

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

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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,¹ Portenoy and Foley² 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 activities¹⁰⁻¹³ 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 standards⁶⁶ 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 compli-

ance (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 AGREE⁶⁷ 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)	<p>Comprehensive history and physical (I; High Confidence)</p> <p>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)</p> <p>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)</p> <p>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)</p> <p>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)</p>	<p>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; moderate confidence)</p> <p>Routine opioid use for treatment of nonsevere acute pain (eg, LBP, sprains, or minor injury without signs of tissue damage) (A; High Confidence)</p>
Postoperative pain (up to 4 weeks)	<p>Comprehensive history and physical (I; High Confidence)</p> <p>Limited use of opioids as adjunctive therapy to more effective treatments (C; High Confidence)</p> <p>Screening of patients for those requiring continuation of opioids beyond the second postoperative week (I; High Confidence)</p> <p>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)</p> <p>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)</p>	<p>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence)</p>
Subacute (1–3 months) and Chronic Pain (>3 months)	<p>Comprehensive history and physical (I; High Confidence)</p> <p>Screening of patients prior to consideration of initiating a trial of opioids (I; High Confidence)</p> <p>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)</p> <p>Maximum daily oral dose recommended based on risk of overdose/death is 50-mg MED (Fig. 1) (C; High Confidence)</p> <p>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)</p> <p>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)</p>	<p>Acute or chronic opioid use for patients who perform safety-sensitive jobs (C; Moderate Confidence)</p> <p>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)</p> <p>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)</p> <p>Intrathecal drug delivery systems for chronic nonmalignant pain conditions (I; High Confidence)</p>

(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 fac-

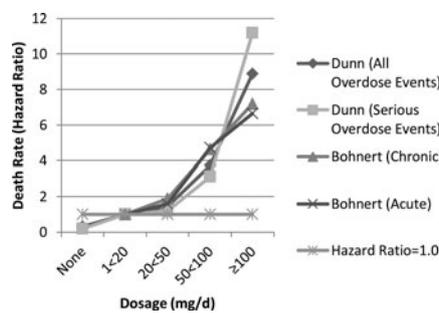


FIGURE 1. Death rate (hazard ratio) vs morphine equivalent dosage (mg/d). Statistical significance present for acute and chronic pain at and above 50 mg/day of oral morphine equivalent dose. Adapted from Dunn²⁰¹ and Bohnert.¹¹⁰

tors 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).

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		Amenorrhoea
Tremor	Demographic			Oligomenorrhoea
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 benzotropine 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 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 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 use²⁸⁷⁻²⁹²) 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 calculator²⁹⁷ 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 drugs³⁶⁷ 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 non-federal 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 non-conflicted 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 con-

flicts 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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REFERENCES

1. Stayner RS, Copenhaver DJ. Opioids, pain management and the law. *Curr Opin Anaesthesiol*. 2012;25:566–571.
2. Portenoy R, Foley K. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain*. 1986;25:171–186.

3. Bannwarth B. Risk–benefit assessment of opioids in chronic noncancer pain. *Drug Safety*. 1999;21:283–296.
4. Bovill JG. Which potent opioid? Important criteria for selection. *Drugs*. 1987;33:520–530.
5. Rupp T, Delaney KA. Inadequate analgesia in emergency medicine. *Ann Emerg Med*. 2004;43:494–503.
6. Garcia AM. State laws regulating prescribing of controlled substances: balancing the public health problems of chronic pain and prescription painkiller abuse and overdose. *J Law Med Ethics*. 2013;41(suppl):142–145.
7. State of Oregon Board of Medical Examiners vs. Paul Andre Bilder MD. Stipulated Order. 1999. Available at: www.drugpolicy.org/docUploads/Bilder_v_Orgeon_Stipulated_Order.pdf.
8. Hoffmann D, Tarzian A. Achieving the right balance in oversight of physician opioid prescribing for pain: the role of state medical boards. *J Law Med Ethics*. 2003;31:3121–3140.
9. Leelyn SW. Failures in pain management: the collision of law and medicine. *T Jefferson L Rev*. 2004;27:133–157.
10. Joint Commission for the Accreditation of Healthcare Organizations. Available at: www.jointcommission.org/pain_management/. Published 2013. Accessed October 30, 2014.
11. Department of Veterans Affairs. *Pain as the 5th Vital Sign Toolkit*. Washington, DC: Department of Veterans Affairs; 2000.
12. Merboth M, Barnason S. Managing pain: the fifth vital sign. *Nurs Clin North Am*. 2000;35:375–383.
13. Berry PH, Dahl JL. The new JCAHO pain standards: implications for pain management nurses. *Pain Manag Nurs*. 2000;1:3–12.
14. Caudill-Slosberg MA, Schwartz LM, Woloshin S. Office visits and analgesic prescriptions for musculoskeletal pain in US: 1980 vs. 2000. *Pain*. 2004;109:514–519.
15. Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. *Pain*. 2008;138:507–513.
16. Substance Abuse and Mental Health Services Administration. *Federal Guidelines for Opioid Treatment*. Rockville, MD: SAMHSA; 2013.
17. Centers for Disease Control and Prevention. Emergency department visits involving non-medical use of selected prescription drugs—United States, 2004–2008. *Morbidity Mortal Wkly Rep (MMWR)*. 2010;59:705–709.
18. Centers for Disease Control and Prevention. Vital signs: risk of overdose from methadone used for pain relief—United States, 1999–2010. *Morbidity Mortal Wkly Rep (MMWR)*. 2012;61:493–497.
19. Warner M, Chen L, Makuc D, Anderson R, Minino A. Drug poisoning deaths in the United States, 1980–2008. *NCHS Data Brief*. 2011;81:1–8.
20. Rosenblatt RA, Catlin M. Opioids for chronic pain: first do no harm. *Ann Fam Med*. 2012;10:300–301.
21. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100:2541–2547.
22. Kuehn B. Safety plan for opioids meets resistance opioid-linked deaths continue to soar. *JAMA*. 2010;303:495–497.
23. Piercefield E, Archer P, Kemp P, Mallonee S. Increase in unintentional medication overdose deaths: Oklahoma, 1994–2006. *Am J Prev Med*. 2010;39:357–363.
24. Al-Asmari AI, Anderson RA. The role of dihydrocodeine (DHC) metabolites in dihydrocodeine-related deaths. *J Anal Toxicol*. 2010;34:476–490.
25. Al-Asmari AI, Anderson RA, Cooper GA. Oxycodone-related fatalities in the west of Scotland. *J Anal Toxicol*. 2009;33:423–432.
26. Dhalla IA, Mamdani MM, Sivilotti ML, Kopp A, Qureshi O, Juurlink DN. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *Can Med Assoc J*. 2009;181:891–896.
27. Porucznik CA, Johnson EM, Sauer B, Crook J, Rolfs RT. Studying adverse events related to prescription opioids: the Utah experience. *Pain Med*. 2011;12(suppl 2):S16–S25.
28. Tanne JH. Deaths from prescription opioids soar in New York. *BMJ*. 2013;346:f921.
29. Wunsch M, Nakamoto K, Behonick G, Massello W. Opioid deaths in rural Virginia: a description of the high prevalence of accidental fatalities involving prescribed medications. *Am J Addict*. 2009;18:5–14.
30. Green TC, Grau LE, Carver HW, Kinzly M, Heimer R. Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997–2007. *Drug Alcohol Depend*. 2011;115:221–228.
31. Centers for Disease Control and Prevention. Alcohol and other drug use among victims of motor-vehicle crashes—West Virginia, 2004–2005. *Morbidity Mortal Wkly Rep (MMWR)*. 2006;55:1293–1296.
32. Hall A, Logan J, Toblin R, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300:2613–2620.
33. Warner M, Chen L, Makuc D. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006. *NCHS Data Brief*. September 2009;22.
34. Kuehn BM. Methadone overdose deaths rise with increased prescribing for pain. *JAMA*. 2012;308:749–750.
35. Utah Department of Health. *Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain*. Salt Lake City, UT: Utah Department of Health; 2009.
36. Yamaguchi T, Shima Y, Morita T, Hosoya M, Matoba M. Clinical guideline for pharmacological management of cancer pain: the Japanese Society of Palliative Medicine recommendations. *Jpn J Clin Oncol*. 2013;43:896–909.
37. Abdulla A, Adams N, Bone M, et al. Guidance on the management of pain in older people. *Age Ageing*. 2013;42(suppl 1):i1–i57.
38. Furlan A, Reardon R, Weppner C. Opioids for chronic noncancer pain: a new Canadian practice guideline. *Can Med Assoc J*. 2010;182:923–930. doi:10.1503/cmaj.100187.
39. Genovese E, Korevaar W, Mueller K, Aronoff G, Bruns D, et al. Chapter 10: Chronic pain. In: Hegmann K, ed. *ACOEM's Occupational Medicine Practice Guidelines*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011.
40. Washington State Department of Labor & Industries. *Guideline for Prescribing Opioids to Treat Pain in Injured Workers*. Washington, DC: Washington State Department of Labor & Industries; 2013.
41. Washington State Department of Labor & Industries, Washington Agency Medical Directors' Group. Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An educational aid to improve care and safety with opioid therapy, 2010 Update. Washington, DC: Washington State Department of Labor & Industries, Washington Agency Medical Directors' Group; 2010.
42. Medical Board of California, Department of Consumer Affairs. *Guidelines for Prescribing Controlled Substances for Pain*. Sacramento, CA: 2007.
43. Canada: National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Available at: <http://nationalpaincentre.mcmaster.ca/opioid/>. Published 2010. Accessed October 30, 2014.
44. Hawkins EJ, Malte CA, Imel ZE, Saxon AJ, Kivlahan DR. Prevalence and trends of benzodiazepine use among Veterans Affairs patients with posttraumatic stress disorder, 2003–2010. *Drug Alcohol Depend*. 2012;124:154–161.
45. Warner EA. Opioids for the treatment of chronic noncancer pain. *Am J Med*. 2012;125:1155–1161.
46. Turk DC, O'Connor AB, Dworkin RH, et al. Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations. *Pain*. 2012;153:1997–2008.
47. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64:465–474.
48. Peppin JF, Passik SD, Couto JE, et al. Recommendations for urine drug monitoring as a component of opioid therapy in the treatment of chronic pain. *Pain Med*. 2012;13:886–896.
49. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol*. 2012;13:e58–e68.
50. Fallon M, Reale C, Davies A, et al. Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. *J Support Oncol*. 2011;9:224–231.
51. Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer

