Contextual Evidence Review for the CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016

Primary Areas of Focus

Contextual evidence is complementary information that assists in translating the clinical research findings into recommendations. CDC conducted contextual evidence reviews on four topics to supplement the clinical evidence review findings:

- **Effectiveness of non-pharmacologic** (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, multimodal pain treatment) **and non-opioid pharmacologic treatments** (e.g., acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs], antidepressants, anticonvulsants), including studies of any duration;
- **Benefits and harms of opioid therapy** (including additional studies not included in the clinical evidence review, such as studies that were not restricted to patients with chronic pain, evaluated outcomes at any duration, performed ecological analyses, or used observational study designs other than cohort and case-cohort control studies) related to specific opioids, high dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/mitigation approaches; in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder);
- **Clinician and patient values and preferences** related to opioids and medication risks, benefits, and use; and
- **Resource allocation** including costs and economic efficiency of opioid therapy and risk mitigation strategies.

CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could complement the CDC recommendations in development (e.g., guidelines on nonpharmacologic and nonopioid pharmacologic treatments; guidelines with recommendations related to specific clinician actions such as urine drug testing or opioid tapering protocols).

Contextual Review Methods

CDC conducted "rapid reviews" of the contextual evidence to supplement the clinical evidence review. Rapid reviews are used when there is a need to streamline the systematic review process to obtain evidence in a short time frame (*1*). Methods used to streamline the process include limiting searches by databases, years, and languages considered, and truncating quality assessment and data abstraction protocols. Given the public health urgency of developing opioid prescribing recommendations, a rapid review was required for the current guideline.

Data Sources and Searches

Data sources for the contextual evidence searches varied by topic, but included PubMed, PsycINFO, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. CDC systematically searched the databases for English-language articles published within the past 10 years (April 2005 to April 2015), with the exception of searches on benefits and harms and nonpharmacologic and nonopioid pharmacologic treatments which were extended back to January 2000. CDC limited and modified search criteria over the course of retrieval to obtain the most relevant articles. Search terms focused on chronic pain and its relation to NSAIDs, acetaminophen, antidepressants, and anticonvulsants (for non-opioid pharmacologic treatment); and CBT, physical therapy, exercise, and interventional treatments (for non-pharmacologic treatment). Search terms also focused on opioids and chronic pain and their relation to overdose, cardiovascular events, motor vehicle crashes, and fractures (for benefits and harms); benzodiazepines (for harms related to co-prescribing); substance use disorders (for harms related to patient risk); prescription drug monitoring programs (PDMPs) and naloxone (for risk stratification/mitigation approaches); pharmacologic treatments and psychosocial therapies for opioid use

disorder (for treatments associated with the potential harms of opioid therapy); knowledge, attitudes, and beliefs (for patient and clinician values and preferences); and cost, cost-benefit, cost effectiveness, and budget impacts (for resource allocation). Searches also focused on clinical practice guidelines related to opioid and nonopioid therapies. Given the need for a rapid review process, grey literature (e.g., literature by academia, organizations, or government in the form of reports, documents, or proceedings not published by commercial publishers) was not systematically searched. CDC considered relevant studies and guidelines to which it was referred by subject matter experts.

Study Selection

For the searches focused on nonpharmacologic and nonopioid pharmacologic treatments and benefits and harms, a primary reviewer downloaded study abstracts found using the above search methods and reviewed them to determine their possible relevance and whether they were of sufficient quality. A second reviewer then reviewed the same set of abstracts as well as the first reviewer's decisions. If the second reviewer's decisions differed from the first, they met to discuss and resolve the difference. In some instances, a third reviewer was consulted. For the searches on the remaining topics, only a primary reviewer reviewed the abstracts for relevance and quality. Only a very small proportion of the downloaded study abstracts were ultimately selected as being relevant to the question at issue and of sufficient scientific rigor to be included. CDC obtained and reviewed full text of the published articles identified for possible inclusion to verify that they met criteria for inclusion.

Because of the large volume of literature and time and resource considerations, CDC selected systematic reviews and clinical guidelines (rather than original studies) from the searches directed toward identifying the effectiveness of nonopioid pharmacologic and nonpharmacologic pain treatment strategies; these often focused on specific therapies as applied to specific pain conditions. CDC also selected systematic reviews of pharmacologic and nonpharmacologic treatment options for opioid use disorder. However, CDC selected original epidemiologic and observational research studies that addressed the other contextual evidence focus areas: benefits and harms, values and preferences, and resource allocation. Specifically, CDC selected original studies that employed a comparison group, including case-control studies, cohort studies, and crossover designs in which a subject serves as his/her own control. CDC excluded studies lacking a control group - for example, case series or population-level estimates of prevalence. Studies could be of any duration to allow for identification of harms that may appear soon after initiation of therapy. For topic areas where the literature search resulted in few studies meeting inclusion criteria and clinical recommendations could not be adequately informed without empirical literature, CDC relaxed selection criteria on the recommendation of subject matter experts to allow for inclusion of the study findings. CDC excluded all studies outside the United States, pediatric studies, studies with no original research design, and studies that were already included in the clinical evidence review. Finally, CDC selected several clinical guidelines for inclusion that provided recommendations on opioid prescribing based on searches and referrals from subject matter experts.

Data Extraction and Synthesis

Given the nature of the studies, the purpose that contextual evidence serves, and the short timeline for developing the guidelines, CDC did not conduct rigorous evidence grading of the findings from the rapid reviews. It is important to note, however, that most of the original studies included in the contextual review focusing on benefits and harms, values and preferences, and resource allocation employed observational methods, often case-control or retrospective cohort studies, as opposed to randomized controlled trials. Thus, the evidence from the contextual evidence review of these areas is considered to be of low quality and should be interpreted with caution. The quality of evidence for nonopioid pharmacologic and nonpharmacologic pain treatments was generally rated as moderate in systematic reviews and clinical guidelines (e.g., for treatment of chronic neuropathic pain, low back pain, osteoarthritis, and fibromyalgia). Similarly, the quality of evidence for pharmacologic and psychosocial opioid use disorder treatment was generally rated as moderate in systematic reviews and clinical guidelines. CDC reviewed each full paper, summarized the main findings in tables, and constructed narrative reviews of each contextual focus area; quantitative results were not synthesized (e.g., with

standard effect sizes). CDC included only the studies and guidelines that directly informed the recommendations in the narrative reviews and tables.

Contextual Evidence Review Findings

Findings on the Effectiveness of Nonpharmacologic and Nonopioid Pharmacologic Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments are used to manage chronic pain. Nonpharmacologic therapies for chronic pain include physical modalities (e.g., exercise, physical therapy, massage), behavioral approaches (e.g., CBT, mindfulness-based stress reduction techniques), and interventional approaches (e.g., percutaneous injection, epidural injection). Major classes of medications used for pain include analgesics such as acetaminophen, NSAIDs, and cyclooxygenase 2 (COX-2) inhibitors; selected anticonvulsants; and selected antidepressants (particularly tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)). The primary purpose of this guideline is not to provide detailed recommendations on the use of nonpharmacologic and nonopioid pharmacologic treatments for chronic pain; however, reviewing the effectiveness of such strategies provides important contextual information to clinicians considering opioid therapy and available options for their patients. To provide this contextual information, findings from existing systematic reviews estimating treatment effectiveness (see Table 1), as well as pain treatment guidelines are summarized (see Table 6). Although the GRADE methodology was not used to rate quality of evidence across all systematic reviews, as can be seen in Table 1, and within previous pain treatment guidelines (e.g., for neuropathic pain, low back pain, osteoarthritis, and fibromyalgia), the overall quality of evidence for nonpharmacologic and nonopioid pharmacologic treatments as rated by study authors can be characterized as moderate. Because the clinical evidence review did not identify any studies of the comparative effectiveness of opioids versus nonopioid therapies on long-term outcomes (>1 year), CDC conducted searches for systematic reviews of the effectiveness of nonpharmacologic and nonopioid pharmacologic treatments that included studies with follow-up periods of any duration. Most studies of nonopioid pharmacologic therapy in the systematic reviews were weeks to months in duration, generally 2 to 14 weeks with some studies of up to 26 weeks. Studies of nonpharmacologic therapy in the systematic reviews were generally longer in duration, with studies of exercise therapy including follow-up at 2 to 6 months and studies of CBT assessing outcomes at 6 months or longer.

Nonpharmacologic Therapies

CBT helps patients understand and modify situational factors and cognitive processes that exacerbate pain and includes training in behavioral techniques such as relaxation and controlled-breathing exercises. A systematic review found CBT had small positive effects on disability and catastrophizing (*2*). Guidelines also recommend that primary care clinicians integrate elements of a cognitive behavioral approach into their practice, for example by encouraging patients to take an active role in the care plan and by supporting patients in engaging in beneficial but potentially anxiety-provoking activities, such as exercise (*3*).

Exercise therapy can help restore normal range of motion and muscle conditioning to improve function, stability, and pain. Exercise has been shown to be effective in improving pain and function in chronic low back pain (*4*) and in improving function and reducing pain with improvements continued for at least 2 to 6 months after completing formal treatment in osteoarthritis of the knee (*5*) and hip (*6*). Previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*7*). In addition, exercise has been shown to improve well-being, fibromyalgia symptoms, and physical function in fibromyalgia (*8*); the Canadian national fibromyalgia guideline panel recommended that persons with fibromyalgia participate in a graduated exercise program (*9*). A systematic review found weight reduction was effective for pain relief in knee osteoarthritis (*10*).

Multimodal integrative therapies group different approaches together to form an ad hoc “program.” A systematic review of multimodal integrative therapies that focused on self-care approaches excluding surgery and prescription medication (e.g., therapies that paired relaxation approaches with CBT or exercise) found generally positive, but sometimes mixed, effects of integrative approaches compared with active controls or single self-care

modalities, suggesting that multimodal integrative therapies might be a promising approach to chronic pain management, although more studies are needed to make strong conclusions about effectiveness (*11*). A systematic review found multidisciplinary biopsychosocial rehabilitation more effective than usual care or physical treatments (e.g., heat, exercise) alone in improving long-term pain and disability (*12*).

Nonopioid Pharmacologic Treatments

Multiple guidelines recommend acetaminophen as first-line pharmacotherapy for osteoarthritis (*13-18*) or for low back pain (*19*). Several guidelines also recommend NSAIDs as first-line treatment for osteoarthritis or low back pain (*14,19*). A systematic review of NSAIDS for non-specific low back pain found NSAIDs to be effective for symptomatic relief in chronic low back pain without sciatica; NSAIDS were not more effective than acetaminophen or than COX-2 inhibitors for low back pain, but were associated with more side effects, including abdominal pain, diarrhea, edema, dry mouth, rash, dizziness, headache, and tiredness (*20*). Guidelines have noted that acetaminophen should be avoided in liver failure and that maximum dosage of 4g/day be reduced 50-75% in patients with hepatic insufficiency or history of alcohol abuse (*18*). Some guidelines have suggested that systemic NSAIDs should be used rarely and with caution in older patients because of gastrointestinal, renal, and cardiovascular risks (*3,18*), that both NSAIDs and COX-2 inhibitors should be used with caution in patients with cardiovascular (*14,19*) and gastrointestinal (*3,19*) risk factors. In a meta-analysis of the cardiovascular safety of seven NSAIDs, although there was variation in harms depending on the specific drug and outcome, and there was some imprecision in estimates, there was an increased risk for myocardial infarction, stroke, and cardiovascular death for NSAIDs compared with placebo (*21*). The Food and Drug Administration (FDA) has recently strengthened existing label warnings that NSAIDs increase risks for heart attack and stroke, including that these risks may increase with longer use or at higher doses (*22*).

Several guidelines agree that first and second-line drugs for neuropathic pain include anticonvulsants (gabapentin or pregabalin) and antidepressants (TCAs and SNRIs) (*23-26*).

