty.[240] Another trial found superior range of motion and fewer venous thromboses after continuous femoral nerve catheter analgesia instead of solely using oral narcotics.[241] Ketorolac appeared superior as a primary pain treatment supplemented with opioids compared with opioids alone for spine and joint procedures.[242] Data also suggest that patient-controlled analgesia may not be superior to intramuscular opioids.[243,244] 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,[245–250] 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

TABLE 2. Risk Factors for Adverse Effects and Death from Opioids[29,30,32,41,54,62,112–116,118–133,136–239]

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

F = Adverse effect includes reported fatality risk.
†Especially with mentation issues, fall risk, and debility.

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 a concern. For patients on chronic opioids preoperatively, especially moderate to high doses, consultation with a physician experienced in managing these complex cases may be necessary. Thus, thoughtful use of short-acting opioids for postoperative pain management is recommended for limited use as adjunctive therapy to more effective treatments with recommendations summarized in Table 1. Prescription drug monitoring programs should be checked. Psychiatric and/or mental health consultation should be considered for those who do not improve as expected and require high doses or ongoing opioid use. For those requiring opioid use beyond 1 month, the subacute/chronic opioid use recommendations given later apply.

Chronic Noncancer Pain

There are 67 high- or moderate-quality placebo-controlled clinical trials addressing opioid use for patients with chronic pain. 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, finding flupirtine equivalent to tramadol for subacute 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 equivalent 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 benztropine 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 LBP.[253] 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 oxycodone for treatment of chronic LBP.[255] There are no trials documenting improved objective functional outcomes, with more than 100 studies documenting many adverse effects.[261] There is quality evidence that opioids are associated with *reduced* pain thresholds.[262] Thus, there is considerable evidence that other medications and treatments should be used prior to consideration of an opioid prescription for chronic/subacute pain patients.[263]

Tramadol is a synthetic opioid and is a controlled substance in some US states. Tramadol is associated with potential abuse[264] 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 opioids. 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.[79]

For subacute and chronic pain, an opioid trial, preceded by full informed consent and a trial agreement, is recommended if other evidence-based approaches for functional restorative pain therapy have been implemented, with documented adherence, and with inadequate improvement in function[63,81] (Tables 1 and 3). Pain or

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 avoidant 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, noncompliance, surreptitious medication use, medication misuse (including self-escalation and sharing medication), aberrant drug screening results, diversion, consumption of medications, or substances advised to not take concomitantly (eg, sedating medications, alcohol, benzodiazepines).[81]

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.

pain scales alone are recommended as insufficient reasons.[82,113,265–276] Examples of functional gains to track include walking distance, numbers of repetitions of specific exercises, return to work, and return to modified work. Maintenance opioids are recommended for those achieving functional gains (Table 3).

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:

www.mdguidelines.com/documents/stateguidelines/apg3_opioid_06_treatment_agreement.pdf).

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 spectroscopy. In certain situations, other screenings (eg, hair particularly for information regarding remote use[287–292]) or blood (for acute toxicity) may be appropriate. Standard urine drug/toxicology screening processes are recommended (consult a qualified medical review officer).[279,293,294] To be useful, one must choose a test that the laboratory states will detect the presence of the opioid (and metabolites) being prescribed, assuming that the patient is actually taking and not diverting the medication. It is also important that the test chosen is able to detect the drugs that might be used/abused surreptitiously, and that increases the risk of accidental overdose mortality (eg, benzodiazepines, barbiturates). If there is an aberrant drug screen result (either positive for unexpected drugs or unexpected metabolites or unexpectedly negative results), there should be a careful evaluation of whether there is a plausible explanation (eg, drug not tested, drug metabolite not tested, laboratory cutpoint, and dosing interval would not capture the drug/metabolite, laboratory error). In the absence of a plausible explanation, those patients with aberrant test results should have the opioid discontinued or weaned.[40,81]

Opioid Rotation

Conversion of opioids to an MED is helpful to transfer from one opioid to another. This is most commonly performed to attempt to achieve a better functional outcome and/or to reduce adverse effects. Quality evidence to support this practice has not been published. Several resources are available[295,296] that include a spreadsheet-based calculator[297] and on-line converting tool.[298] To avoid drug overdoses, when transferring from one opioid to another, the MED prescribed should be approximately 50% of the prior dose.[299–302]

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.[305–308] 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 few 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,[139,140] 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 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.[259,314–318] 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,[322,323] 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 OPRMI gene variations,[357–361] with the CYP cytochromes (CYP 3A4/3A5, CYP2D6, CYP2C9, CYP2D9) responsible for metabolism through the cytochrome P450 system,[362] 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.[363–366] Cytochrome-blocking drugs[367] 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

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 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 can safely be 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 major adverse effects reviewed elsewhere in addition to concerns regarding the inability to control escalating doses.[309] The ability to prospectively identify patients who are able to realize both long-term safety and efficacy of opioids is another area of much-needed 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 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.[395–398] 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.

APPLICABILITY AND IMPLEMENTATION ISSUES

Strengths of this guideline include its systematic synthesis of many quality studies. The evidence is largely consistent for many of the guideline questions, including both strong and weak opioids. Findings include a lack of studies showing superiority of opioids for pain treatment. The dose–response relationship between morphine equivalent dose and risk of fatality has been reproduced, and duplicated between acute and chronic pain patients. Therefore, the overall evidence base is strongly supportive of most of this guideline's recommendations. This guideline has also identified additional interventions that, if implemented, would likely reduce the adverse effects and mortality.

Weaknesses of this guideline include the relatively few comparative trials and heavy industry sponsorship of trials and conflicts of interest in the vast majority of studies. Implementation of this guideline could potentially result in pain, which could be undertreated when it may be successfully treated with opioids, although the guideline includes provisions to avoid that.

SUMMARY

The ACOEM Evidence-based Practice Opioids Panel concludes that quality evidence currently fails to demonstrate superiority of opioids to other medications and treatments for treatment of pain. It recommends comprehensive history and physical examinations. Selective use of the lowest effective, short-acting opioid dose is recommended as adjunctive treatment for patients with acute and postoperative pain that is inadequately treated with NSAIDs or other treatments. The strongest risk factors for overdose and deaths include concomitant use of benzodiazepines, illicit substances, unemployment status, psychiatric disorders, and a substance(s) abuse history. Opioid consent and treatment agreements are recommended for treatment of subacute and chronic pain with opioids. Carefully conducted trials on highly select patients with subacute and chronic pain are recommended, as well as opioid maintenance only with documented functional gain(s). A strong and reproducible dose–response relationship identifies a recommended MED limit of 50 mg/day for acute or chronic pain. Higher doses are recommended to require documented commensurately greater functional benefit(s).

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