- pain: Part 2—guidance. *Pain Physician*. 2012;15(suppl):S67–S116.
52. Manchikanti L, Helm Sn, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15(suppl):ES9–E38.
 53. Office of the Army Surgeon General, Pain Management Task Force. Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and Their Families. Falls Church, VA: 2010.
 54. American Society of Anesthesiologists Task Force on Chronic Pain Management. Practice Guidelines for Chronic Pain Management. An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*. 2010;112:1–24.
 55. The Royal Australasian College of Physicians. *Prescription Opioid Policy: Improving Management of Chronic Non-malignant Pain and Prevention of Problems Associated With Prescription Opioid Use*. Sydney, Australia: 2009.
 56. US Veterans Affairs Administration. *Clinical Practice Guideline: Management of Opioid Therapy for Chronic Pain*. Available at: http://www.va.gov/painmanagement/docs/cpg_opioidtherapy_fulltext.pdf. Published 2010. Accessed October 28, 2014.
 57. Albert S, Brason F II, Sanford C, et al. Project Lazarus: community-based overdose prevention in rural North Carolina. *Pain Med*. 2011;12(suppl s2):S77–S85.
 58. Kahan M, Wilson L, Mailis-Gagnon A, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain. Clinical summary for family physicians. Part 2: special populations. *Can Fam Physician*. 2011;57:1269–1276.
 59. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A. Canadian guidelines for safe and effective use of opioids for chronic noncancer pain. Clinical summary for family physicians. Part 1: general population. *Can Fam Physician*. 2011;57:1257–1266.
 60. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758–1765.
 61. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic noncancer pain in the United States: a research guideline for developing an evidence-base. *J Pain*. 2010;11:807–829.
 62. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10:113–130.
 63. Federation of State Medical Boards. *Model Policy on the Use of Opioid Analgesics in the Treatment of Chronic Pain*. Washington, D.C.: 2013.
 64. Hughes M, Biggs J, Thiese M, Graziano K, Robbins R, Effiong A. Recommended opioid prescribing practices for use in chronic non-malignant pain: a systematic review of treatment guidelines. *J Managed Care Med*. 2011;14:52–58.
 65. Nuckols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med*. 2014;160:38–47.
 66. Institute of Medicine. Standards for developing trustworthy clinical practice guidelines. Available at: <http://www.iom.edu/~media/Files/Report%20Files/2011/Clinical-Practice-Guidelines-We-Can-Trust/Clinical%20Practice%20Guidelines%202011%20Insert.pdf>. Published 2011. Accessed October 28, 2014.
 67. The AGREE Research Trust. *Appraisal of Guidelines for Research & Evaluation II (AGREE II) Instrument*. Hamilton, Ontario, Canada: McMaster University; 2009.
 68. American College of Occupational and Environmental Medicine. Summary: Methodology for Updates to the ACOEM Practice Guidelines. Available at: www.acoem.org/guidelines_summary.aspx. Published 2006. Accessed October 28, 2014.
 69. American College of Occupational and Environmental Medicine. Methodology for the update of the occupational medicine practice guidelines. Available at: www.acoem.org/uploadedFiles/Knowledge_Centers/Practice_Guidelines/ACOEM%20Practice%20Guidelines%20Methodology.pdf. Published 2006. Accessed October 28, 2014.
 70. Harris JS, Sinnott PL, Holland JP, et al. Methodology to update the practice recommendations in the American College of Occupational and Environmental Medicine's Occupational Medicine Practice Guidelines, second edition. *J Occup Environ Med*. 2008;50:282–295.
 71. Talmage J, Andersson G, Carragee E, et al. Chapter 8: Cervical and thoracic spine disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;2:1–332.
 72. Talmage J, Belcourt R, Galper J, et al. Chapter 9: Low back disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;2:333–796.
 73. Kaufman L, Green A, Haas N, et al. Chapter 11: Shoulder disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;3:1–378.
 74. McKenzie J, Jacobs J, Caruso G, et al. Chapter 14: Hip and groin disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;4:1–440.
 75. Haas N, Beecher P, Easley M, et al. Chapter 16: Ankle and foot disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;4:1099–1453.
 76. Hoffman H, Belcourt R, Byrne K, et al. Chapter 12: Elbow disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;3:379–570.
 77. Melhorn J, Arbesman M, Franzblau A, et al. Chapter 13: Hand, wrist, and forearm disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;3:571–927.
 78. Lichtblau E, Coward D, Howell S, et al. Chapter 15: Knee disorders. In: Hegmann K, ed. *Occupational Medicine Practice Guidelines: Evaluation and Management of Common Health Problems and Functional Recovery in Workers*. 3rd ed. Elk Grove Village, IL: American College of Occupational and Environmental Medicine; 2011;4:441–1098.
 79. Hegmann K, Weiss M, Bowden K, et al. ACOEM Practice Guidelines: opioids and safety-sensitive work. *J Occup Environ Med*. 2014;56:e46–e53.
 80. Gourlay DL, Heit HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. *Pain Med*. 2005;6:107–112.
 81. International Association of Industrial Accident Boards and Commissions. *Reducing Inappropriate Opioid Use in Treatment of Injured Workers. A Policy Guide*. Madison, WI: 2013.
 82. Food and Drug Administration. *Letter to Dr. Andrew Kolodny in Response to the Citizen Petition Submitted by Physicians for Responsible Opioid Prescribing*. Silver Spring, MD: US Food and Drug Administration; 2013.
 83. Webster LR. Eight principles for safer opioid prescribing. *Pain Med*. 2013;14:959–961.
 84. Jovey RD. Use of opioid analgesics for the treatment of chronic noncancer pain—a consensus statement and guidelines from the Canadian Pain Society, 2002. *Pain Res Manag*. 2002;8:3A–28A.
 85. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics*. 2007;119:460–467.
 86. Muncie HL, Jr, King DE, DeForge B. Treatment of mild to moderate pain of acute soft tissue injury: diflunisal vs acetaminophen with codeine. *J Fam Pract*. 1986;23:125–127.
 87. Ekman EF, Ruoff G, Kuehl K, et al. The COX-2 specific inhibitor valdecoxib versus tramadol in acute ankle sprain: a multicenter