Three anticonvulsants (pregabalin, gabapentin, carbamazepine) are FDA-approved for treatment of neuropathic pain. Guidelines note that pregabalin is potentially teratogenic and should be avoided in women of child-bearing age (*26*), that gabapentin and pregabalin can produce dose-related dizziness that can be mitigated by starting with low dosages and increasing cautiously (*23*), and that gabapentin and pregabalin require dosage adjustment in renal failure (*25*). A systematic review found pregabalin at doses of 300 mg to 600 mg was more effective than placebo for pain relief in patients with postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, or fibromyalgia in studies lasting 4-26 weeks (*27*). A systematic review found gabapentin was superior to placebo among patients with postherpetic neuralgia and diabetic neuropathy (*28*). Common adverse events included dizziness (19%), somnolence (14%), gait disturbance (9%), and peripheral edema (7%), but serious adverse events (4%) were not more frequent than those occurring with placebo (*28*). A systematic review found carbamazepine more effective than placebo for chronic neuropathic pain; however, the review authors found the included studies had low reporting quality, and none lasted longer than 4 weeks (*29*).

TCAs and SNRIs have analgesic effects, often at lower dosages than those needed for antidepressant effects, and with a shorter time to onset of effect than for treatment of depression (days instead of weeks). These antidepressants have demonstrated effectiveness in neuropathic pain conditions, including diabetic neuropathy and post-herpetic neuralgia with low numbers needed to treat (2-3) (*30,31*). Antidepressants (*32*), particularly TCAs (*33*), have improved chronic back pain in short-term trials ($\leq$ 8 weeks). Guidelines note that TCAs might be unsafe at high doses and in the elderly and patients with significant cardiovascular disease given potential sedation (*26*), dizziness, blood pressure increases, and ECG changes (*25*). Duloxetine, an SNRI, has some evidence for efficacy for pain relief in fibromyalgia (*34,35*) and painful diabetic neuropathy (*34*). Antidepressants can be particularly useful in patients with concurrent pain and depression.

CDC found very limited evidence on comparative effectiveness of opioid therapy and other medications (or nonpharmacologic treatments) for chronic pain. A recent systematic review analyzed results from 10 randomized controlled trials of 4-12 weeks duration, four of which compared efficacy, tolerability, and safety of morphine

with antidepressants (nortriptyline), anticonvulsants (gabapentin), and an antiarrythmic (mexilitene) for neuropathic pain, and six of which compared tramadol with NSAIDs/COX-2 inhibitors for osteoarthritis or low back pain (*36*). The review found that opioids did not differ from non-opioids in pain reduction, and that non-opioids were superior to opioids for improvement in physical function and in tolerability. However, most patients were in trials comparing nonopioid drugs with tramadol, a synthetic, centrally acting analgesic that binds to the mu opioid receptor and also inhibits reuptake of serotonin and of norepinephrine. Tramadol was considered to be an opioid in this review but was not included as an opioid for the purposes of this report, and when patients from tramadol trials (n randomized=2,788) were removed from results of the review, results for pain and function for patients receiving opioids (morphine) compared with alternative drugs (n randomized=223) had wide, overlapping confidence intervals. Improved tolerability for alternative drugs versus morphine remained significant. Another review found no difference between antidepressants and opioids or tramadol on pain and function in two studies on chronic low back pain (*37*). However, both studies were included in the review of 10 studies above.

Interventional approaches such as epidural injection for certain conditions (e.g., lumbar radiculopathy) including percutaneous corticosteroid injection and epidural injection can provide short-term improvement in pain and in function that can facilitate exercise therapy (*38-40*). However, epidural injection has been associated with rare but serious adverse events including loss of vision, stroke, paralysis, and death (*41*).

Findings on Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. Considerations related to benefits and harms include numbers of patients affected as well as magnitude of benefits relative to harms. Therefore, CDC reviewed epidemiologic evidence on the number of persons experiencing chronic pain, the proportion potentially benefitting from opioids, and the number of persons affected by serious opioid-related harms (see Table 2). Benefits and harms of opioids for chronic pain outside of end-of-life care were evaluated in the clinical evidence review based on studies of adults with chronic pain prescribed long-term opioid therapy with outcomes reported after >1 year of opioid therapy. Because overdose outcomes reported for opioid therapy occurring <1 year are also relevant to patients on chronic opioid therapy, CDC conducted searches for studies reporting overdose not limited to patients with chronic pain or to a minimum follow-up period (see Table 2). To assess balance of benefits and harms in populations potentially at greater risk for harm (e.g., older patients, pregnant women, patients with substance use disorders or mental health conditions), searches for studies of these populations were conducted without restrictions on indication for opioid use or minimum length of follow-up (see Table 2). Finally, CDC sought contextual evidence regarding benefits and harms of risk stratification and risk mitigation strategies (see Table 2).

Prevalence Estimates of Pain and Opioid-Related Harms

A frequently cited Institute of Medicine report (*42*) stated that at least 100 million Americans suffer from chronic pain conditions. This estimate relied on a study (*43*) that attempted to quantify prevalence of chronic pain conditions among adults in 10 developed and seven developing countries using data from the World Mental Health Surveys. Respondents were asked if they had ever had "arthritis or rheumatism… chronic back or neck problems… frequent or severe headaches" and "other chronic pain." Subjects were then asked whether these conditions had been present in the past 12 months but were not asked how long these conditions were present. Therefore, this estimate reflects the number of American adults reporting common, predominantly musculosketetal pain conditions that can be chronic. In the United States, the overall age-standardized prevalence of these conditions within the last 12 months (for any length of time) was 43.0%.

Other estimates using different definitions of chronic pain have found lower prevalence rates. A National Health and Nutrition Examination Survey (*44*) found a weighted prevalence of 14.6% for current, chronic, non-minor pain lasting ≥3 months among adults. Back pain was the most common type of pain (weighted prevalence 10.1%). An internet-based, cross-sectional 2008 survey of 53,524 adults in five European countries found 8.9% reported daily pain of mild to severe intensity; an additional 5.9% reported pain 2-6 times per week, and another 5.5%

experienced pain weekly or less frequently. The most common conditions associated with pain were back pain, joint pain, neck pain, and headache (*45*). Most recently, analysis of data from the 2012 National Health Interview Study revealed an estimated prevalence of daily pain of 11.2% among the adult population (*46*).

The numbers of persons experiencing chronic pain who would potentially benefit from opioids is challenging to estimate given absence of studies evaluating long-term benefits of these medications for chronic pain, as determined in the clinical evidence review (Key Question 1; KQ1). No guidelines were identified that recommended opioids as preferred treatments for the common conditions (back pain, arthritis, or headache) used for estimates of the prevalence of chronic pain.

From 1999 to 2014, more than 165,000 persons in the United States suffered fatal overdoses related to opioid pain medication (*47*). The Drug Abuse Warning Network estimated over 420,000 emergency department visits related to the misuse or abuse of narcotic pain relievers in 2011, the most recent year for which data are available (*48*). As noted above, several nonpharmacologic and nonopioid pharmacologic therapies are recommended for chronic pain conditions. Some of these therapies are associated with specific risks but are generally not associated with drug dependence, and the numbers of fatal overdoses associated with the nonopioid drugs studied are a fraction of those associated with opioids (*49*). For example, acetaminophen, NSAIDs, and opioid pain medication were involved in 881, 228, and 16,651 pharmaceutical overdose deaths in the United States in 2010 (*49*).

Benefits and Harms Associated with Specific Opioids or Opioid Formulations

In 2014, the FDA approved class-wide safety labeling changes for all extended release/long-acting (ER/LA) opioid analgesics intended to treat pain, noting serious risks of ER/LA opioids and updating the indication for this class of medications to "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment" and including "limitations of use" language reserving ER/LA opioids "for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain." (*50*). A survey of patients receiving chronic opioid therapy for chronic non-cancer pain found time-scheduled opioid use to be associated with substantially higher total average daily opioid dosage compared with as-needed opioid use depending on pain (97.2 versus 37.2 morphine milligram equivalents [MME]/day, p<.001) (*51*). Some authors have suggested that immediate-release opioids used for short durations intermittently might reduce tolerance and risk of dependence compared with continuous opioid use (*52*).

Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid-related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (*53*). This might result in part from the complicated pharmacokinetics and pharmacodynamics of methadone, including a long and variable half-life and peak respiratory depressant effect occurring later and lasting longer than peak analgesic effect (*54*).

Benefits and Harms Associated with High-dose Opioid Therapy

Studies examining the efficacy of high-dose opioids for chronic pain outside of end-of-life care were not identified. In addition to the studies identified in the clinical evidence review (KQ2), the contextual review found five additional studies on the association of opioid dosage and overdose risk (*55-59*). These had been excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain only. Similar to the clinical evidence review, the contextual review found that opioid-related overdose risk is dose-dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (*55,57*) as well as the two studies in the clinical evidence review (*60, 61*) used wide but consistent ranges of dosages (1 to <20 MME/day, 20 to <50 MME/day, 50 to <100 MME/day, ≥100 MME/day) to evaluate association of prescribed opioid dosages with overdose risk. In these four studies, compared with opioids prescribed at <20

MME/day, the odds of overdose among patients prescribed opioids for chronic non-malignant pain were between 1.3 (*61*) and 1.9 (*55*) for dosages of 20 to <50 MME/day, between 1.9 (*61*) and 4.6 (*55*) for dosages of 50 to <100 MME/day, and between 2.0 (*61*) and 8.9 (*60*) for dosages of ≥100 MME/day. In a subset of these studies, absolute risk difference approximation could be calculated. Compared with dosages of 1 to <20 MME/day, for dosages of 50 to <100 MME/day there was an absolute risk difference approximation of 0.15% for fatal overdose (*55*) and 1.40% for any overdose (*60*). For dosages of ≥100 MME/day relative to dosages of 1 to <20 MME/day there was an absolute risk difference approximation of 0.25% for fatal overdose and 4.04% for any overdose (*60*). Another study reported odds for the same broad categories as above, but stratified by total opioid dosage received over 6 months as well as daily opioid dosage. This study found that among patients receiving 50-99 MME/day, overdose risk was significantly elevated for patients receiving more than 1,830 MME total over 6 months (*59*). Another study reported on dose-dependent overdose mortality with greater specificity at higher MME ranges (e.g., starting at >0 to 39.9 MME/day, rising in 20 MME/day increments through 200 MME/day, at which increments changed to a difference of 50 MME/day; e.g., 200 to 249.9 MME/day, 250 to 299.9 MME/day . . . up to 500 to 5,000 MME/day). This study found that prescription opioid overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase, but grew more gradually. Such leveling off might be due to increased opioid tolerance, or greater diversion by patients at high MME/day levels (*62*). Two additional studies reported odds of overdose at a single dose threshold: 12.2 for dosages >40 MME/day (*58*) and 11.2 for dosages >100 MME/day (*56*). Based on such findings, many guidelines published during or after 2012 have recommended caution or more specific safeguards at daily dosages of 100 (*63*) 90 (*63*), or 80 (*64*) MME/day. A range of 50-100 MME/day has also been proposed as a threshold for caution (*52,65*). While overdose risk increased with dosage in all of the studies reviewed, there was not a dosage level below which overdose risk was eliminated. For example, although overdose risk was up to 9 times higher at 100 MME/day than at 1 to < 20 MME/day, risk was also substantially elevated (2 to 5 times higher) at 50 to <100 MME/day compared with 1 to < 20 MME/day and up to two times higher at 20 to < 50 MME/day compared with 1 to <20 MME/day. In these studies, while risk progressively increased as dosage increased at the individual level, prescribed opioid dosages at or above 100 MME/day were relatively rare, and a minority of patients prescribed opioids and experiencing overdose (34% (*55*), 38% (*57*), and 40% (*55,61*) in the studies reporting this information) were prescribed opioids at this level. In comparison, 58% (*55*), 59% (*61*), and 62% (*57*) of patients experiencing fatal overdose were prescribed ≥ 50 MME/day of opioids. However, the broad ranges of dosages used for these analyses do not allow for determination of whether there is a specific dosage threshold above which most overdoses of prescribed opioids occur and below which most patients prescribed opioids do not experience overdose. A recent study analyzed opioid dosage as a continuous rather than a categorical value in relation to unintentional opioid overdose death among Veterans Health Administration patients with chronic pain and therefore allowed assessment of risk at more specific levels of opioid dosage (*66*). This analysis found that while only 24% of patients not experiencing fatal overdose ("controls") were prescribed opioids at dosages of > 50 MME/day, 59% of patients experiencing fatal overdose were prescribed opioids at this level. Corresponding percentages for patients prescribed > 90 MME/day were 12% among controls not experiencing fatal overdose and 33% among patients experiencing fatal overdose. On average, case-patients were prescribed higher opioid dosages (mean 98 MME/day; median 60 MME/day) than controls (mean 48 MME/day, median 25 MME/day).

Benefits and Harms Associated with Co-prescription of Opioids with Benzodiazepines

Given that benzodiazepines and opioids both depress the central nervous system and can decrease respiratory drive, concurrent use might put patients at greater risk for fatal overdose. Three studies of fatal overdose deaths found evidence of concurrent benzodiazepine use in 31%-61% of decedents (*61,62,67*). In one of these studies (*61*), among decedents who received an opioid prescription, those whose deaths were related to opioids were more likely to have obtained opioids from multiple physicians and pharmacies than decedents whose deaths were not related to opioids. The few studies of co-prescribing benzodiazepines with opioids used for chronic pain generally offer indirect evidence of their combined risks. One study (not included in the evidence review for clinical questions because patients were not restricted to those with chronic pain) found concurrent use of benzodiazepines among veterans using opioids raised the risk of drug overdose deaths four-fold (HR=3.86, 95% confidence interval [CI] = 3.49-4.26) compared with patients not using benzodiazepines, with increased benzodiazepine dose associated with increased risk for overdose death (*68*). This finding together with findings

from epidemiologic series suggests that co-prescribing these medications might substantially increase risk of overdose death. Abrupt withdrawal from benzodiazepines can be associated with hallucinations, seizures, and in rare cases, death (*69,70*). While opioid withdrawal can be very unpleasant and distressing, it is not known to be fatal except under unusual circumstances (e.g., use of anesthesia-assisted rapid opioid detoxification) (*71*).

Benefits and Harms Associated with Duration of Opioid Use

Physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (*72,73*) and is associated with withdrawal symptoms on stopping opioids (*74,75*). Patients can experience tolerance and loss of effectiveness of opioids over time (*75*). A secondary analysis of randomized clinical trial data found pain relief (defined as a reduction in pain score of ≥ 30%) with morphine or fentanyl at 6 months could be predicted by pain relief at 1 month, and that absence of pain relief at 1 month had a stronger predictive value than presence of pain relief at 1 month (*76*); in other words, patients who did not have pain relief at 1 month were unlikely to experience pain relief at 6 months.

Benefits and Harms in Populations Potentially at Greater Risk for Harm

Patients with Sleep Apnea or Other Causes of Sleep-disordered Breathing

Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed. Although there is no clear consensus regarding the development of obstructive sleep apnea syndrome or development of hypoxemia caused by long-term opioid therapy, research suggests that a significant proportion patients on such therapy develop central sleep apnea and irregular breathing patterns (e.g., respiratory pauses, gasping) (*77*). Opioid therapy can decrease respiratory drive, worsen central sleep apnea in obstructive sleep apnea, and cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (*78*). In addition, a case-control analysis of risk of life-threatening respiratory central nervous system depression or overdose among veterans prescribed opioids (not included in the evidence review for clinical questions because the sample was not restricted to patients prescribed opioids for chronic pain) found that sleep apnea and chronic pulmonary disease as well as renal disease, moderate or severe liver disease, and age > 55 years were associated with increased risk for life-threatening respiratory central nervous system depression or overdose (*57*). Another retrospective case-control study found risks for respiratory depression or decreased oxygen saturation in a postoperative setting; risks were elevated for older patients and those with chronic obstructive pulmonary disease or multiple comorbidities. Although more case-patients than controls experienced sleep apnea, the condition was not a significant predictor of respiratory events in multivariate models (*79*). Finally, in a study of 140 chronic pain patients on around-the-clock opioid therapy who had undergone polysomnography, an abnormal apnea-hypopnea index was recorded for 75% of patients (a rate higher than the general population); of those, 39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea. In particular, relations were found between the apnea-hypopnea index and methadone, and increased methadone dose was associated with more severe sleep apnea; benzodiazepines had an additive effect (*80*).

Patients with Renal or Hepatic Insufficiency

Reduced renal and/or hepatic function results in decreased ability to process and excrete drugs, which can result in greater peak effect and longer duration of action (*72*). These factors make patients more susceptible to accumulation of opioids and can reduce dosages needed to achieve therapeutic effects as well as the dosages associated with respiratory depression and overdose.

Older Adults

Age-related changes in patients aged ≥ 65 years include reduced renal function and medication clearance, even in the absence of renal disease (*81*), and other factors that result in a reduced therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. A randomized controlled trial

compared analgesic and respiratory effects of remifentanil compared with placebo following an induced painful stimulus to evaluate remifentanil's potential for procedural analgesia. This study found that compared with subjects aged 20-48 years, those aged 60-75 years experienced both analgesia and respiratory depression at lower remifentanil doses than the younger subjects (*82*).

Some older adults also experience cognitive decline, and many receive multiple medications for comorbid medical conditions. For example, in the United States, an estimated 8.7% of persons aged 65-80 years filled benzodiazepine prescriptions in 2008 compared with 2.6% of persons aged 18-35 years (*83*). All of these factors can make opioid use and prescription drug abuse particularly dangerous in this age group (*84*). Older adults can suffer from cognitive impairment, which can interfere with their ability to accurately report pain or adverse events, and can affect medication compliance (*85*). The epidemiology of drug abuse in older adults has not been well studied, but the motivations for taking medications and patterns of misuse are thought to be qualitatively different from other populations (e.g., accumulating a large amount of medications through prescriptions by multiple clinicians and saving them for later use, rather than obtaining opioids illicitly to "get high") (*86,87*). As cited in the clinical evidence review, in one study of patients with a history of long-term opioid prescriptions, life-time opioid dependence was associated with age < 65 years, suggesting a lower risk of dependence among older patients compared to younger patients (*88*). Case-control (*89,90*) and panel (*91*) studies have found associations between opioid use and fall and fracture risk in older adults.

Concerns about pharmacologic pain management in older adults are not limited to opioids; in addition to opioids, antidepressants and anticonvulsants have been associated with falls in older adults (*91*). NSAIDs are associated with risks for gastrointestinal, renal, and cardiac toxicity that are greater in older adults (*18*). An analysis of Medicare recipients (mean age 80 years) prescribed NSAIDs, COX-2 inhibitors, or opioids found that opioid use was associated with greater risk for cardiovascular events, fracture, safety events requiring hospitalization, and all-cause mortality than NSAIDs; risk for gastrointestinal tract bleeding was similar for users of NSAIDs and opioids (*92*). Because of concerns about both NSAIDs and opioids in older adults, acetaminophen has been recommended as first-line pharmacologic treatment for persistent pain (particularly musculoskeletal pain) in older adults (*18*). Previous guidelines have suggested that initial opioid dosage for older patients should not exceed more than 50%-75% of the initial suggested dosage for adults (*93,94*).

Pregnant Women

Opioids used in pregnancy might be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use during pregnancy with birth defects (neural tube defects (*95,96*), congenital heart defects (*96*), and gastroschisis (*96*)), pre-term delivery (*97*), poor fetal growth (*97*), and stillbirth (*97*). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome (*98*). In addition, opioid withdrawal in pregnancy has been associated with spontaneous abortion and premature labor (*99,100*).

Pain management during pregnancy is further complicated by risks posed by systemic NSAIDs for oligohydramnios and premature closure of the ductus arteriosus, particularly when used for prolonged periods or during the third trimester (*101,102*). For these reasons, acetaminophen is considered to be safer during pregnancy (*94*). Previous guidelines have recommended that if opioids are used during pregnancy, clinicians should plan for management of additional risks to the patient and newborn, including arrangement of in-hospital delivery at a facility prepared to assess for and manage neonatal opioid withdrawal syndrome (*93*).

Because neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (*103*), previous guidelines have recommended that codeine should be avoided whenever possible in mothers who are breast feeding, and if used, should be limited to the lowest possible dose and to a 4-day supply (*93*).

Patients with Depression and Other Mental Health Conditions

Despite cautions expressed in previous guidelines regarding opioid treatment for patients with psychiatric co-morbidities (*23*), persons with depression and other mental health conditions use opioids at a higher rate than patients without depression (*104,105*). This finding has been described as "adverse selection" given patients with mental health co-morbidities might be at higher risk than other patients for misuse and abuse of opioids and for opioid use disorder (*106*). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, and that among depressed patients, longer-term antidepressant use (91-180 days) was associated with decreased risk for drug overdose; however, investigators were unable to distinguish unintentional overdose from suicide attempts (*107*). There are many possible reasons for association of opioid use with mental health disorders, including association of depression with chronic pain (*106*) and frequently increased physical symptoms including pain among patients with depression (*104*). Patients with co-occurring pain and depression are likely to benefit from maximizing treatment for depression.

Patients with Alcohol and Substance Use Disorders

Illicit drugs and alcohol are listed as contributory factors on a substantial proportion of death certificates for opioid-related overdose deaths (*108,109*). Patients with histories of substance use disorders are more likely than other patients to receive long-term opioid treatment for chronic pain (*110*) even though they are at increased risk for opioid abuse when prescribed opioid analgesics (*111,112*). Patients with a diagnosis of substance use disorder who are prescribed opioids are also at greater risk for overdose than patients without this diagnosis who are prescribed opioids. In case-control and case cohort studies, frequency of substance abuse/dependence is higher among patients who experience overdose than among patients who do not experience overdose (12% versus 6% (*60*), 40% versus 10% (*55*), 26% versus 9% (*57*)).

Benefits and Harms Associated with Risk Stratification Approaches

Limited evidence regarding benefits and harms of risk stratification approaches to inform opioid prescribing was found in both the clinical and contextual evidence reviews. Use of tools such as behavioral assessments, PDMPs, and urine drug testing to assess and stratify patients by risk status have the potential value of determining which patients will benefit from greater caution and increased monitoring, provided that these tools have sufficient sensitivity and specificity to accurately predict increased risk. For example, one study found a majority of fatal overdoses could be retrospectively identified based on two pieces of information (multiple prescribers and high total daily opioid dosage, both important risk factors for overdose (*56,113*)) that are available to prescribers in the PDMP (*56*). Ability to detect current risk based on PDMP data might vary by state given wide variation in timeliness of reporting of dispensed prescriptions to the PDMP (*114*). Evaluations of PDMPs at the state level have typically examined effects on prescribing rates and problematic use, less commonly examined effects on health outcomes, and have overall generated mixed findings (*115*). Early evaluations of PDMPs found reductions in prescribing rates; later evaluations found lower prescribing rates of Schedule II drugs being offset with higher Schedule III drug prescribing, or no changes in prescribing at all. Studies have also differed in findings related to state mortality rates, with some showing no changes in mortality and others showing a slower rate of increase in mortality associated with specific drug types. Conclusions about PDMP effectiveness are limited by cross-sectional, observational study designs, lack of detailed data on prescribing patterns prior to PDMP implementation, and confounding variables left unaddressed in analyses (*115*).

Potential harms of risk stratification include underestimation of risks of opioid therapy when screening tools are not adequately sensitive as well as potential overestimation of risk, which could lead to inappropriate clinical decisions. For example, there are many reasons a patient prescribed opioids might not test positive for prescribed opioids on urine drug testing. In addition to diversion, these might include patients not taking opioids because of lack of efficacy or actual or feared adverse drug effects, as well as tests that are falsely negative because of analytical limitations (*116*). Urine drug tests can also be falsely positive because of issues such as the presence of metabolites from prescribed opioids that appear to represent non-prescribed opioids (*117*). Clinicians frequently

misinterpret findings from urine drug tests. Only 20%-30% of physicians who commonly order urine drug tests to monitor chronic opioid therapy correctly answered more than half of seven questions about urine drug test findings (*118,119*). In some cases, clinicians have discharged patients from their practice on the basis of PDMP (*120*) or urine drug test (*117*) results. Such actions might damage patients' trust in the health care system, might increase patient motivation to seek opioids from other licit or illicit sources, and might result in missed opportunities for potentially life-saving interventions (e.g., advice about overdose prevention, referral to substance use disorder treatment). In addition, patients might feel stigmatized by urine drug testing (*117*). Guidelines differ on whether urine drug tests should be used routinely when opioids are prescribed or should be used selectively depending on the clinician's judgment about the patient's level of risk (*93,94*). Some note that routine or random use of urine drug tests might de-stigmatize their use (*93*).