- randomized, controlled trial. *Am J Sports Med.* 2006;34:945–955.
88. Lovell SJ, Taira T, Rodriguez E, Wackett A, Gulla J, Singer AJ. Comparison of valdecoxib and an oxycodone-acetaminophen combination for acute musculoskeletal pain in the emergency department: a randomized controlled trial. *Acad Emerg Med.* 2004;11:1278–1282.
 89. Baratta R. A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome. *Curr Ther Res Clin Exp.* 1976;20:233–240.
 90. Veenema K, Leahey N, Schneider S. Ketorolac versus meperidine: ED treatment of severe musculoskeletal low back pain. *Am J Emerg Med.* 2000;18:404–407.
 91. Innes GD, Croskerry P, Worthington J, Beveridge R, Jones D. Ketorolac versus acetaminophen-codeine in the emergency department treatment of acute low back pain. *J Emerg Med.* 1998;16:549–556.
 92. Brown FL, Jr, Bodison S, Dixon J, Davis W, Nowoslawski J. Comparison of difflunisal and acetaminophen with codeine in the treatment of initial or recurrent acute low back strain. *Clin Ther.* 1986;9(suppl C):52–58.
 93. Ordog GJ. Transcutaneous electrical nerve stimulation versus oral analgesic: a randomized double-blind controlled study in acute traumatic pain. *Am J Emerg Med.* 1987;5:6–10.
 94. Chang AK, Bijur PE, Campbell CM, Murphy MK, Gallagher EJ. Safety and efficacy of rapid titration using 1 mg doses of intravenous hydromorphone in emergency department patients with acute severe pain: the “1+1” protocol. *Ann Emerg Med.* 2009;54:221–225.
 95. Chang AK, Bijur PE, Davitt M, Gallagher EJ. Randomized clinical trial comparing a patient-driven titration protocol of intravenous hydromorphone with traditional physician-driven management of emergency department patients with acute severe pain. *Ann Emerg Med.* 2009;54:561–567 e2.
 96. Chang AK, Bijur PE, Gallagher EJ. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. *Ann Emerg Med.* 2011;58:352–359.
 97. Chang AK, Bijur PE, Davitt M, Gallagher EJ. Randomized clinical trial of an intravenous hydromorphone titration protocol versus usual care for management of acute pain in older emergency department patients. *Drugs Aging.* 2013;30:747–754.
 98. Chang AK, Bijur PE, Lupow JB, Gallagher EJ. Randomized clinical trial of the 2 mg hydromorphone bolus protocol versus the “1+1” hydromorphone titration protocol in treatment of acute, severe pain in the first hour of emergency department presentation. *Ann Emerg Med.* 2013;62:304–310.
 99. Chang AK, Bijur PE, Lupow JB, John Gallagher E. Randomized clinical trial of efficacy and safety of a single 2-mg intravenous dose of hydromorphone versus usual care in the management of acute pain. *Acad Emerg Med.* 2013;20:185–192.
 100. Chang AK, Bijur PE, Meyer RH, Kenny MK, Solorzano C, Gallagher EJ. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med.* 2006;48:164–172.
 101. Turturro MA, Paris PM, Larkin GL. Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial. *Ann Emerg Med.* 1998;32:139–143.
 102. Turturro MA, Paris PM, Yealy DM, Menegazzi JJ. Hydrocodone versus codeine in acute musculoskeletal pain. *Ann Emerg Med.* 1991;20:1100–1103.
 103. Jalili M, Fathi M, Moradi-Lakeh M, Zehabchi S. Sublingual buprenorphine in acute pain management: a double-blind randomized clinical trial. *Ann Emerg Med.* 2012;59:276–280.
 104. Bounes V, Barthelemy R, Diez O, Charpentier S, Montastruc JL, Ducasse JL. Sufentanil is not superior to morphine for the treatment of acute traumatic pain in an emergency setting: a randomized, double-blind, out-of-hospital trial. *Ann Emerg Med.* 2010;56:509–516.
 105. Marco CA, Plewa MC, Buderer N, Black C, Roberts A. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: a double-blind, randomized, controlled trial. *Acad Emerg Med.* 2005;12:282–288.
 106. Trevino CM, deRoon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? *J Pain.* 2013;14:424–430.
 107. Webster B, Verma S, Gatchel R. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine.* 2007;32:2127–2132.
 108. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington State, 2002–2005. *Clin J Pain.* 2009;25:743–751.
 109. Cifuentes M, Webster B, Genevay S, Pransky G. The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. *Pain.* 2010;151:22–29.
 110. Bohner AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011;305:1315–1321.
 111. Craft RM. Sex differences in drug- and non-drug-induced analgesia. *Life Sci.* 2003;72:2675–2688.
 112. Cheng M, Sauer B, Johnson E, Porucznik C, Hegmann K. Comparison of opioid-related deaths by work-related injury. *Am J Ind Med.* 2013;56:308–316.
 113. Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain.* 2006;125:172–179.
 114. Atluri S, Sudarshan G. Development of a screening tool to detect the risk of inappropriate prescription opioid use in patients with chronic pain. *Pain Physician.* 2004;7:333–338.
 115. Shah NG, Lathrop SL, Reichard RR, Landen MG. Unintentional drug overdose death trends in New Mexico, USA, 1990–2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction.* 2008;103:126–136.
 116. Webster L, Cochella S, Dasgupta N, et al. An analysis of the root causes for opioid-related overdose deaths in the United States. *Pain Med.* 2011;12(suppl 2):S26–S35.
 117. Dunn KE, Sigmon SC, Strain EC, Heil SH, Higgins ST. The association between outpatient buprenorphine detoxification duration and clinical treatment outcomes: a review. *Drug Alcohol Depend.* 2011;119:1–9.
 118. Paulozzi L, Baldwin G, Franklin G, et al. CDC Grand Rounds: prescription drug overdoses—a U.S. epidemic. *Morbidity Mortal Wkly Rep (MMWR).* 2012;61:10–13.
 119. Paulozzi LJ, Logan JE, Hall AJ, McKinstry E, Kaplan JA, Crosby AE. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction.* 2009;104:1541–1548.
 120. Grattan A, Sullivan M, Saunders K, Campbell C, Von Korff M. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Ann Fam Med.* 2012;10:304–311.
 121. Manchikanti L, Damron KS, McManus CD, Barnhill RC. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: a prospective, observational study. *Pain Physician.* 2004;7:431–437.
 122. Nyhlen A, Fridell M, Backstrom M, Hesse M, Krantz P. Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: a prospective longitudinal study 1970–2006. *BMC Psychiatry.* 2011;11:122.
 123. Hadidi MS, Ibrahim MI, Abdallat IM, Hadidi KA. Current trends in drug abuse associated fatalities—Jordan, 2000–2004. *Forensic Sci Int.* 2009;186:44–47.
 124. Wysowski DK. Surveillance of prescription drug-related mortality using death certificate data. *Drug Saf.* 2007;30:533–540.
 125. Wysowski DK, Governale LA, Swann J. Trends in outpatient prescription drug use and related costs in the US: 1998–2003. *Pharmacoeconomics.* 2006;24:233–236.
 126. Toblin RL, Paulozzi LJ, Logan JE, Hall AJ, Kaplan JA. Mental illness and psychotropic drug use among prescription drug overdose deaths: a medical examiner chart review. *J Clin Psychiatry.* 2010;71:491–496.
 127. Centers for Disease Control and Prevention. Unintentional deaths from drug poisoning by urbanization of area—New Mexico, 1994–2003. *Morbidity Mortal Wkly Rep (MMWR).* 2005;54:870–873.
 128. Fared A, Casarella J, Roberts M, et al. High dose versus moderate dose methadone

- maintenance: is there a better outcome? *J Ad- dict Dis.* 2009;28:399–405.
129. Deyo RA, Smith DH, Johnson ES, et al. Opioids for back pain patients: primary care prescribing patterns and use of services. *J Am Board Fam Med.* 2011;24:717–727.
 130. Goodridge D, Lawson J, Rocker G, Marciniuk D, Rennie D. Factors associated with opioid dispensation for patients with COPD and lung cancer in the last year of life: a retrospective analysis. *Int J Chron Obstruct Pulmon Dis.* 2010;5:99–105.
 131. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage.* 2004;28:497–504.
 132. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA.* 2012;307:940–947.
 133. Mills K, Teesson M, Ross J, Darke S, Shahanan M. The costs and outcomes of treatment for opioid dependence associated with posttraumatic stress disorder. *Psychiatr Serv.* 2005;56:940–945.
 134. Volinn E, Fargo JD, Fine PG. Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain.* 2009;142:194–201.
 135. Dersh J, Mayer T, Gatchel R, Polatin P, Theodore B, Mayer E. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. *SPINE.* 2008;33:2219–2227.
 136. Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med.* 2013;173:196–201.
 137. Raffaelli W, Marconi G, Fanelli G, Taddei S, Borghi GB, Casati A. Opioid-related side-effects after intrathecal morphine: a prospective, randomized, double-blind dose–response study. *Eur J Anaesthesiol.* 2006;23:605–610.
 138. Coffey RJ, Owens ML, Broste SK, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiology.* 2009;111:881–891.
 139. Hay JL, White JM, Bochner F, Somogyi AA, Semple TJ, Rounsefell B. Hyperalgesia in opioid-managed chronic pain and opioid-dependent patients. *J Pain.* 2009;10:316–322.
 140. Ram KC, Eisenberg E, Haddad M, Pud D. Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain—new perspective of opioid-induced hyperalgesia. *Pain.* 2008;139:431–438.
 141. Tarkkila P, Tuominen M, Lindgren L. Comparison of respiratory effects of tramadol and oxycodone. *J Clin Anesth.* 1997;9:582–585.
 142. Sandler AN, Chovaz P, Whiting W. Respiratory depression following epidural morphine: a clinical study. *Can Anaesth Soc J.* 1986;33:542–549.
 143. Ladd LA, Kam PC, Williams DB, Wright AW, Smith MT, Mather LE. Ventilatory responses of healthy subjects to intravenous combinations of morphine and oxycodone under imposed hypercapnic and hypox- aemic conditions. *Br J Clin Pharmacol.* 2005;59:524–535.
 144. Tantucci C, Paoletti F, Bruni B, et al. Acute respiratory effects of sublingual buprenorphine: comparison with intramuscular morphine. *Int J Clin Pharmacol Ther Toxicol.* 1992;30:202–207.
 145. Bailey PL, Sperry RJ, Johnson GK, et al. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology.* 1991;74:43–48.
 146. Bulow HH, Linnemann M, Berg H, Lang-Jensen T, LaCour S, Jonsson T. Respiratory changes during treatment of postoperative pain with high dose transdermal fentanyl. *Acta Anaesthesiol Scand.* 1995;39:835–839.
 147. Thompson PI, Joel SP, John L, Wedzicha JA, Maclean M, Slevin ML. Respiratory depression following morphine and morphine-6-glucuronide in normal subjects. *Br J Clin Pharmacol.* 1995;40:145–152.
 148. Dahan A. Respiratory depression with opioids. *J Pain Palliat Care Pharmacother.* 2007;21:63–66.
 149. Dahan A, Aarts L, Smith T. Incidence, reversal, and prevention of opioid-induced respiratory depression. *Anesthesiology.* 2010;112:226–238.
 150. Dahan A, Overdyk F, Smith T, Aarts L, Niesters M. Pharmacovigilance: a review of opioid-induced respiratory depression in chronic pain patients. *Pain Physician.* 2013;16:E85–E94.
 151. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth.* 2006;96:627–632.
 152. White MJ, Berghausen EJ, Dumont SW, et al. Side effects during continuous epidural infusion of morphine and fentanyl. *Can J Anaesth.* 1992;39:576–582.
 153. Yassen A, Olofsen E, Romberg R, et al. Mechanism-based PK/PD modeling of the respiratory depressant effect of buprenorphine and fentanyl in healthy volunteers. *Clin Pharmacol Ther.* 2007;81:50–58.
 154. Olofsen E, van Dorp E, Teppema L, et al. Naloxone reversal of morphine- and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic-pharmacodynamic modeling study. *Anesthesiology.* 2010;112:1417–1427.
 155. Jungquist C, Flannery M, Perlis M, Grace J. Relationship of chronic pain and opioid use with respiratory disturbance during sleep. *Pain Manage Nurs.* 2012;13:70–79.
 156. Jungquist CR, Karan S, Perlis ML. Risk factors for opioid-induced excessive respiratory depression. *Pain Manag Nurs.* 2011;12:180–187.
 157. Talbert RL, Peters JI, Sorrells SC, Simmons RS. Respiratory effects of high-dose butorphanol. *Acute Care.* 1988;12(suppl):147–156.
 158. Caspi J, Klausner JM, Safadi T, Amar R, Rozin RR, Merin G. Delayed respiratory depression following fentanyl anesthesia for cardiac surgery. *Crit Care Med.* 1988;16:238–240.
 159. Goldberg ME, Torjman M, Bartkowski RR, Mora CT, Boerner T, Seltzer JL. Time- course of respiratory depression after an alfentanil infusion-based anesthetic. *Anesth Analg.* 1992;75:965–971.
 160. Clemens KE, Quednau I, Klaschik E. Is there a higher risk of respiratory depression in opioid-naïve palliative care patients during symptomatic therapy of dyspnea with strong opioids? *J Palliat Med.* 2008;11:204–216.
 161. Niesters M, Mahajan RP, Aarts L, Dahan A. High-inspired oxygen concentration further impairs opioid-induced respiratory depression. *Br J Anaesth.* 2013;110:837–841.
 162. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth.* 2005;17:537–542.
 163. Taylor S, Kirton OC, Staff I, Kozol RA. Postoperative day one: a high risk period for respiratory events. *Am J Surg.* 2005;190:752–756.
 164. Sam WJ, MacKey SC, Lotsch J, Drover DR. Morphine and its metabolites after patient-controlled analgesia: considerations for respiratory depression. *J Clin Anesth.* 2011;23:102–106.
 165. Oertel BG, Felden L, Tran PV, et al. Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. *Clin Pharmacol Ther.* 2010;87:204–211.
 166. Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P. Ventilatory effects of continuous epidural infusion of fentanyl. *Anesth Analg.* 1988;67:971–975.
 167. Dinis-Oliveira RJ, Carvalho F, Moreira R, et al. Clinical and forensic signs related to opioids abuse. *Curr Drug Abuse Rev.* 2012;5:273–290.
 168. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression: finding the right balance. *Drugs.* 2011;71:1807–1819.
 169. Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. *Anesth Analg.* 2008;107:956–961.
 170. Sumida S, Lesley MR, Hanna MN, Murphy JD, Kumar K, Wu CL. Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. *J Opioid Manag.* 2009;5:301–305.
 171. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Can J Anaesth.* 1989;36:165–185.
 172. George JA, Lin EE, Hanna MN, et al. The effect of intravenous opioid patient-controlled analgesia with and without background infusion on respiratory depression: a meta-analysis. *J Opioid Manag.* 2010;6:47–54.
 173. Jarzyna D, Jungquist CR, Pasero C, et al. American Society for Pain Management Nursing guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs.* 2011;12:118–45 e10.
 174. Kato R, Shimamoto H, Terui K, Yokota K, Miyao H. Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. *J Anesth.* 2008;22:112–116.