Benefits and Harms Associated with Risk Mitigation Approaches

Limited evidence was found regarding benefits and harms of risk mitigation approaches to reduce risks of opioid prescribing. Co-prescribing naloxone, an antidote to opioid overdose, with prescription opioids has been suggested as a way to both increase the availability of medication to reverse opioid overdose and to convey the serious risks of opioid therapy to patients (*121*). Relevant studies on effectiveness of co-prescribing naloxone with opioids were not identified. However, naloxone distribution through community-based programs providing prevention services for substance users has been demonstrated at the community level to be associated with decreased risk of opioid overdose death (*122*).

Concerns have been raised that prescribing changes such as dose reduction can be associated with unintended negative consequences such as patients seeking heroin or other illicitly obtained opioids (*121*). With the exception of a study noting an association between abuse-deterrent OxyContin formulation and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (*123*), CDC did not identify studies evaluating this potential outcome. Given that abrupt discontinuation of opioids can be associated with increased pain and unpleasant withdrawal effects compared with continuation of opioids (*124*), patients might be more likely to seek opioids from other sources when prescribed opioids are abruptly discontinued or rapidly tapered. Tapers reducing dosage by 10%-50% of the original dosage weekly have been recommended (*125*). Concerns have also been raised that policies that influence prescribing can result in a restricted supply and interfere with optimal pain care for persons with pain; however research examining the impacts on unintended consequences such as barriers to appropriate pain treatment is lacking (*126*).

Concerns about unintended consequences of opioid risk mitigation strategies highlight challenges related to the multiple prevention approaches needed to reduce opioid-related harms. Patients who have not yet initiated long-term opioids are unlikely to experience harms from opioid withdrawal, etc. related to more judicious opioid prescribing and are likely to have the greatest ratio of benefits to risks associated with judicious prescribing practices. Many patients already on long-term opioids will have more complex needs for risk reduction and are likely to require conscientious follow-up and skilled communication to balance appropriate opioid prescribing with overdose prevention, treatment of opioid use disorder, and careful management of opioid withdrawal when needed.

Effectiveness of Treatments for Opioid Use Disorder

Methadone and buprenorphine for opioid dependence have been found to increase retention in treatment and to decrease illicit opioid use among patients with opioid use disorder primarily involving heroin (*127-129*). Although findings are mixed, some studies suggest that effectiveness is enhanced when psychosocial treatments (e.g., contingency management, community reinforcement, psychotherapeutic counseling, family therapy) are used in conjunction with medication-assisted therapy; for example, by reducing opioid misuse and increasing retention during maintenance therapy, and improving compliance after detoxification (*130,131*). The quality of evidence rated by systematic review authors can be characterized as moderate (see Table 3).

Findings on Clinician and Patient Values and Preferences

Clinician and patient values and preferences provide important context for developing recommendations. They can inform the weight given to benefits and harms of chronic opioid therapy, particularly in the context of the limited clinical evidence on effectiveness of opioid therapy for chronic pain and the availability of effective nonpharmacologic and nonopioid pharmacologic therapies. Understanding clinician values and preferences also allows for an estimation of the effort and resources required to effectively communicate the recommendations and provide implementation support so that adoption is facilitated. These factors can influence the strength of the recommendations. Thus, CDC reviewed evidence that can provide information about values and preferences associated with opioid prescribing from a clinician perspective, opioid use from a patient perspective, and clinician-patient communication (see Table 4).

Many physicians lack confidence in their ability to prescribe opioids safely (*132,133*), to predict (*134*) or detect (*134, 135*) prescription drug abuse, and to discuss abuse with their patients (*135*). Attitudes among primary care clinicians might be changing; in a nationally representative 2014 survey of U.S. internists, family physicians, and general practitioners, 45% stated they were less likely to prescribe opioids than a year ago (*136*). Most (88%) expressed confidence in clinical skills related to opioid prescribing. Although clinicians have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids, most (90%) stated prescription drug abuse was a “moderate” or “big” problem in their community, and large proportions were “very” concerned about opioid addiction (55%) and death (48%) (*137*).

In a survey of providers at five clinics associated with a Veterans Affairs medical center, providers noted feeling pressured to treat with opioids, difficulties interpreting patients' reports of pain, worries about secondary gain/diversion, and "abusive" or "difficult" patients. Providers also felt frustrated, ungratified, and guilty when providing chronic pain care and described the associated emotional toll, and emphasized that positive provider-patient relationships are essential for good pain care (*138*).

Clinicians do not consistently use practices intended to decrease the risk of abuse, such as PDMPs (*139,140*), urine drug screening (*141*), and opioid treatment agreements (*142*). Burden of clinician access to PDMP data varies by state given variation in policies regarding who has access to PDMP data and whether or not clinicians can delegate access to other members of the health care team (*114*). Emergency physicians described the processes of registering for PDMP access and logging into the PDMP to access information as cumbersome and time-consuming and noted that these factors limit their PDMP use given multiple competing time pressures and negative impacts on patient flow (*143*). Presumably these barriers apply to primary care clinicians as well. Emergency physicians who were able to access the PDMP reported positive experiences using it, making statements such as “it’s amazingly helpful” (*143*). Providers in other surveys have reported that PDMPs provide information that is useful for their clinical practice (*144*). In a survey of participants attending a pain conference, urine drug testing was more often used to detect unreported substances than to confirm opioid use (*141*). Clinicians might avoid urine drug testing because of competing clinical demands, perceived inadequate time to discuss the rationale for testing and to order confirmatory testing if needed, feeling unprepared to address results, including ambivalence about how to address results such as positive tests for marijuana, believing patients are not at risk for misuse, or concerns about potential harm to the clinician-provider relationship (*117*). Few primary care clinicians believed opioid treatment agreements prevented opioid misuse (*142*).

Many patients do not have an opinion about “opioids,” or know what this term means (*145*). Most are familiar with “narcotics.” About a third associated “narcotics” with addiction or abuse, and about half feared “addiction” from long-term “narcotic” use (*145*). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for non-cancer pain (*146*), 96% of patients taking opioids for chronic pain (*147*)), and side effects, rather than pain relief, have been found to explain most of the variation in patients’ preferences related to taking opioids (*147*). Many respond to side effects by taking less than the prescribed dose (*146*). For example, patients taking hydrocodone for non-cancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (*146*).

In focus groups, patients with chronic pain expressed ambivalence about opioids, emphasized effectiveness of setting goals for increasing motivation and functioning, and expressed a desire to connect with others experiencing pain to share strategies for managing daily life (*148*). Veterans taking at least 50 MME/day expressed reliance on opioids and difficulties obtaining opioids despite ambivalence about their benefits (*149*), and more than 80% of patients prescribed ≥ 50 MME/day in two large health care plans continued on these moderately high dosages at 1 year regardless of pain reduction, problems, concerns, side effects, or perceived helpfulness (*150*).

Findings on Resource Allocation

Resource allocation (cost) is an important consideration in understanding the feasibility of clinical recommendations. This includes cost of recommended practices, costs of alternatives, and costs averted if effective practices are implemented. Practices that have high costs relative to their anticipated benefits are less likely to be recommended. Practices that ultimately reduce health care costs are more likely to receive a strong recommendation. To consider resource allocation, CDC searched for evidence on costs of opioid therapy compared with nonpharmacologic and nonopioid pharmacologic treatments; costs of misuse, abuse, and overdose from prescription opioids; and costs of specific risk mitigation strategies, e.g., urine drug testing (see Table 5).

Perceptions that opioid therapy for chronic pain was less expensive than more time-intensive nonpharmacologic management approaches led managed care organizations to stop reimbursement for services such as comprehensive pain management clinics, leaving clinicians and patients with fewer effective options for management of chronic pain (*42,121,151*). However, a 2012 study evaluating direct medical costs of pharmacologic and non-pharmacologic treatment for osteoarthritis and chronic low back pain (*152*) estimated that many pain treatments, including acetaminophen, NSAIDs, TCAs, and massage therapy, were associated with lower mean and median annual costs compared with opioid therapy. COX-2 inhibitors, SNRIs, anticonvulsants, topical analgesics, physical therapy, and CBT were also associated with lower median annual costs compared with opioid therapy. These estimates are for direct treatment costs only; cost-benefit estimates for opioid therapy are challenging given lack of evidence to inform estimates of benefits (*124*).

In addition to the direct costs associated with opioid treatment, other related costs include costs of opioid-related side effects, costs of misuse and abuse of prescription opioid medications, and costs associated with lost productivity. Yearly direct and indirect costs related to prescription opioids have been estimated (based on studies published since 2010) to be $53.4 billion for non-medical use of prescription opioids (*153*); $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids (*154*); and $20.4 billion for direct and indirect costs related to opioid-related overdose alone (*155*). In 2012, total expenses for outpatient prescription opioids were estimated to be $9.0 billion, an increase of 120 percent from 2002 (*156*).

Limited information was found on costs of strategies to decrease risks associated with opioid therapy. A 2011 study estimated urine drug testing, including screening and confirmatory tests, to cost between $211 and $363 per test (*157*). Unfortunately, it is challenging to determine whether the benefits of urine drug testing outweigh the costs, given the limited rigorous evidence of the effectiveness of urine drug testing as a risk mitigation strategy (*124*).

Previous Guidelines on Opioid Prescribing for Acute Pain, Chronic Pain, and Medication-Assisted Treatment

CDC selected guidelines and recommendations for review that could supplement or complement the new CDC guideline; that is, recommendations that are related to opioid prescribing but address areas beyond the current scope, or guidelines that provide detailed implementation instruction. In particular, guidelines related to opioid treatment for acute pain, non-opioid treatment for chronic pain, use of urine drug testing and opioid tapering when treating chronic pain, and medication-assisted treatment were identified. See Table 6 for a summary of the guidelines and recommendations reviewed and referenced in the new CDC guideline document.

Guidelines related to non-opioid treatment for pain are summarized in the above section "Findings on the Effectiveness of Nonpharmacologic and Nonopioid Pharmacologic Treatments." The Washington State Agency Medical Directors' Group (2015) Interagency Guideline on Prescribing Opioids for Pain (*94*) contains detailed guidance on urine drug testing, opioid tapering, and opioid prescribing for acute pain. A systematic review published in the Mayo Clinic Proceedings (*158*) provides additional recommendations on opioid tapering. In summary, these guidelines and recommendations were found to recommend a range of tapering schedules (*125*). A variety of guidelines and reviews on opioid prescribing for chronic pain were found to address dosage thresholds at which increased caution is recommended (*52,64,65,125*); these dosage thresholds have generally decreased in the last few years (*63*). Guidelines by the American College of Occupational and Environmental Medicine are oriented toward treatment of acute, subacute, chronic, and postoperative pain among a target population of working-age adults (*159*). Several guidelines on opioid prescribing for acute pain address the specific number of days of opioid supply that clinicians should prescribe; these guidelines recommend prescribing $\leq$ 3 days of opioids in most cases (*160-164*). Finally, the American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use (*165*), Part 5, was found to contain detailed guidance on management of buprenorphine treatment for opioid use disorder. Where relevant, these sources are referenced in the background of the new CDC guideline document, as well as the supporting text of the recommendation statements.