175. Smith LH. Opioid safety: is your patient at risk for respiratory depression? *Clin J Oncol Nurs*. 2007;11:293–296.
176. Macintyre PE, Loadman JA, Scott DA. Opioids, ventilation and acute pain management. *Anaesth Intensive Care*. 2011;39:545–558.
177. Mahla ME, White SE, Moneta MD. Delayed respiratory depression after alfentanil. *Anesthesiology*. 1988;69:593–595.
178. Pasero C. Opioid-induced sedation and respiratory depression: evidence-based monitoring guidelines. *J Perianesth Nurs*. 2012;27:208–211.
179. Berland D, Rodgers P. Rational use of opioids for management of chronic nonterminal pain. *Am Fam Physician*. 2012;86:252–258.
180. Burgess F. Methadone analgesia: balancing the risks and benefits. *Pain Med News*. Dec. 2009; 101–106. Available at: http://www.painmedicineneeds.com/download/Methadone_PMNSE09_WM.pdf. Accessed October 30, 2014.
181. Zacny J. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *Exp Clin Psychopharmacol*. 2005;3:432–466.
182. Vella-Brincat J, Macleod A. Adverse effects of opioids on the central nervous systems of palliative care patients. *J Pain Palliat Care Pharmacother*. 2007;21:15–25.
183. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician*. 2008;11(suppl):S5–S62.
184. Dimsdale J, Norman D, DeJardin D, Wallace M. The effect of opioids on sleep architecture. *J Clin Sleep Med*. 2007;3:33–36.
185. Abs R, Abs R, Verhelst J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85:2215–2222.
186. Vuong C, Van Uum S, O'Dell L, Lutfy K, Friedman T. The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocr Rev*. 2010;31:98–132.
187. Chaney M. Side effects of intrathecal and epidural opioids. *Can J Anaesth*. 1995;42:891–903.
188. Chu L, Angst M, Clark D. Opioid-induced hyperalgesia in humans. Molecular mechanisms and clinical considerations. *Clin J Pain*. 2008;24:479–496.
189. Lee M, Silverman S, Hansen H, Patel V, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14:145–161.
190. Silverman S. Opioid induced hyperalgesia: clinical implications for the pain practitioner. *Pain Physician*. 2009;12:679–684.
191. Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*. 2006;104:570–587.
192. Chang G, Chen L, Mao J. Opioid tolerance and hyperalgesia. *Med Clin North Am*. 2007;91:199–211.
193. Gibson JE, Hubbard RB, Smith CJ, Tata LJ, Britton JR, Fogarty AW. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. *Am J Epidemiol*. 2009;169:761–768.
194. Engeland A, Skurtveit S, Morland J. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. *Ann Epidemiol*. 2007;17:597–602.
195. Dubois S, Bedard M, Weaver B. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. *Accid Anal Prev*. 2010;42:30–37.
196. Howard ME, Desai AV, Grunstein RR, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. *Am J Respir Crit Care Med*. 2004;170:1014–1021.
197. Kidner CL, Mayer TG, Gatchel RJ. Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am*. 2009;91:919–927.
198. Franklin GM, Stover BD, Turner JA, Fulton-Keohoe D, Wickizer TM. Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine*. 2008;33:199–204.
199. Chen SL, Lee SY, Tao PL, et al. Dextromethorphan attenuated inflammation and combined opioid use in humans undergoing methadone maintenance treatment. *J Neuroimmune Pharmacol*. 2012;7:1025–1033.
200. Butler S, Fernandez K, Benoit C, Budman S, Jamison R. Validation of the revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R). *J Pain*. 2008;9:360–372.
201. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152:85–92.
202. Centers for Disease Control and Prevention. Adult use of prescription opioid pain medications—Utah, 2008. *Morbidity Mortal Wkly Rep (MMWR)*. 2010;59:153–157.
203. Walter SR, Thein HH, Amin J, et al. Trends in mortality after diagnosis of hepatitis B or C infection: 1992–2006. *J Hepatol*. 2011;54:879–886.
204. Gammaitoni AR, Galer BS, Lacouture P, Domingos J, Schlagheck T. Effectiveness and safety of new oxycodone/acetaminophen formulations with reduced acetaminophen for the treatment of low back pain. *Pain Med*. 2003;4:21–30.
205. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med*. 2007;146:116–127.
206. Maruta T, Swanson DW, Finlayson RE. Drug abuse and dependency in patients with chronic pain. *Mayo Clin Proc*. 1979;54:241–244.
207. Chabal C, Erjavec MK, Jacobson L, Mariano A, Chaney E. Prescription opiate abuse in chronic pain patients: clinical criteria, incidence, and predictors. *Clin J Pain*. 1997;13:150–155.
208. Michna E, Ross E, Hynes W, et al. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. *J Pain Symptom Manage*. 2004;28:250–258.
209. Barletta JF. Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. *Pharmacotherapy*. 2012;32(suppl):12S–18S.
210. O'Neill P, Knickenberg C, Bogahalanda S, Booth AE. Use of intrathecal morphine for postoperative pain relief following lumbar spine surgery. *J Neurosurg*. 1985;63:413–416.
211. Braden JB, Russo J, Fan MY, et al. Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med*. 2010;170:1425–1432.
212. Ivers N, Dhalla I, Allan G. Opioids for osteoarthritis pain: benefits and risks. *Can Fam Physician*. 2012;58:e708.
213. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23:287–299.
214. Currow DC, McDonald C, Oaten S, et al. Once-daily opioids for chronic dyspnea: a dose increment and pharmacovigilance study. *J Pain Symptom Manage*. 2011;42:388–399.
215. Andresen H, Gullans A, Veselinovic M, et al. Fentanyl: toxic or therapeutic? Postmortem and antemortem blood concentrations after transdermal fentanyl application. *J Anal Toxicol*. 2012;36:182–194.
216. Modesto-Lowe V, Brooks D, Petry N. Methadone deaths: risk factors in pain and addicted populations. *J Gen Intern Med*. 2010;25:305–309.
217. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H. Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction*. 2009;104:993–999.
218. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. A community-based evaluation of sudden death associated with therapeutic levels of methadone. *Am J Med*. 2008;121:66–71.
219. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician*. 2008;11(suppl):S63–S88.
220. Sadeghian S, Karimi A, Dowlatshahi S, et al. The association of opium dependence and postoperative complications following coronary artery bypass graft surgery: a propensity-matched study. *J Opioid Manag*. 2009;5:365–372.
221. Safaii N, Kazemi B. Effect of opium use on short-term outcome in patients undergoing coronary artery bypass surgery. *Gen Thorac Cardiovasc Surg*. 2010;58:62–67.
222. Agusti A, Pages E, Cuxart A, et al. Exposure to medicines among patients admitted for hip fracture and the case-fatality rate at 1 year: a longitudinal study. *Eur J Clin Pharmacol*. 2012;68:1525–1531.
223. Basbaum AI, Julius D. Toward better pain control. *Sci Am*. 2006;294:60–67.
224. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of