Table 1. Effectiveness and harms of nonpharmacologic and nonopioid pharmacologic treatments

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings	Study Quality
Busch et al., 2007	Exercise training versus untreated control or non-exercise intervention	Systematic review of 33 randomized clinical trials in fibromyalgia patients	Global well-being, selected signs and symptoms, and physical function	Exercise training improves global well-being and physical function. Supervised aerobic exercise training has beneficial effects on physical capacity and fibromyalgia symptoms.	Four studies were classified as high quality, 15 as moderate quality, and 14 as low quality
Chaparro et al., 2014	Non-injectable opioids versus placebo or other treatments	Systematic review of 15 randomized controlled trials of patients with chronic low back pain	Pain	One trial found tramadol similar to celecoxib for pain relief. Two trials did not find a difference between opioids and antidepressants for pain or function.	Low to moderate quality evidence
Collins et al., 2000	Antidepressants versus placebo; anticonvulsants versus placebo	Systematic review of 19 randomized controlled trials for diabetic neuropathy or postherpetic neuralgia	Pain	For diabetic neuropathy, the NNT for ≥50% pain relief was 3.4 for antidepressants (12 trials, 10 evaluated TCAs and 3 selective serotonin reuptake inhibitors) and 2.7 for anticonvulsants (3 trials). For postherpetic neuralgia, the NNT was 2.1 for antidepressants (3 studies evaluating TCAs) and 3.2 for anticonvulsants (1 study evaluating gabapentin).	The mean and median quality score for included studies was 4 on a scale of 1 to 5
Fransen et al., 2015	Exercise versus a non-exercise group (active or no treatment)	Systematic review of 54 randomized or quasi-randomized controlled trials for knee osteoarthritis	Reduced joint pain or improved physical function and quality of life	Exercise reduced pain, improved function, and improved quality of life immediately after treatment; in studies providing post-treatment follow-up data, improved pain and function were sustained for 2 – 6 months.	High quality evidence for reduced pain and improved quality of life and moderate quality evidence for improved function
Fransen et al., 2014	Exercise versus a non-exercise group (active or no treatment)	Systematic review of 10 randomized controlled trials or quasi-randomized trials for hip osteoarthritis	Reduced joint pain and improved physical function and quality of life	Exercise reduced pain and improved function immediately after treatment; in studies providing post-treatment follow-up data, improved pain and function were sustained for at least 3 – 6 months.	High quality evidence for reduced pain and improved function
Hauser et al., 2013	Duloxetine versus placebo; milnacipran versus placebo	Systematic review of 10 randomized controlled trials for fibromyalgia patients	Benefits and harms	Duloxetine and milnacipran reduced pain by a small amount compared with placebo	Risk of bias in included studies was low
Hayden et al., 2005	Exercise therapy versus no treatment, other conservative treatments	Systematic review consisting of 61 randomized controlled trials for low back pain	Pain, function	Exercise therapy reduces pain and improves function with small magnitudes of effect. Effectiveness of exercise therapy appears to be greater in populations visiting a health care provider compared with the general population.	Only a small number of studies rated as high quality; potential publication bias
Lee et al., 2014	Complementary and integrative multimodal (CIM) therapies versus single self-care CIM, nonself-care CIM, usual care/no treatment, other multimodal program, or other control	Systematic review of 26 randomized controlled trials for management of chronic pain	Pain symptoms	Integrative multimodal therapies resulted in positive, but sometimes mixed, effects on pain symptoms compared with active controls or single self-care modalities. More studies are needed to make strong conclusions about effectiveness.	Large majority of poor quality, including weaknesses in randomization and allocation concealment
Lunn et al., 2014	Duloxetine versus placebo or other controls	Systematic review of 18 randomized controlled trials for neuropathic pain, chronic pain conditions without identified cause, or fibromyalgia	Benefits and harms of duloxetine	Duloxetine at 60 mg and 120 mg daily, but not lower dosages, were effective in reducing pain in diabetic peripheral neuropathy pain and in fibromyalgia.	Moderate quality evidence for diabetic neuropathy; lower quality evidence for fibromyalgia; some risk of bias

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings	Study Quality
Moore et al., 2009	Pregabalin versus placebo or any active control	Systematic review of 25 double-blind, randomized controlled trials for postherpetic neuralgia, painful diabetic neuropathy, central neuropathic pain, or fibromyalgia	Analgesic efficacy and associated adverse events	Pregabalin was effective in patients with postherpetic neuralgia, diabetic neuropathy, central neuropathic pain, and fibromyalgia at doses of 300 mg, 450 mg, and 600 mg (but not at 150 mg) daily. NNTs were generally ≤6 for moderate benefit in postherpetic neuralgia and diabetic neuropathy but ≥7 for fibromyalgia.	Studies all had Oxford quality scores based on randomization, blinding, and reporting of dropout ≥3 (out of maximum of 5)
Moore et al., 2014	Gabapentin versus placebo	Systematic review of 37 randomized controlled trials for neuropathic pain or fibromyalgia	Analgesic efficacy and adverse effects	Gabapentin was significantly more effective than placebo in reducing pain in diabetic neuropathy and postherpetic neuralgia. Evidence was insufficient for other conditions.	"Second tier" evidence (some risk of bias, but adequate numbers in the trials)
Roelofs et al., 2008	Non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase 2 (COX-2) inhibitors versus control	Systematic review of 65 randomized controlled trials for nonspecific low back pain	Acute low back pain	NSAIDs are more effective than placebo for acute and chronic low back pain without sciatica, but have more side effects. NSAIDs are not more effective than acetominophen but had more side effects. No type of NSAIDs, including COX-2 inhibitors, was found to be more effective than other NSAIDs.	Mixed high- and low-quality studies
Saarto et al., 2010	Antidepressants versus placebo or other controls	Systematic review of 61 randomized controlled trials for neuropathic pain.	Pain	TCAs and venlafaxine have low NNTs (3.6 and 3.1 respectively) for at least moderate pain relief.	Study quality limited by insufficient reporting detail
Salerno et al., 2002	Antidepressants versus placebo	Systematic review of 9 randomized controlled trials for chronic back pain	Back pain	Antidepressants were associated with small but significant improvement in pain severity; improvements in function were not significant. Most (6) studies evaluated TCAs.	Moderate quality studies
Staiger et al., 2003	Antidepressants versus placebo	Systematic review of 7 randomized controlled trials in patients with chronic low back pain.	Back pain	Four of five studies evaluating TCA and tetracyclic antidepressants found significant improvement in chronic low back pain. Other antidepressants studied (2 studies evaluating selective serotonin reuptake inhibitors and 1 evaluating trazodone) did not show significant pain improvement.	Mixed quality (quality scores ranged from 11 to 19 out of 22)
Trelle et al., 2011	NSAIDs versus other NSAIDs or placebo	Meta-analysis of 31 randomized controlled trials comparing any NSAID with other NSAID or placebo for any medical condition	Myocardial infarction, stroke, cardiovascular death, death from any cause	Compared with placebo, NSAIDs were associated with increased risk of myocardial infarction, stroke, and cardiovascular death.	Generally high
Welsch et al., 2015	Opioids (including tramadol) versus non-opioids (including acetaminophen, NSAIDs/COX-2 inhibitors, mexilitene, anticonvulsants, antidepressants, and muscle relaxants)	Systematic review of 10 randomized controlled trials in patients with neuropathic pain, low back pain, or osteoarthritis	Efficacy (including various pain measures), tolerability, and safety	There was no significant difference between opioids and non-opioid analgesics in pain reduction; non-opioids were superior to opioids in improving physical function and was better tolerated. When patients from tramadol trials (n randomized=2,788) were removed from results of the review, results for pain and function for patients receiving opioids (morphine) compared with alternative drugs (n randomized=223) had wide, overlapping confidence intervals. Improved tolerability for alternative drugs versus morphine remained significant.	One study had a high, two studies a moderate, and seven studies a low study quality

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings	Study Quality
Wiffen et al., 2014	Carbamazepine versus placebo or other active control	Systematic review consisting of 10 randomized controlled trials in adults with chronic neuropathic pain or fibromyalgia	Pain relief	Carbamazepine provided better pain relief than placebo for trigeminal neuralgia, diabetic neuropathy, and post stroke pain for ≤4 weeks. Dizziness and drowsiness were commonly reported with carbamazepine. In 4 studies, 65% of patients receiving carbamazepine versus 27% receiving placebo experienced at ≥1 adverse event. In 8 studies, 3% of patients receiving carbamazepine withdrew because of adverse events (versus 0% on placebo).	Third tier evidence (trials involving small numbers of participants; considered likely to be biased, with outcomes of limited clinical utility, or both)
Williams et al., 2012	Cognitive behavioral therapy or behavioral therapy	Systematic review of 42 randomized controlled trials for patients with non-malignant chronic pain except headache	Pain disability, mood, and catastrophic thinking	Cognitive behavioral therapy was found to have small to moderate effects on pain, disability, mood, and catastrophic thinking immediately after treatment when compared with usual treatment or deferred cognitive behavioral therapy, but only effects on mood persisted at follow-up. Behavioral therapy had a positive effect on mood immediately post-treatment.	Mean quality of study design 15.8 out of 26 (standard deviation 4.3, range 9 to 24 out of 26)

Abbreviations: NNT = number needed to treat, TCA = tricyclic antidepressants, NSAID = non-steroidal anti-inflammatory drug; COX-2 = cyclooxygenase 2 inhibitors

Table 2. Benefits and harms associated with acute or chronic opioid therapy

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Berlin et al., 2013	Case series investigation of serious adverse events following AAROD	Patients undergoing AAROD treatment at an outpatient clinic in New York City, 2011 – 2012	Hospitalization for any cause or death, <72 hours after undergoing AAROD	Of 75 patients undergoing AAROD, two died and five experienced serious adverse events requiring hospitalization (serious adverse event rate 9.3%).
Bohnert et al., 2016	Matched case-control study examining association between opioid dosage and fatal overdose	Veterans Health Administration patients with chronic pain receiving opioid therapy, 2004-2009	Unintentional fatal opioid overdose	24% of controls had dosages above 50 MME, but 59% of cases had dosages above this level.
Bohnert et al., 2011	Case-cohort study examining the association between prescribed opioid dosage in MME/day and risk of opioid overdose death	Veterans Health Administration patients receiving opioid therapy for pain in 2004-2005	Fatal opioid overdose	Among patients with chronic pain, receiving 20-<50 MME/day, 50-<100 MME/ day, and ≥100 MME/day was associated with adjusted hazard ratios for overdose death of 1.88, 4.63, and 7.18 compared with 1 to <20 MME/day.
Boudreau et al., 2009	Prevalence estimate of long-term opioid use for non-cancer pain	Adults enrolled in two U.S. health plans, 1997-2005	Long-term prescription opioid use (prescribed opioids for >90 days with >120 days' supply or >10 opioid prescriptions in a given year)	From 1997-2005, prevalent long-term use doubled in the two plans: from 23.9 to 46.8 per 1,000 and from 21.5 to 39.2 per 1,000 enrollees.
Braden et al., 2009	Association of depression and long-term opioid use	Patients in two large U.S. health maintenance organizations, 1997-2006	Initiation of long-term opioid use (>90 days), prevalence of long-term opioid use	Incident and prevalent long-term opioid use rates were three times higher in those with a history of depression.
Broussard et al., 2011	Large multisite population-based case-control study to assess association between maternal opioid use and birth defects	Infants with and without birth defects	Any congenital heart defect; 15 specific types of congenital heart defects; spina bifida; combinations of cleft palate and cleft lip; anencephaly or craniorachischisis	Maternal use of opioids from 1 month prior to conception through the first trimester was associated with conoventricular and atrioventricular septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis.
CDC WONDER, 2016	Opioid analgesic poisoning death rates, 1999-2014	U.S. population	Poisoning death	From 1999-2014, there were more than 165,000 deaths involving opioid pain medication in the United States.
Cicero et al., 2012	Effect of the abuse-deterrent formulation of OxyContin on rate of abuse of OxyContin and other opioids	Patients with opioid dependence entering treatment programs with a prescription opioid as the primary drug of abuse	Self-reported primary drug of abuse	21 months after release of the abuse-deterrent formulation, respondents preferring OxyContin decreased from 35.6% to 12.8%. Preference for other opioids increased. Heroin use nearly doubled.
Dasgupta et al., 2015	Prospective observational cohort study investigating fatal overdose among patients receiving opioid pain medication	Residents of North Carolina receiving a prescription for opioid pain medication	Overdose death involving opioid pain medication	Overdose risk increased steadily in a dose-dependent manner; rate of increase decreased after 200 MME/day. Evidence of concurrent benzodiazepine prescription in the past year was 80% and benzodiazepines were determined to be involved in 61% of deaths involving opioid pain medications.

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Dunn et al., 2010	Cohort study examining rates of opioid overdose and association with opioid dosage among patients receiving chronic opioid therapy	Health maintenance organization patients who received 3 or more opioid prescriptions within 90 days for chronic non-cancer pain	Opioid-related overdose (fatal or non-fatal)	Compared with receiving 1 to <20 MME/day, receiving 20 to <50 MME/day, 50 to <100 MME day, and ≥100 MME/day was associated with adjusted hazard ratios for overdose of 1.4, 3.7, and 8.9.
Edlund et al., 2010	Prescription opioid use for chronic non-cancer pain among persons with and without mental health/substance use disorders	Two populations: a national, commercially insured population and Arkansas Medicaid enrollees, 2000 and 2005	Percentage of patients with chronic opioid use (>90 days in past year)	Chronic opioid use was more common among those with than among those without a mental health or substance use disorder.
Edlund et al., 2007	Longitudinal analysis to identify risk factors for diagnosed opioid abuse or dependence	Veterans Health Administration patients from the South Central U.S. region, receiving chronic opioids (≥91 days) and without a cancer or prior opioid use disorder diagnosis	Diagnosed opioid abuse or dependence	Non-opioid substance abuse diagnosis was the strongest predictor of opioid abuse/dependence (OR=2.34, p<0.001). Greater days' supply of opioids predicted opioid abuse/dependence.
Egan et al., 2004	Randomized crossover study assessing association of respiratory depression with varying dose levels of remifentanil	Healthy volunteers aged 18-59 years (younger group) and ≥60 years (older group)	Respiratory depression score on Respiratory Intervention Scale; time to and duration of analgesia as measured by pressure algometry	Older subjects experienced more significant respiratory depression at lower doses than did younger subjects.
Gomes et al., 2011	Case-control study examining association between opioid dose level and opioid-related mortality	Ontario residents aged 15 - 64 years who received an opioid for non-malignant pain through public prescription drug coverage, 1997-2006	Coroner's determination of opioid-related death	Compared with receiving 1 to <20 MME/day, receiving 20-49 MME/day, 50-99 MME day, and 100 - 199 MME/day was associated with odds ratios for fatal overdose of 1.3, 1.9, and 2.0.
Gwira Baumblatt et al., 2014	Matched case-control study examining association between opioid dosage or number of prescribers or pharmacies with overdose death	Patients enrolled in Tennessee Controlled Substances Monitoring Program 2007 - 2011	Fatal overdose	Opioid-related overdose death was associated with ≥100 MME/day, ≥4 prescribers, and ≥4 pharmacies (adjusted odds ratios 11.2, 6.5, and 6.0). At least one of these risk factors was present in 55% of overdose deaths.
Hadi et al., 2006	Case series examining association between prescription opioid use during pregnancy and neonatal outcomes	Women who took prescribed opioids during pregnancy, 1999-2002	Neonatal data including gestational age at birth, head circumference, length, birth weight, Apgar score, need for resuscitation, Neonatal Abstinence Score	Five out of 13 (38.5 percent) neonates were diagnosed with opioid discontinuation syndrome.
Hall et al., 2008	Identifying factors associated with unintentional prescription drug overdose deaths	All West Virginia residents who died of unintentional pharmaceutical overdoses in 2006	Fatal overdose	Of decedents using opioid analgesics (93.2%), 16.0% had illicit drugs and 13.5% had alcohol listed as contributing to death.
Hardt et al., 2008	Prevalence estimates for chronic pain in the United States	National Health and Nutrition Examination Survey	Population prevalence of chronic pain (weighted estimates)	Weighted prevalence estimated at 3.6% for widespread and 11.0% for regional chronic pain. Most common pain location was back (weighted prevalence estimate 10.1 %).
Irvine et al., 2014	Survey of clinicians about their use of PDMPs	Clinicians in Oregon	Registration in PDMP, use of PDMP, discussing PDMP data with patients	PDMP users reported discussing worrisome data with patients (nearly all users); making mental health/substance abuse referrals (54%); discharging patients from their practice (35%).

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Jones & McAninch, 2015	ED visits and overdose deaths associated with nonmedical use of opioid analgesics and benzodiazepines, 2004-2011	Patients seen at EDs participating in the Drug Abuse Warning Network; U.S. population	ED visits and drug overdose deaths involving opioids and benzodiazepines	From 2004 to 2011, the rates of nonmedical use-related ED visits and of overdose deaths involving both opioid analgesics and benzodiazepines approximately tripled. Benzodiazepines were involved in 31% of opioid analgesic overdose deaths in 2011.
Jones et al., 2014	ED visits and deaths associated with opioid pain medications and benzodiazepines, 2010	Patients presenting to EDs participating in the DAWN ED; population of 13 states submitting drug-related death data through DAWN-ME	Percentages of drug abuse-related ED visits and drug-related deaths that involved alcohol, for both opioid pain medications and benzodiazepines	Of opioid pain medication misuse-related ED visits, an estimated 18.5% involved alcohol. Of opioid pain medication overdose deaths, 22.1% involved alcohol.
Jones et al., 2013	Overdose deaths associated with pharmaceutical drugs in the U.S., 2010	U.S. population	Drug overdose deaths involving pharmaceutical drugs	Of the 22,134 pharmaceutical-related overdose deaths in the U.S. in 2010, the most commonly involved drugs were opioids (75.2%), benzodiazepines (29.4%), antidepressants (17.6%), and antiepileptic and antiparkinsonism drugs (7.8%).
Kalso et al., 2007	Secondary analysis of randomized trial data to identify predictors of treatment response to transdermal fentanyl or sustained-release oral morphine for 13 months	680 patients with chronic low back pain (median duration 87 months)	Pain relief of at least 30% from baseline to any point during trial	Of patients with <30% pain reduction at 1 month, 14% had ≥30% pain reduction at 6 months. Of patients with ≥30% pain reduction at 1 month, 40% had ≥30% pain reduction at 6 months.
Koren et al., 2006	Meta-analysis to estimate risk of premature closure of the ductus arteriosus following short-term NSAID use during pregnancy	Women exposed to NSAIDs or placebo during the third trimester of pregnancy	Premature closure of the fetal ductus arteriosus	Risk of ductal closure was significantly higher (odds ratio=15.0) among women exposed to NSAIDs compared with those receiving either placebo or other non-NSAIDs.
Langley, 2011	Prevalence estimate of chronic pain (internet survey)	Adults in the United Kingdom, France, Spain, Germany, and Italy	Self-reported pain, health-related quality of life	The population prevalence of daily pain was 8.9% with 3.5% reporting severe daily pain and 4.7% moderate daily pain.
Lann & Molina, 2009	Descriptive report of fatal case of benzodiazepine withdrawal	Decedent referred to medical examiner	Fatal benzodiazepine withdrawal	The decedent had abruptly stopped taking alprazolam after taking approximately 200 mg in a 6-day period.
Liang & Turner, 2015	Longitudinal cohort study examining association between opioid dosage levels and overdose	Health naintenance program enrollees who filled at least 2 Schedule II or III opioid analgesic prescriptions from January 2009 through July 2012	Fatal overdose	Overdose risk was associated with daily opioid dosage. In addition, among patients prescribed 50-100 MME/day, overdose risk was significantly greater for patients prescribed >1830 MME cumulatively over 6 months.
Madadi et al., 2009	Case-control study examining association between codeine use during breast feeding and infant central nervous system depression	Mothers counseled about codeine use during breast feeding through the Canadian Motherisk Program information and counseling service from 2004-2007	Central nervous system depression in infant	Mothers of symptomatic infants consumed a mean 59% higher codeine dose than mothers of asymptomatic infants.
Nahin, 2015	Prevalence estimates for chronic pain in the United States	National Health Interview Survey	Population prevalence of chronic pain (weighted estimates)	Weighted prevalence estimated at 11.2% for daily (chronic) pain.

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
National Alliance for Model State Drug Laws, 2014	Descriptions of state-specific laws and policies applicable to PDMPs	Each U.S. state	Metrics such as status of program, housing entity, data collection interval, persons authorized to receive information, delegates allowed, and mandatory enrollment and access	There is wide variation in timeliness of reporting of dispensed prescriptions to the PDMP and policies regarding who has access to PDMP data and whether or not providers can delegate access to other members of the health care team.
Park et al., 2015	Case-control study examining the association between benzodiazepine prescribing and risk of drug overdose death for patients receiving opioid analgesics	U.S. veterans who received opioid analgesics through the Veterans Health Administration between 2004 and 2009 and veterans who died of a drug overdose while receiving opioid analgesics	Drug overdose death	Risk of drug overdose death increased four-fold among veterans using benzodiazepines concurrently with opioids compared with patients not using benzodiazepines; risk of drug overdose death increased as daily benzodiazepine dose increased.
Paulozzi et al., 2012,	Prevalence estimate of overdose deaths involving methadone	Decedents in the National Vital Statistics System, multiple cause of death files	Methadone-related death	Methadone accounted for 1.7% of the opioid prescriptions in 2009. Among DAWN ME states, methadone accounted for 31.4% of the deaths, but only 9.8% of the MME. The rate of methadone deaths per amount sold in MME was significantly higher than that for any other opioid.
Paulozzi et al., 2012,	Matched case-control study examining association between overdose death and patterns of use of opioid analgesics	New Mexico residents who died of unintentional drug overdoses and patients with prescriptions in the Prescription Monitoring Program, April 2006 – March 2008	Fatal overdose	Patients receiving a daily average dose of >40 MME had a 12.2 greater odds of overdose compared with those with lower opioid dosages or no opioid prescriptions.
Reid et al., 2002	Prevalence estimates of psychiatric comorbidity and prescription opioid abuse behaviors	Primary care patients in a Veterans Administration clinic and from an urban hospital-based primary care center with chronic non-cancer pain who received ≥6 months of opioid prescriptions, Apr. 1997-Mar. 1998	Prescription opioid abuse behaviors	Current and lifetime history of substance use disorder predicted prescription opioid abuse behavior.
Rementeria & Nunag, 1973	Case report of stillborn infant born to drug-addicted mother	One stillborn infant whose mother had withdrawal symptoms shortly before delivery	Fetal death associated with maternal withdrawal	Statistics are presented to show an increased stillborn and neonatal mortality rate in the over-all pregnant drug-addicted population.
Rolita et al., 2013	Nested case-control study comparing association of opioids, COX-2 selective inhibitors, and NSAIDS with falls or fractures	Community-dwelling patients aged 65-89 years with a diagnosis of osteoarthritis in a large health system, 2001-2009	Fall or fracture	Patients receiving opioids were significantly more likely to suffer a fall or fracture than those treated with COX-2 inhibitors or NSAIDs.
Rowe et al., 1976	Longitudinal study with cross-sectional analysis of the effect of age on creatinine clearance in men	Males in the Baltimore Longitudinal Study	24-hour creatinine clearance	Cross-sectional analysis by 10-year age groups showed a linear decline in clearance from 140 ml/min/1.73m^2 at age 30 years to 97 at age 80 years. Longitudinal data showed an acceleration of the rate of decline in creatinine clearance with advancing age.

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Solomon et al., 2010	Cohort study examining the comparative safety of non-selective NSAIDs, selective COX-2 inhibitors, and opioids	Medicare beneficiaries from Pennsylvania and New Jersey who initiated therapy with an non-selective NSAID, a COX-2 inhibitor, or an opioid from January 1, 1999, through December 31, 2005	Cardiovascular events, gastrointestinal tract bleeding, fracture, other safety event requiring hospitalization, all-cause mortality	Compared with non-selective NSAIDs, opioids exhibited elevated risk for cardiovascular events, fracture, safety events requiring hospitalization, and all-cause mortality.
Spector et al., 2007	Case-control study examining association between opioid analgesics and fracture risk	Nursing home residents aged ≥65 years, nationally representative sample of nursing homes from the Medical Expenditure Panel Survey, 1996-1997	Fracture	Patients receiving opioids were found to have an increased odds of suffering a fracture compared with those not treated with opioids.
Sullivan et al., 2006	Association between regular prescription opioid use and common mental health disorders and problem drug use	Responders to a nationally representative telephone community survey in 1998 and 2001	Self-reported regular prescription opioid use of ≥1 month	Common mental health disorders significantly predicted opioid use and opioid initiation. This might be due to patients with depression experiencing increased rates of psychological and physical pain symptoms.
Taylor et al., 2005	Retrospective case control study examining association between postoperative opioid analgesics and respiratory events.	Non-trauma inpatients aged >18 years undergoing surgery requiring >24 hours of postoperative stay in large urban academic hospital, 2002-2004	Respiratory events	Being aged ≥65 years, having COPD, and having multiple comorbidities were risk factors for having respiratory depression or decreased oxygen saturation.
Tsang et al., 2008	Prevalence estimate of common chronic pain conditions	10 developed and 7 developing countries, including the United States; data from adult population surveys	Self-reported arthritis or rheumatism, chronic back or neck problems, frequent or severe headaches, other chronic pain	Overall U.S. prevalence of common, predominantly musculoskeletal pain conditions that might be chronic was estimated at 43%.
Turner & Liang, 2015	Retrospective cohort review to examine the association between drug overdose and mental health disorders	Adults enrolled in a nationwide health maintenance organization, 2009 – 2012 with non-cancer pain who filled >1 Schedule II or III opioids	Drug overdose	Depressed patients were at higher risk for overdose than persons without depression, particularly at higher opioid dosages (≥100 MME); longer-term antidepressant use was protective for persons with depression.
Vestergaard et al., 2006	Case-control study examining the association between opioids and fracture risk	Danish residents in the National Hospital Discharge Register who sustained a fracture	Fracture	Increased fracture risk is associated with use of most opioids, including among older adults; effects might be related to the risk of falls given that increase in fracture risk was seen at low doses.
Von Korff et al., 2011	Survey about problems associated with time-scheduled and pain-contingent opioid dosing for chronic pain	Patients receiving opioid therapy for chronic, non-cancer pain in a large health plan	Opioid use; problems and concerns related to opioid use	Patients receiving time-scheduled dosing received substantially higher average daily opioid doses than those using pain-contingent dosing (97.2 versus 37.2 milligrams average daily dose morphine equivalents, p<.001), and reported higher levels of opioid control concerns.