- excitatory amino acid receptors and protein kinase C. *J Neurosci*. 1994;14:2301–2312.
225. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain*. 1995;62:259–274.
226. Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med*. 2003;349:1943–1953.
227. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain*. 2008;24:469–478.
228. Ballantyne J. Chapter 5. Opioid tolerance, dependence and hyperalgesia. In: Mao J, ed. *Opioid-Induced Hyperalgesia*. Boca Raton, FL: CRC Press; 2009.
229. Ballantyne JC. “Safe and effective when used as directed”: the case of chronic use of opioid analgesics. *J Med Toxicol*. 2012;8:417–423.
230. Mitra S. Opioid-induced hyperalgesia: pathophysiology and clinical implications. *J Opioid Manag*. 2008;4:123–130.
231. Bannister K, Dickenson AH. Opioid hyperalgesia. *Curr Opin Support Palliat Care*. 2010;4:1–5.
232. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain*. 2008;9:28–36.
233. Cicero T, Bell R, Wiest W, Allison J, Polakoski K, Robins E. Function of the male sex organs in heroin and methadone users. *N Engl J Med*. 1975;292:882–887.
234. Mendelson J, Meyer R, Ellingboe J, Mirin S, McDougale M. Effects of heroin and methadone on plasma cortisol and testosterone. *J Pharmacol Exp Ther*. 1975;195:296–302.
235. Mendelson JH, Mello NK. Plasma testosterone levels during chronic heroin use and protracted abstinence. A study of Hong Kong addicts. *Clin Pharmacol Ther*. 1975;17:529–533.
236. Katz N, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain*. 2009;25:170–175.
237. Finch P, Roberts L, Price L, Hadlow N, Pullan P. Hypogonadism in patients treated with intrathecal morphine. *Clin J Pain*. 2000;16:251–254.
238. Paice J, Penn R, Ryan W. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. *J Pain Symptom Manage*. 1994;9:126–131.
239. Daniell H. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3:377–384.
240. Buvaendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110:199–207.
241. Nader A, Kendall MC, Wixson RL, Chung B, Polakow LM, McCarthy RJ. A randomized trial of epidural analgesia followed by continuous femoral analgesia compared with oral opioid analgesia on short- and long-term functional recovery after total knee replacement. *Pain Med*. 2012;13:937–947.
242. Gora-Harper M, Record K, Darkow T, Tibbs P. Opioid analgesics versus ketorolac in spine and joint procedures: impact on healthcare resources. *Ann Pharmacother*. 2001;35:1320–1326.
243. Choiniere M. Efficacy and costs of patient-controlled analgesia versus regularly administered intramuscular opioid therapy. *Anesthesiology*. 1998;89:1377–1388.
244. Rittenhouse B, Choiniere M. An economic evaluation of pain therapy after hysterectomy. Patient-controlled analgesia versus regular intramuscular opioid therapy. *Intl J Technol Assess Health Care*. 1999;15:548–562.
245. Chang DJ, Desjardins PJ, King TR, Erb T, Geba GP. The analgesic efficacy of etoricoxib compared with oxycodone/acetaminophen in an acute postoperative pain model: a randomized, double-blind clinical trial. *Anesth Analg*. 2004;99:807–815, table of contents.
246. Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. *Acta Anaesthesiol Scand*. 2002;46:322–328.
247. Sell S, Phillips O, Handel M. No difference between two doses of diclofenac in prophylaxis of heterotopic ossifications after total hip arthroplasty. *Acta Orthop Scand*. 2004;75:45–49.
248. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. *Clin Ther*. 2001;23:228–241.
249. Dahl V, Raeder JC, Drosdal S, Wathne O, Brynildsrud J. Prophylactic oral ibuprofen or ibuprofen-codeine versus placebo for postoperative pain after primary hip arthroplasty. *Acta Anaesthesiol Scand*. 1995;39:323–326.
250. Ittichaikulthol W, Prachanpanich N, Kositchaiwat C, Intapan T. The postoperative analgesic efficacy of celecoxib compared with placebo and parecoxib after total hip or knee arthroplasty. *J Med Assoc Thai*. 2010;93:937–942.
251. Vojtassak J, Vojtassak J, Jacobs A, Rynn L, Waechter S, Richarz U. A phase IIIb, multicentre, randomised, parallel-group, placebo-controlled, double-blind study to investigate the efficacy and safety of OROS hydromorphone in subjects with moderate-to-severe chronic pain induced by osteoarthritis of the hip or the knee. *Pain Res Treat*. 2011:1–9.
252. Li C, Ni J, Wang Z, et al. Analgesic efficacy and tolerability of flupirtine vs. tramadol in patients with subacute low back pain: a double-blind multicentre trial*. *Curr Med Res Opin*. 2008;24:3523–3530.
253. O'Donnell JB, Ekman EF, Spalding WM, Bhadra P, McCabe D, Berger MF. The effectiveness of a weak opioid medication versus a cyclo-oxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drug in treating flare-up of chronic low-back pain: results from two randomized, double-blind, 6-week studies. *J Int Med Res*. 2009;37:1789–1802.
254. Parr G, Darekar B, Fletcher A, Bulpitt CJ. Joint pain and quality of life: results of a randomised trial. *Br J Clin Pharmacol*. 1989;27:235–242.
255. Jamison RN, Raymond SA, Slawsky EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine*. 1998;23:2591–2600.
256. Pavelka K, Pelisková Z, Stehlíková H, Ratcliffe S, Repas C. Intraindividual differences in pain relief and functional improvement in osteoarthritis with diclofenac or tramadol. *Clin Drug Invest*. 1998;16:421–429.
257. Khoromi S, Cui L, Nackers L, Max M. Morphine, nortriptyline and their combination vs. placebo in patients with chronic lumbar root pain. *Pain*. 2007;130:66–75.
258. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. *Anesth Analg*. 2000;91:1493–1498.
259. Moulin D, Iezzi A, Amireh R, Sharp WK, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet*. 1996;347:143–147.
260. Wu CL, Agarwal S, Tella PK, et al. Morphine versus mexiletine for treatment of postamputation pain: a randomized, placebo-controlled, crossover trial. *Anesthesiology*. 2008;109:289–296.
261. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther*. 2005;7:R1046–R1051.
262. Edwards RR, Wasan AD, Michna E, Greenbaum S, Ross E, Jamison RN. Elevated pain sensitivity in chronic pain patients at risk for opioid misuse. *J Pain*. 2011;12:953–963.
263. Saper J, Lake A III. Sustained opioid therapy should rarely be administered to headache patients: clinical observations, literature review, and proposed guidelines. *Headache Curr*. 2006;3:67–70.
264. Vaglienti RM, Huber SJ, Noel KR, Johnstone RE. Misuse of prescribed controlled substances defined by urinalysis. *W V Med J*. 2003;99:67–70.
265. Mahowald ML, Singh JA, Majeski P. Opioid use by patients in an orthopedics spine clinic. *Arthritis Rheum*. 2005;52:312–321.
266. Reneman MF, Jorritsma W, Schellekens JM, Goeken LN. Concurrent validity of questionnaire and performance-based disability measurements in patients with chronic non-specific low back pain. *J Occup Rehabil*. 2002;12:119–129.
267. Gross DP, Battie MC. Construct validity of a kinetophysical functional capacity evaluation administered within a worker's compensation environment. *J Occup Rehabil*. 2003;13:287–295.
268. Reneman MF, Schiphorts Preuper HR, Kleen M, Geertzen JH, Dijkstra PU. Are pain intensity and pain related fear related to functional capacity evaluation performances of patients with chronic low back pain? *J Occup Rehabil*. 2007;17:247–258.
269. Schiphorst Preuper H, Reneman M, Boonstra A, et al. Relationship between psychological factors and performance-based and

- self-reported disability in chronic low back pain. *Eur Spine J*. 2008;17:1448–1456.
270. Brouwer S, Dijkstra PU, Stewart RE, Goeken LN, Groothoff JW, Geertzen JH. Comparing self-report, clinical examination and functional testing in the assessment of work-related limitations in patients with chronic low back pain. *Disabil Rehabil*. 2005;27:999–1005.
 271. Buelow AK, Haggard R, Gatchel RJ. Additional validation of the Pain Medication Questionnaire in a heterogeneous sample of chronic pain patients. *Pain Pract*. 2009;9:428–434.
 272. Smeets RJ, van Geel AC, Kester AD, Knotnerus JA. Physical capacity tasks in chronic low back pain: what is the contributing role of cardiovascular capacity, pain and psychological factors? *Disabil Rehabil*. 2007;29:577–586.
 273. Morasco BJ, Cavanagh R, Gritzner S, Dobscha SK. Care management practices for chronic pain in veterans prescribed high doses of opioid medications. *Fam Pract*. 2013;30:671–678.
 274. Fox CD, Steger HG, Jennison JH. Ratio scaling of pain perception with the submaximum effort tourniquet technique. *Pain*. 1979;7:21–29.
 275. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: a ratio measure? *Pain Pract*. 2003;3:310–316.
 276. Lund I, Lundeberg T, Sandberg L, Budh CN, Kowalski J, Svensson E. Lack of interchangeability between visual analogue and verbal rating pain scales: a cross sectional description of pain etiology groups. *BMC Med Res Methodol*. 2005;5:31.
 277. Katz N, Fanciullo G. Role of urine toxicology testing in the management of chronic opioid therapy. *Clin J Pain*. 2002;18(suppl):S76–S82.
 278. Graziotti P, Goucke R; for the Directors of the Australian Pain Society. *The Use of Oral Opioids in Patients With Chronic Nonmalignant Pain: Management Strategies*. Perth, Australia: Australian Pain Society; 2002.
 279. Heit H, Gourlay D. Urine drug testing in pain medicine. *J Pain Symptom Manage*. 2004;27:260–267.
 280. Wiedemer N, Harden P, Arndt I, Gallagher R. The opioid renewal clinic: a primary care, managed approach to opioid therapy in chronic pain patients at risk for substance abuse. *Pain Med*. 2007;8:573–584.
 281. Michna E, Jamison R, Pham L, et al. Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. *Clin J Pain*. 2007;23:173–179.
 282. Phillips K, Ch'ien AP, Norwood BR, Smith C. Chronic low back pain management in primary care. *Nurse Pract*. 2003;28:26–31.
 283. Hariharan J, Lamb GC, Neuner JM. Long-term opioid contract use for chronic pain management in primary care practice. A five year experience. *J Gen Intern Med*. 2007;22:485–490.
 284. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. *BMC Health Serv Res*. 2006;6:46.
 285. Chelminski PR, Ives TJ, Felix KM, et al. A primary care, multi-disciplinary disease management program for opioid-treated patients with chronic non-cancer pain and a high burden of psychiatric comorbidity. *BMC Health Serv Res*. 2005;5:3.
 286. Manchikanti L, Manchukonda R, Pampati V, et al. Does random urine drug testing reduce illicit drug use in chronic pain patients receiving opioids? *Pain Physician*. 2006;9:123–129.
 287. Lees R, Kingston R, Williams TM, Henderson G, Lingford-Hughes A, Hickman M. Comparison of ethyl glucuronide in hair with self-reported alcohol consumption. *Alcohol Alcohol*. 2012;47:267–272.
 288. Politi L, Zucchella A, Morini L, Stramesi C, Poletti A. Markers of chronic alcohol use in hair: comparison of ethyl glucuronide and cocaethylene in cocaine users. *Forensic Sci Int*. 2007;172:23–27.
 289. Lamoureux F, Gaulier JM, Sauvage FL, Merceroille M, Vallejo C, Lachatre G. Determination of ethyl-glucuronide in hair for heavy drinking detection using liquid chromatography–tandem mass spectrometry following solid-phase extraction. *Anal Bioanal Chem*. 2009;394:1895–1901.
 290. Cooper GA, Kronstrand R, Kintz P. Society of hair testing guidelines for drug testing in hair. *Forensic Sci Int*. 2012;218:20–24.
 291. Kulaga V, Velazquez-Armenta Y, Aleksa K, Vergee Z, Koren G. The effect of hair pigment on the incorporation of fatty acid ethyl esters (FAEE). *Alcohol Alcohol*. 2009;44:287–292.
 292. Appenzeller BM, Agirman R, Neuberg P, Yegles J, Wennig R. Segmental determination of ethyl glucuronide in hair: a pilot study. *Forensic Sci Int*. 2007;173:87–92.
 293. Auerbach K. Drug testing methods. In: Lessenger J, Roper G, eds. *Drug Courts: A New Approach to Treatment and Rehabilitation*. New York, NY: Springer Science+Business Media; 2007:215–233.
 294. Jortani S, Stauble E, Wong S. Chapter 1. Pharmacogenetics in clinical and forensic toxicology: opioid overdoses and deaths. In: Mozayani A, Raymon L, eds. *Handbook of Drug Interactions a Clinical and Forensic Guide*. New York, NY: Humana Press; 2012:3–22.
 295. American Society of Health-System Pharmacists. 2011 update to demystifying opioid conversion calculations: a guide for effective dosing. Available at: <http://www.ashp.org/DocLibrary/Bookstore/P1985/2011-Update.aspx>. Published 2011. Accessed October 28, 2014.
 296. Eastern Metropolitan Region Palliative Care Consortium. Opioid conversion ratios—guide to practice 2010. Available at: <http://www.emrpcc.org.au/wp-content/uploads/2013/03/EMRPCC-Opioid-Conversion2010-Final2.pdf>. Published 2010. Accessed October 28, 2014.
 297. Ph.D Pharm WA State. Opioid dose calculator. 2012. Available at: www.agency.meddirectors.wa.gov/Files/DosingCalc.xls.
 298. GlobalRPH Opioid Analgesic Converter. Available at: <http://www.globalrph.com/narconconv.htm>. Accessed October 28, 2014.
 299. National Cancer Institute Pain (PDQ). Pharmacologic management. <http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/page3>. Accessed July 13, 2012.
 300. Agency for Healthcare Research and Quality. Morbidity & mortality rounds on the web. Case & commentary. Strassels SA. Miscalculated risk. Hospital medicine. <http://webmm.ahrq.gov/case.aspx?caseID=132#table1>. Published August 2006. Accessed July 13, 2012.
 301. American Academy of Hospice and Palliative Medicine. Guidelines for prescribing opiates for hospice and palliative care patients. <http://www.aahpm.org/pdf/guidelinesforopioids.pdf>. Accessed July 16, 2012.
 302. Federal Drug Administration. Introduction for the FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics. Available at: www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. Accessed July 14, 2012.
 303. American Academy of Pain Medicine, NPF, American Pain Foundation, and National Hospice and Palliative Care Organization. *Recommendations to Physicians Caring for Katrina Disaster Victims on Chronic Opioids*. Chicago, IL: AAPM; 2005.
 304. Kral L. Opioid tapering: safely discontinuing opioid analgesics. Available at: http://pain-topics.org/pdf/Safely_Tapering_Opioids.pdf. 2006. Accessed July 16, 2012.
 305. Portenoy R, Bennett D, Rauck R, et al. Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain*. 2006;7:583–591.
 306. Hojsted J, Nielsen P, Eriksen J, Hansen O, Sjøgren P. Breakthrough pain in opioid-treated chronic non-malignant pain patients referred to a multidisciplinary pain centre: a preliminary study. *Acta Anaesthesiol Scand*. 2006;50:1290–1296.
 307. Fine P, Messina J, Xie F, Rathmell J. Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study. *J Pain Symptom Manage*. 2010;40:747–760.
 308. Simpson D, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007;29:588–601.
 309. Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain*. 2011;12:288–296.
 310. Lemming D, Sorensen J, Graven-Nielsen T, Arendt-Nielsen L, Gerdle B. The responses to pharmacological challenges and experimental pain in patients with chronic

- whiplash-associated pain. *Clin J Pain*. 2005;21:412–421.
311. Lemming D, Sorensen J, Graven-Nielsen T, Lauber R, Arendt-Nielsen L, Gerdle B. Managing chronic whiplash associated pain with a combination of low-dose opioid (remifentanyl) and NMDA-antagonist (ketamine). *Eur J Pain*. 2007;11:719–732.
 312. Miele VJ, Price KO, Bloomfield S, Hogg J, Bailes JE. A review of intrathecal morphine therapy related granulomas. *Eur J Pain*. 2006;10:251–261.
 313. Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage*. 2006;31:393–406.
 314. Webster LR, Butera PG, Moran LV, Wu N, Burns LH, Friedmann N. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain*. 2006;7:937–946.
 315. Gilson A, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1997–2002. *J Pain Symptom Manage*. 2004;28:176–188.
 316. Joranson D, Berger J. Regulatory issues in pain management. *J Am Pharm Assoc*. 2000;40(suppl 1):S60–S61.
 317. Fishbain D, Cole B, Lewis J, Rosomoff H, Rosomoff R. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Med*. 2008;9:444–459.
 318. Hojsted J, Sjogren P. Addiction to opioids in chronic pain patients: a literature review. *Eur J Pain*. 2007;11:490–518.
 319. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112:372–380.
 320. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage*. 2008;35:214–228.
 321. Furlan A, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *Can Med Assoc J*. 2006;174:1589–1594.
 322. Jones T, Moore T, Levy J, et al. A comparison of various risk screening methods in predicting discharge from opioid treatment. *Clin J Pain*. 2012;28:93–100.
 323. Moore TM, Jones T, Browder JH, Daffron S, Passik SD. A comparison of common screening methods for predicting aberrant drug-related behavior among patients receiving opioids for chronic pain management. *Pain Med*. 2009;10:1426–1433.
 324. Jones T, Moore T. Preliminary data on a new opioid risk assessment measure: the Brief Risk Interview. *J Opioid Manag*. 2013;9:19–27.
 325. Adams L, Gatchel R, Robinson R, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. *J Pain Symptom Manage*. 2004;27:440.
 326. Chou R, Fanciullo GJ, Fine PG, Miaskowski C, Passik SD, Portenoy RK. Opioids for chronic noncancer pain: prediction and identification of aberrant drug-related behaviors: a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *J Pain*. 2009;10:131–146.
 327. Akbik H, Butler S, Budman S, Fernandez K, Katz N, Jamison R. Validation and clinical application of the Screener and Opioid Assessment for Patients with Pain (SOAPP). *J Pain Symptom Manage*. 2006;32:287–293.
 328. Turk D. Predicting opioid misuse by chronic pain patients. A systematic review and literature synthesis. *Clin J Pain*. 2008;24:497–508.
 329. Ballantyne JC, LaForge KS. Opioid dependence and addiction during opioid treatment of chronic pain. *Pain*. 2007;129:235–255.
 330. Manchikanti L, Atluri S, Trescot AM, Giordano J. Monitoring opioid adherence in chronic pain patients: tools, techniques, and utility. *Pain Physician*. 2008;11(suppl):S155–S180.
 331. Passik S, Kirsh K, Casper D. Addiction-related assessment tools and pain management: instruments for screening, treatment planning, and monitoring compliance. *Pain Med*. 2008;9(S2):S145–S166.
 332. Smith HS, Kirsh KL, Passik SD. Chronic opioid therapy issues associated with opioid abuse potential. *J Opioid Manag*. 2009;5:287–300.
 333. Hartrick C, Gatchel R, Conroy S. Identification and management of pain medication abuse and misuse: current state and future directions. *Expert Rev Neurother*. 2012;12:601–610.
 334. Wu S, Compton P, Bolus R, et al. The Addiction Behaviors Checklist: validation of a new clinician-based measure of inappropriate opioid use in chronic pain. *J Pain Symptom Manage*. 2006;32:342–351.
 335. Compton P, Darakjian J, Miotto K. Screening for addiction in patients with chronic pain and “problematic” substance use: evaluation of a pilot assessment tool. *J Pain Symptom Manage*. 1998;16:355–363.
 336. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med*. 2005;6:432–442.
 337. Coombs R, Coombs C. Drug testing attitudes of mandatory participants. *J Subst Misuse Nurs Health Soc Care*. 1996;1:85–90.
 338. Friedman R, Li V, Mehrotra D. Treating pain patients at risk: evaluation of a screening tool in opioid-treated pain patients with and without addiction. *Pain Med*. 2003;4:182–185.
 339. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. *J Pain*. 2006;7:671–681.
 340. Jamison RN, Serrailier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. *Pain Res Treat*. 2011;2011:941808.
 341. Wasan A, Butler S, Budman S, Benoit C, Fernandez K, Jamison R. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. *Clin J Pain*. 2007;23:307–315.
 342. Passik S, Kirsh K, Whitcomb L, et al. Monitoring outcomes during long-term opioid therapy for noncancer pain: results with the Pain Assessment and Documentation Tool. *J Opioid Manag*. 2005;1:257–266.
 343. Butler S, Budman S, Fernandez K, Fanciullo G, Jamison R. Cross-validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *J Addict Med*. 2009;3:66–73.
 344. Butler S, Budman S, Fernandez K, et al. Development and validation of the Current Opioid Misuse Measure. *Pain*. 2007;130:144–156.
 345. Butler S, Budman S, Fernandez K, Jamison R. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain*. 2004;112:65–75.
 346. Martel MO, Wasan AD, Jamison RN, Edwards RR. Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. *Drug Alcohol Depend*. 2013;132:335–341.
 347. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: a randomized trial. *Pain*. 2010;150:390–400.
 348. Butler S, Budman S, Fanciullo G, Jamison R. Cross validation of the Current Opioid Misuse Measure (COMM) to monitor chronic pain patients on opioid therapy. *Clin J Pain*. 2010;26:770–776.
 349. Meltzer EC, Rybin D, Saitz R, et al. Identifying prescription opioid use disorder in primary care: diagnostic characteristics of the Current Opioid Misuse Measure (COMM). *Pain*. 2011;152:397–402.
 350. Parhami I, Hyman M, Siani A, et al. Screening for addictive disorders within a workers’ compensation clinic: an exploratory study. *Subst Use Misuse*. 2012;47:99–107.
 351. Hojsted J, Nielsen PR, Kendall S, Frich L, Sjogren P. Validation and usefulness of the Danish version of the Pain Medication Questionnaire in opioid-treated chronic pain patients. *Acta Anaesthesiol Scand*. 2011;55:1231–1238.
 352. Holmes C, Gatchel R, Adams L, et al. An opioid screening instrument: long-term evaluation of the utility of the Pain Medication Questionnaire. *Pain Pract*. 2006;6:74–88.
 353. Park J, Lavin R. Risk factors associated with opioid medication misuse in community-dwelling older adults with chronic pain. *Clin J Pain*. 2010;26:647–655.
 354. Dowling LS, Gatchel RJ, Adams LL, Stowell AW, Bernstein D. An evaluation of the predictive validity of the Pain Medication Questionnaire with a heterogeneous group of patients with chronic pain. *J Opioid Manag*. 2007;3:257–266.
 355. Paice JA, Cohen FL. Validity of a verbally administered numeric rating scale to