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Walley et al., 2013	Interrupted time series analysis of opioid overdose rates and implementation of overdose education and naloxone distribution	19 Massachusetts communities (geographically distinct cities and towns) with at least five fatal opioid overdoses in each of the years 2004 to 2006	Opioid overdose deaths and acute care hospital utilization	Opioid overdose death rates were lower in communities where overdose education and naloxone distribution was implemented compared with communities with no implementation
Webster et al., 2008	Observational study of chronic pain patients on opioid therapy who received overnight polysomnographies	Patients in a private clinic specializing in the treatment of chronic pain	Apnea-hypopnea index and central apnea index	Abnormal apnea-hypopnea index was recorded for 75% of patients (a rate higher than the general population); of those, 39% had obstructive sleep apnea, 4% had sleep apnea of indeterminate type, 24% had central sleep apnea, and 8% had both central and obstructive sleep apnea. In particular, relations were found between the apnea-hypopnea index and methadone, and increased methadone dose was associated with more severe sleep apnea; benzodiazepines had an additive effect.
Whiteman et al., 2014	Cross-sectional analysis to compare perinatal maternal and fetal outcomes between opioid users and nonusers	Women discharged from nonfederal community hospitals (National Inpatient Sample of the Healthcare and Cost Utilization Project), from 1998 to 2009	Selected maternal and fetal outcomes	Opioid use was associated with increased odds of threatened preterm labor, early onset delivery, poor fetal growth, and stillbirth.
Yazdy et al., 2013	Case-control study examining the association between maternal opioid use in the periconceptional period and neural tube defects	Mothers in birth hospitals and tertiary care centers and their offspring	Neural tube defect	A higher percentage of mothers of infants with neural tube defects reported using an opioid medication than mothers of infants with no major malformations.
Yokell et al., 2014	Prevalence estimate of opioid overdoses presenting to U.S. emergency departments	2010 Nationwide Emergency Department Sample; weights were applied to generate national estimates	Opioid overdose	An estimated 135,971 ED visits for opioid overdose in 2010. Prescription opioids (including methadone) were involved in 67.8% of all opioid overdoses.
Zedler et al., 2014	Association between opioid dose and overdose	Patients dispensed an opioid by the Veterans Health Administration, 2010-2012	Respiratory/central nervous system depression, overdose	Compared with patients with 1 to <20 MME/day, the odds of overdose was 1.5 for patients prescribed 20 to <50 MME/day, 2.2 for patients prescribed 50 to <100 MME/day, and 4.1 for patients prescribed ≥100 MME/day.

Abbreviations: AAROD = anesthesia-assisted rapid opiate detoxification, MME = morphine milligram equivalents, PDMP = prescription drug monitoring program, ED = emergency department, DAWN = Drug Abuse Warning Network, NSAID = non-steroidal anti-inflammatory drug; COX-2 = cyclooxygenase-2

Table 3. Effectiveness of Pharmacologic and Psychosocial Treatments for Opioid Use Disorder

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings	Study Quality
Amato et al., 2011	Psychosocial and pharmacological treatments versus pharmacological (only) treatments for opioid detoxification	Systematic review of 11 studies that were either randomized control trials or controlled clinical trials; participants were heroin- or opioid-dependent (not specified)	Dropout from detoxification program, use of opioid drugs during treatment, use of opioid drugs at follow-up	Psychosocial therapies in addition to pharmacological treatments are an effective option for opioid detoxification. Dropout from treatment programs was significantly reduced when psychosocial therapies were used in conjunction with pharmacological treatments (compared with pharmacological treatments only).	Overall moderate quality of evidence; High quality evidence for dropout when only studies with low risk of bias; moderate evidence for dropout among all studies; moderate evidence for use of opiate during treatment; high quality evidence for using opioids at follow-up when only studies with low risk of bias; moderate evidence for using opioids at follow-up among all studies
Fullerton et al., 2014	Methadone Maintenance Treatment versus treatments not involving opioid replacement	Systematic review of 7 randomized control trials and 2 quasi-experimental studies for methadone maintenance treatment for persons with opioid use disorder; Review of 15 reviews of methadone maintenance treatment also included; Study participants were heroin or opioid dependent (not specified)	Retention in treatment programs, decreasing illicit opioid use	Methadone maintenance treatment options positively impact patient retention in treatment programs. Methadone maintenance treatment options are also effective in reducing heroin use among patients. Both treatment retention and heroin use reduction were found to be the most effective when higher doses of methadone were used.	Overall quality of evidence for effectiveness of methadone maintenance treatment on retention and opioid use is high
Mattick et al., 2009	Methadone maintenance treatment versus treatment that did not involve opioid replacement therapy	Systematic review of 11 randomized clinical trials (two were double blind) for opioid dependence; participants were typical of heroin-dependent persons	Retention in treatment, mortality, proportion of urine or hair analysis results positive for heroin or morphine, self-reported heroin use, criminal activity	Methadone maintenance treatment is effective at reducing heroin use and retaining patients in treatment and should be supported as a treatment option for heroin dependence.	High quality of evidence for retention in treatment; moderate for mortality; high for morphine positive urine or hair analysis, and moderate for criminal activity
Mattick et al., 2014	Buprenorphine versus placebo or methadone for the treatment of opioid dependence	Systematic review of 31 randomized controlled trials of buprenorphine for patients with opioid dependence; participants were typical of heroin-dependent persons	Retention in treatment, use of opioids, use of other substances, criminal activity, mortality	Buprenorphine is an effective treatment for opioid dependence when compared with a placebo; in reducing heroin use among patients, buprenorphine is only effective at high doses (16 mg or more). Buprenorphine is less effective than methadone for patient retention. No difference was found in efficacy between buprenorphine and methadone in reducing heroin use.	Quality of evidence for treatment retention is high; evidence quality for use of opioids is moderate

Table 4. Clinician and patient values and preferences

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Anastassopoulos et al., 2013	Survey of patients about opioid satisfaction	Nationwide sample of patients taking hydrocodone for non-cancer pain	Overall satisfaction, side effects, and adherence	Almost three-fourths (73.3 percent) experienced at least one side effect, and 67.3% reported being bothered. About three fourths were satisfied with hydrocodone relieving pain. More than one fourth (27.6 percent) reported taking hydrocodone less than instructed, often (41%) because of side effects.
Dobscha et al., 2008	Survey of providers about attitudes toward chronic pain and satisfaction	VA primary care clinicians	Confidence in ability to treat; frustration	Seventy-one percent of clinicians felt confident in their ability to treat chronic pain. However, 73% agreed that patients with chronic pain are a major source of frustration and 38% reported dissatisfaction with their ability to provide optimal pain treatment.
Gregorian et al., 2010	Survey of patients and clinicians about preference for specific opioid medications	Acute and chronic pain patients and physicians	Medication preference, side effects, pain relief	Almost all patients (96% of chronic, 92% of acute) reported experiencing at least 1 side effect while on opioid medication. Opioid side effects, rather than pain relief, explained the majority of variance for medication preference for both patients (74% for chronic, 73% for acute) and treating physicians (73% for chronic, 74% for acute).
Hagemeier et al., 2013	Survey of prescribers and pharmacists about their perceptions of prescription drug abuse	Prescribers and pharmacists in rural Appalachia	Perceptions of legitimate use, overprescribing, dispensing, treatment availability, and patient communication	On average, providers agreed, but did not strongly agree, that they are confident in detecting patient drug abuse or discussing drug abuse issues with patients.
Hooten et al., 2011	Survey of clinicians about beliefs and attitudes about prescribing opioids for chronic pain	Physicians, physician assistants, and advance practice nurses with prescribing privileges attending a continuing medical education conference	Likelihood of prescribing, improvements in pain and quality of life, abuse, addiction, care complexity	Most respondents had favorable beliefs and attitudes toward improvements in pain and quality of life attributed to prescribing opioids. However, most also had negative beliefs and attitudes about medication abuse and addiction.
Hwang et al., 2015	Survey of physicians about beliefs and practices related to prescription opioid abuse	Internists, family physicians, and general practitioners.	Drug abuse, use, prescribing, patient outcomes, prescriber outcomes, adverse events	Most physicians (90%) reported prescription drug abuse to be a “big” or “moderate” problem in their communities. 45% reported they were less likely to prescribe than a year ago. A majority were very concerned about addiction (55%) and death (48%). A majority reported adverse events such as tolerance (62%) and physical dependence (56%) when opioids are used as directed.
Keller et al., 2012	Survey of physicians about concerns, perceptions, and practices	Primary care physicians in upstate New York	Reasons for prescribing and use, knowledge of opioid treatment and dependence	Most physicians (71.5%) rated their knowledge/comfort of treatment/management of opioid dependence as being low. Many physicians evaluated their own medical training in these areas as unsatisfactory.
Mangione et al, 2008	Survey of patients about opioids and narcotics	Outpatients in an urban Veterans Administration hospital	Definition of "narcotic" and "opioid," when used, outcomes	Patients were more likely to know what a narcotic was than what an opioid was. While 50% of patients related "narcotics" to pain management, more than a third cited addiction or abuse; 56% feared addiction from long-term use.
Matthias et al., 2010	In-depth interviews with providers about experiences treating chronic pain	Providers from Veterans Administration clinics	Difficulties and barriers to effective pain management	Difficulties encountered by providers when caring for patients with chronic pain include feeling pressured to treat with opioids, having concerns about the believability of patients' reports of pain, worrying about diversion and difficult patients, and feeling emotional consequences from chronic pain care, including feeling frustrated, ungratified, and guilty.
Moore et al., 2013	Focus groups and interviews with patients to inform the development of a self-management intervention	Chronic pain patients	Appeal, motivation, interest, and comprehensiveness of topics, components, and features	Patients stressed ambivalence about opioid use (effectiveness, addiction, stigmatization); interrelationships among thoughts, mood, and pain; recognizing physical limitations and need for pacing; goal setting; changes in identity caused by pain; and wanting to connect with peers.

Author, Year	Topic/Intervention	Participants/Population	Primary Outcomes	Key Findings
Payne et al., 2011	Focus groups of clinicians about presentation of misuse and abuse	Physicians and five nurse practitioners from ambulatory care practices serving older adults	Problem of abuse, criteria for determining abuse, barriers to identification	Primary care clinicians found it challenging to predict which patients were at increased risk. Primary care clinicians identified multiple barriers to identifying affected patients, including lack of communication, nonspecific symptoms, and the lack of a clear definition of misuse and abuse.
Simmonds et al., 2015	Focus groups of patients about facilitators and barriers to multimodal chronic pain management	Veterans at a Veterans Health Administration clinic taking ≥50 MME/day for >6 months	Quality of life, experiences with multimodal pain care, social support	Patients reported uncontrollable impact of pain, reliance on opioids, and challenges in obtaining opioids despite ambivalence about benefits, poor access to non-pharmacologic therapies, frustrations with health care, and poor social support.
Starrels et al., 2014	Interviews with physicians about experiences with and attitudes toward OTAs	Internists and family medicine physicians	OTA adoption, effects, utility, and risk for misuse	A low percentage of clinicians reported consistent adoption and use of OTAs. Views were diverse. Adoption was related to perceptions of the effect on the therapeutic alliance and beliefs about utility of OTAs in preventing opioid misuse. Few clinicians reported a belief that OTAs prevent opioid misuse.
Thielke et al., 2014	Surveys of patients about views on opioid benefits and harms	Patients in 2 large health plans prescribed ≥50 MME/day for chronic non-cancer pain	Psychosocial problems, concerns, benefits, and side effects	At 1 year, over 80% of participants continued higher-dose opioid use even when reporting problems, concerns, side effects, pain reduction, and lack of helpfulness. Greater problems and concerns were negatively associated with higher-dose use 1 year later.