- measure cancer pain intensity. *Cancer Nurs*. 1997;20:88–93.
356. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills*. 1984;59:974.
357. Bunten H, Liang WJ, Pounder DJ, Seneviratne C, Osselton D. OPRM1 and CYP2B6 gene variants as risk factors in methadone-related deaths. *Clin Pharmacol Ther*. 2010;88:383–389.
358. Buchard A, Linnet K, Johansen SS, Munkholm J, Fregerslev M, Morling N. Post-mortem blood concentrations of R- and S-enantiomers of methadone and EDDP in drug users: influence of co-medication and p-glycoprotein genotype. *J Forensic Sci*. 2010;55:457–463.
359. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med*. 2009;361:827–828.
360. Fishbain D, Lewis J, Gao J. Allegations of medical malpractice in chronic opioid analgesic therapy possibly related to collaborative/split treatment and the P-450 enzyme system: forensic case report. *Pain Med*. 2010;11:1419–1425.
361. Musshoff F, Stamer UM, Madea B. Pharmacogenetics and forensic toxicology. *Forensic Sci Int*. 2010;203:53–62.
362. Haddad A, Davis M, Lagman R. The pharmacological importance of cytochrome CYP3A4 in the palliation of symptoms: review and recommendations for avoiding adverse drug interactions. *Support Care Cancer*. 2007;15:251–257.
363. Argoff CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain*. 2010;26(suppl 10):S16–S20.
364. Stingl JC, Brockmoller J, Viviani R. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. *Mol Psychiatry*. 2013;18:273–287.
365. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther*. 2013;17:165–184.
366. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther*. 2012;91:321–326.
367. Chauvin B, Drouot S, Barrail-Tran A, Taburet AM. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. *Clin Pharmacokinet*. 2013;52:815–831.
368. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368:704.
369. Poulsen L, Brosen K, Arendt-Nielsen L, Gram LF, Elbaek K, Sindrup SH. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. *Eur J Clin Pharmacol*. 1996;51:289–295.
370. Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain*. 1998;76:27–33.
371. Stamer UM, Lehnen K, Hothker F, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. *Pain*. 2003;105:231–238.
372. Stamer UM, Stuber F. Codeine and tramadol analgesic efficacy and respiratory effects are influenced by CYP2D6 genotype. *Anaesthesia*. 2007;62:1294–1295; author reply 5–6.
373. Stamer UM, Stuber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg*. 2008;107:926–929.
374. Stamer UM, Zhang L, Stuber F. Personalized therapy in pain management: where do we stand? *Pharmacogenomics*. 2010;11:843–864.
375. Zwisler ST, Enggaard TP, Mikkelsen S, Brosen K, Sindrup SH. Impact of the CYP2D6 genotype on post-operative intravenous oxycodone analgesia. *Acta Anaesthesiol Scand*. 2009;54:232–240.
376. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The antinociceptive effect and adverse drug reactions of oxycodone in human experimental pain in relation to genetic variations in the OPRM1 and ABCB1 genes. *Fundam Clin Pharmacol*. 2010;24:517–524.
377. Zwisler ST, Enggaard TP, Noehr-Jensen L, et al. The hypoalgesic effect of oxycodone in human experimental pain models in relation to the CYP2D6 oxidation polymorphism. *Basic Clin Pharmacol Toxicol*. 2009;104:335–344.
378. Jannetto PJ, Wong SH, Gock SB, Laleli-Sahin E, Schur BC, Jentzen JM. Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol*. 2002;26:438–447.
379. Herbild L, Andersen SE, Werge T, Rasmussen HB, Jurgens G. Does pharmacogenetic testing for CYP450 2D6 and 2C19 among patients with diagnoses within the schizophrenic spectrum reduce treatment costs? *Basic Clin Pharmacol Toxicol*. 2013;113:266–272.
380. Crettol S, Deglon JJ, Besson J, et al. ABCB1 and cytochrome P450 genotypes and phenotypes: influence on methadone plasma levels and response to treatment. *Clin Pharmacol Ther*. 2006;80:668–681.
381. Crettol S, Deglon JJ, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*. 2005;78:593–604.
382. Eap CB, Crettol S, Rougier JS, et al. Stereoselective block of hERG channel by (S)-methadone and QT interval prolongation in CYP2B6 slow metabolizers. *Clin Pharmacol Ther*. 2007;81:719–728.
383. Pedersen RS, Damkier P, Brosen K. Enantioselective pharmacokinetics of tramadol in CYP2D6 extensive and poor metabolizers. *Eur J Clin Pharmacol*. 2006;62:513–521.
384. Wang Y, Al-Gazzar A, Seibert C, Sharif A, Lane C, Griffiths WJ. Proteomic analysis of cytochromes P450: a mass spectrometry approach. *Biochem Soc Trans*. 2006;34(Pt 6):1246–1251.
385. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte: an update of guidelines. *Clin Pharmacol Ther*. 2011;89:662–673.
386. Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE, Sellers EM. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. *Clin Pharmacol Ther*. 1993;54:463–472.
387. Kirchheiner J, Keulen JT, Bauer S, Roots I, Brockmoller J. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol*. 2008;28:78–83.
388. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip. A randomized, double-blind, multi-centre study. *Pain*. 1990;43:309–318.
389. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin*. 2010;26:1505–1518.
390. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6:21–28.
391. Peloso PM, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol*. 2004;31:2454–2463.
392. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther*. 2003;25:1123–1141.
393. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol*. 2000;27:772–778.
394. Breckenridge J, Clark J. Patient characteristics associated with opioid versus nonsteroidal anti-inflammatory drug management of chronic low back pain. *J Pain*. 2003;4:344–350.
395. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med*. 2010;153:158–166.
396. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289:454–465.
397. Shah RV, Albert TJ, Bruegel-Sanchez V, Vaccaro AR, Hilibrand AS, Grauer JN. Industry support and correlation to study outcome for papers published in Spine. *Spine*. 2005;30:1099–1104.
398. Steinbrook R. Peer review and federal regulations. *N Engl J Med*. 2004;350:103–104.