Abbreviations: OTA = opioid treatment agreement

Table 5. Resource allocation

Author, Year	Objective (Topic)	Study/Participant Characteristics	Primary Outcomes	Key Findings (Results/Conclusions)
Birnbaum et al., 2011	Economic analysis of the societal costs of prescription opioid abuse, dependence, and misuse	Administrative claims data and secondary sources	Health care, criminal justice, and lost workplace productivity costs	Total costs of prescription opioid abuse in 2007 in the United States were estimated to be $55.7 billion ($25.6B in workplace productivity; $25B in health care; $5.1B in criminal justice costs). Prescription opioid abuse, dependence, and misuse imposes a large economic burden on the United States.
Gore et al., 2012	Descriptive cost analysis of pharmacologic and alternative treatments for patients with osteoarthritis and chronic low back pain.	Claims data from patients with a diagnosis of osteoarthritis or chronic low back pain who received pain-related treatments	Direct medical costs (e.g., outpatient visits, hospitalizations, treatments)	The mean cost of 11 of the 20 alternative therapies studied (e.g., acetaminophen, NSAIDs, massage therapy, cognitive behavioral therapy) were lower than the mean cost of opioid treatment.
Hansen et al., 2011	Economic analysis of the cost burden of nonmedical use of prescription opioids	Administrative data and secondary sources	Substance abuse treatment, medical complications, lost productivity, and criminal justice costs	Total costs of nonmedical use of prescription opioids in 2006 in the United States were estimated to be $53.4 billion ($42B in lost productivity; $8.2B in criminal justice; $2.2B in treatment; $944M in medical complications costs). Nonmedical use of prescription opioids places a heavy economic burden on the United States.
Inocencio et al., 2013	Economic analysis of the cost burden of opioid-related poisoning	Administrative data and secondary sources	Medical, nonmedical, and lost productivity costs	Total costs of opioid-related poisoning in 2011 in the U.S. were estimated to be $20.4 billion.
Laffer et al., 2011	Economic analysis of the cost of urine drug testing	Secondary sources	Costs of laboratory testing (screening, confirmation, quantification)	The average estimated cost per urine drug test is between $211 and $363.
Stagnitti, 2015	Cost of expenses for outpatient opioid use	Administrative data	Expenses of opioid prescriptions purchased or obtained in an outpatient setting	In 2012, using data from the Medial Expenditure Panel Survey, the total expenses for outpatient prescription opioids was estimated to be $9.0 billion, a 120% increase from 2002.

Abbreviations: NSAID = non-steroidal anti-inflammatory drug

Table 6. Guidelines

Name, Year	Focus	Relevant Recommendations
American Academy of Emergency Medicine, 2013	Emergency department opioid prescribing guidelines for the treatment of non-cancer-related pain	Prescribe a short course (up to 3 days) of opioid medication for most acute pain conditions.
American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation; 2011	Treatment of painful diabetic neuropathy	If clinically appropriate, pregabalin should be offered; gabapentin and sodium valproate should be considered for the treatment of painful diabetic neuropathy. Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Venlafaxine may be added to gabapentin for a better response.
American College of Emergency Physicians, Maryland Chapter, 2014	Maryland emergency department and acute care facility guidelines for prescribing opioids	We will prescribe no more than a short course of pain medications. Generally, most patients require no more than 3 days.
American College of Emergency Physicians Opioid Guideline Writing Panel, 2012	Prescribing of opioids for adult patients in the emergency department	All recommendations pertaining to acute non-cancer pain.
American College of Occupational and Environmental Medicine	Opioid therapy for working-age adults	All recommendations pertaining to working-age adults.
American College of Physicians and American Pain Society; 2007	Diagnosis and treatment of low back pain	For most patients, first-line medication options are acetaminophen or NSAIDs. For patients who do not improve with self-care options, clinicians should consider the addition of non-pharmacologic therapy with proven benefits.
American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee, 2012	Nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee	We strongly recommend that patients with knee OA should do the following: Participate in cardiovascular (aerobic) and/or resistance land-based exercise; Participate in aquatic exercise; Lose weight (for persons who are overweight)
American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons; 2009	Pharmacological management of persistent pain in older persons	Acetaminophen should be considered as initial and ongoing pharmacotherapy in the treatment of persistent pain, particularly musculoskeletal pain; Non-selective NSAIDs and COX-2 selective inhibitors may be considered rarely, and with extreme caution, in highly selected individuals
American Society of Anesthesiologists Task Force on Acute Pain Management, 2012	Acute pain management in perioperative setting	All recommendations pertaining to acute pain management.
Arizona Department of Health Services, 2014	Opioid prescribing for acute and chronic pain	Chronic Opioid Therapy should be used in the lowest possible doses to achieve treatment goals. Opioid related adverse events increase with dosages >50-100 MME per day and reaching these doses should trigger a re-evaluation of therapy.
Canadian National Opioid Use Guideline Group, 2010	Use of opioids for chronic non-cancer pain	Opioid therapy for elderly patients can be safe and effective with appropriate precautions, including lower starting doses, slower titration, longer dosing interval, more frequent monitoring, and tapering of benzodiazepines. When using urine drug screening (UDS) to establish a baseline measure of risk or to monitor compliance, be aware of benefits and limitations, appropriate test ordering and interpretation, and have a plan to use results. Pregnant patients taking long-term opioid therapy should be tapered to the lowest effective dose slowly enough to avoid withdrawal symptoms, and then therapy should be discontinued if possible.
Canadian Pain Society, 2007	Pharmacological management of chronic neuropathic pain	TCAs and anticonvulsants (gabapentin and pregabalin) are considered first line agents in the management of chronic neuropathic pain. Serotonin noradrenaline reuptake inhibitors (SNRIs) are considered to be second line to TCAs.
Centers for Disease Control and Prevention, 2015	Common elements in guidelines for prescribing guidelines for chronic pain	Conducting a physical exam, pain history, past medical history, and family/social history; Conducting urine drug testing, when appropriate; Considering all treatment options, weighing benefits and risks of opioid therapy, and using opioids when alternative treatments are ineffective; Starting patients on the lowest effective dose; Implementing pain treatment agreements; Monitoring pain and treatment progress with documentation and using greater vigilance at high doses; Using safe and effective methods for discontinuing opioids.

Name, Year	Focus	Relevant Recommendations
Deyo et al., 2015 State of the Art Review	Opioids for low back pain	Consider intermittent opioid prescription, with clear expectations for short duration of use. Prescription of a few days to a week of short acting opioids may reduce risks of tolerance, dependence, and dose related adverse effects. Keep the opioid dose as low as possible. When the dose reaches 50-100 MME per day, re-evaluate treatment and consider specialist consultation. Higher doses have unproven benefits and increased risks, and make discontinuation difficult.
European Federation of Neurological Societies, 2010	Pharmacological treatment of neuropathic pain	Recommend TCAs, gabapentin, pregabalin, and SNRIs (duloxetine, venlafaxine) as first-line treatment in painful polyneuropathy. We recommend TCA or gabapentin/pregabalin as first-line treatment in post-herpetic neuralgia. We recommend pregabalin, amitriptyline or gabapentin as first line in central neuropathic pain.
European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutic Trials, 2007	Management of hand osteoarthritis	Because of its efficacy and safety paracetamol (up to 4 g/day) is the oral analgesic of first choice and, if successful, is the preferred long term oral analgesic.
European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutic Trials, 2005	Management of hip osteoarthritis	Because of its efficacy and safety paracetamol (up to 4 g/day) is the oral analgesic of first choice for mild-moderate pain and, if successful, is the preferred long term oral analgesic.
European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutic Trials, 2003	Management of knee osteoarthritis	Paracetamol is the oral analgesic to try first and, if successful, the preferred long term oral analgesic.
Institute for Clinical Systems Improvement, 2014	Acute pain assessment and opioid prescribing	Avoid prescribing more than three days supply or 20 pills of low-dose, short-acting opioids, unless circumstances clearly warrant additional opioid therapy.
Institute for Clinical Systems Improvement, 2013	Assessment and management of chronic pain	All recommendations related to nonpharmacologic and nonopioid pharmacologic therapies and establishing a diagnosis.
Berna et al., 2015	Tapering long-term opioid therapy in chronic non-cancer pain	Recommendations on taper speed, medication choice, other pharmacologic interventions, preventing taper failure, withdrawal symptom management, pain management, and psychological management.
National Fibromyalgia Guideline Panel (Canadian), 2013	Diagnosis and management of fibromyalgia syndrome	Recommendations on alternative treatments with Grade A evidence, including: Nonpharmacological strategies with active patient participation should be an integral component of the therapeutic plan for the management of fibromyalgia. Cognitive behavioural therapy, even for a short time, is useful and can help reduce fear of pain and fear of activity. Individuals with fibromyalgia should participate in a graduated exercise program of their choosing to obtain global health benefits and probable effects on fibromyalgia symptoms. All categories of antidepressant medications including tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors may be used for treatment of pain and other symptoms in patients with fibromyalgia. Anticonvulsant medication use should be explained as having pain-modulating properties and treatment should begin with the lowest possible dose followed by up-titration, with attention to adverse events.
New York City Department of Health and Mental Hygiene, 2011	Preventing misuse of prescription opioid drugs	For acute pain if opioids are warranted, prescribe only short-acting agents. A 3-day supply is usually sufficient.
New York City Department of Health and Mental Hygiene, 2013	Emergency department discharge opioid prescribing guidelines	Prescribe no more than a short course of opioid analgesics for acute pain. Most patients require no more than three days.
Nuckols et al., 2014	Systematic review of opioid prescribing guidelines for chronic pain	Summary of opioid prescribing guidelines for chronic pain. There is considerable variability in recommendations, audience, use of evidence, and mitigation of conflict of interest in existing guidelines.
O'Connor & Dworkin, 2009	Treatment of neuropathic pain	Initiate symptom treatment with antidepressant medication (either secondary amine TCA, nortriptyline or desipramine, or SNRI, duloxetine, venlafaxine), gabapentin or pregabalin (among other options for patients with specific types of neuropathic pain).

Name, Year	Focus	Relevant Recommendations
Ohio Governor's Cabinet Opiate Action Team, 2013	Opioid prescribing for the treatment of chronic, non-terminal pain	Providers treating chronic, non-terminal pain patients who have received opioids ≥ 80 MME for longer than three continuous months should strongly consider doing the following to optimize therapy and ensure patient safety: established informed consent, review functional status and documentation, review progress toward treatment objectives, use Ohio Automated Rx Reporting System, consider a pain treatment agreement, and reconsider having the patient evaluated by providers who specialize in the treatment of the body part that is the source of pain.
Osteoarthritis Research Society International, 2008	Management of hip and knee osteoarthritis	Acetaminophen (up to 4 g/day) can be an effective initial oral analgesic for treatment of mild to moderate pain in patients with knee or hip osteoarthritis. In the absence of an adequate response, or in the presence of severe pain and/or inflammation, alternative pharmacologic therapy should be considered based on relative efficacy and safety, as well as concomitant medications and co-morbidities.
Washington State Agency Medical Directors' Group, 2015	Acute and chronic pain	All recommendations related to prescribing opioids in the acute and subacute phase and opioids for perioperative pain. All recommendations on how to discontinue opioids. All recommendations for managing chronic pain during pregnancy and neonatal abstinence syndrome. All recommendations for managing chronic pain in older adults. Also, for prescribing opioids for chronic non-cancer pain: Repeat random urine drug tests at the frequency determined by the patient's risk category to identify aberrant behavior, undisclosed drug use and/or abuse and verify compliance with treatment.

Abbreviations: NSAID = non-steroidal anti-inflammatory drug, COX-2 = cyclooxygenase 2 inhibitors, TCA = tricyclic antidepressants, SNRI = serotonin noradrenaline reuptake inhibitors,

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