

1 **CDC Clinical Practice Guideline for Prescribing Opioids—United States, 2022**

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This clinical practice guideline is

- A clinical tool to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together
- Intended for primary care clinicians and other clinicians providing pain care for outpatients aged ≥18 years old with:
 - acute pain (duration <1 month);
 - subacute pain (duration of 1-3 months); or
 - chronic pain (duration of >3 months)
- Intended to be flexible to enable person-centered decision-making, taking into account an individual's expected health outcomes and well-being.

This clinical practice guideline is not

- A replacement for clinical judgment or individualized, person-centered care
- Intended to be applied as inflexible standards of care across patients, and/or patient populations by healthcare professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or discontinuation of opioids for patients
- A law, regulation, and/or policy that dictates clinical practice or a substitute for FDA-approved labeling
- Applicable to the following types of pain treatment:
 - sickle cell disease-related pain;
 - cancer pain;
 - palliative care; or
 - end-of-life care

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Summary

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This clinical practice guideline updates and expands the CDC Guideline for Prescribing Opioids

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for Chronic Pain — United States, 2016 (Dowell, Haegerich, & Chou, 2016) and provides evidence-based

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recommendations for clinicians providing pain care, including those prescribing opioids, for outpatients

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aged ≥18 years with acute pain (duration <1 month), subacute (duration of 1-3 months) pain, or chronic

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(duration of >3 months) pain, and excluding of sickle cell disease-related pain management, cancer pain

34 treatment, palliative care, and end-of-life care. Content on use of opioids for acute pain and on tapering
35 opioids for patients already receiving higher dosages for subacute or chronic pain has been substantially
36 expanded. This update includes recommendations for primary care and other clinicians (including
37 physicians, nurse practitioners, physician assistants, and oral health practitioners) managing pain in
38 outpatient settings. Applicable settings include clinician offices, clinics, and urgent care centers. The
39 recommendations do not apply to inpatient care received while hospitalized or to care received while in
40 an emergency department or other observational setting from which a patient might be admitted to
41 inpatient care but do apply to prescribing for pain management upon discharge (from emergency
42 departments, hospitals, or other facilities).

43 This clinical practice guideline addresses:

- 44 1) Determining whether or not to initiate opioids for pain;
- 45 2) Opioid selection and dosage;
- 46 3) Opioid duration and follow-up; and
- 47 4) Assessing risk and addressing potential harms of opioid use.

48 CDC developed this clinical practice guideline using the Grading of Recommendations
49 Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made based
50 on a systematic review of the available scientific evidence while considering benefits and harms,
51 patients', caregivers', and clinicians' values and preferences, and resource allocation (e.g., costs to
52 patients or health systems, including clinician time). As described in more detail below, CDC obtained
53 input on this updated clinical practice guideline in a wide variety of avenues including conversations
54 with patients, caregivers, and clinicians, through *Federal Register* notices and comments from the public,
55 peer reviewers, and a federally chartered advisory committee.

56 The clinical evidence reviews found that nonopioid therapies are effective for many common
57 types of acute pain and found insufficient evidence to determine long-term (>1 year) benefits of opioid
58 therapy for chronic pain. Recommendations include that opioids should be used only when benefits for
59 pain and function are expected to outweigh risks. Before starting opioids for subacute or chronic pain,
60 clinicians should discuss with patients the known risks and realistic benefits of opioid therapy, work with
61 patients to establish treatment goals for pain and function and consider how opioid therapy will be
62 discontinued if benefits do not outweigh risks. When opioids are initiated, clinicians should prescribe the
63 lowest effective dosage of immediate-release opioids for no longer than needed for the expected
64 duration of pain severe enough to require opioids. During ongoing opioid therapy, clinicians should
65 collaborate with patients to evaluate and carefully weigh benefits and risks of continuing opioid therapy
66 and exercise care when increasing, continuing, or reducing opioid dosage. Before starting and
67 periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related
68 harms and should work with patients to incorporate relevant strategies to mitigate risk, including
69 offering naloxone when factors that increase risk for opioid overdose are present, and reviewing
70 potential interactions with any other prescribed medications or substances used. Clinicians should offer
71 or arrange treatment with medication for patients with opioid use disorder.

72
73 It is imperative that people with pain receive the most appropriate and effective pain treatment
74 with careful consideration of the benefits and risks of all treatment options. Clinicians should collaborate
75 with patients when making treatment decisions and designing a treatment plan, including when
76 initiating or changing pain management strategies and, particularly, when considering initiating,
77 increasing, tapering, or discontinuing opioids. Clinicians should avoid abrupt discontinuation of opioids,
78 especially for patients receiving high dosages of opioids, should avoid dismissing patients from care, and
79 should ensure (provide or arrange) appropriate care for patients with pain and patients with

80 complications from opioid use (e.g., opioid use disorder). Special attention should be given to ensure
81 high quality and equitable care across sociodemographic groups, for example, through linguistically
82 tailored care and cost assistance programs to ensure access to appropriate pharmacotherapy,
83 psychological support, and physical therapy as needed. This voluntary clinical practice guideline provides
84 recommendations only and is intended to be flexible to support, not supplant, clinical judgment and
85 individualized, person-centered decision-making. This clinical practice guideline should not be applied as
86 inflexible standards of care across patient populations by healthcare professionals, health systems,
87 pharmacies, third-party payers, or state, local, and federal organizations or entities.

88 This clinical practice guideline is intended to improve communication between clinicians and
89 patients about the risks and benefits of pain treatment, including opioid therapy for pain, improve the
90 safety and effectiveness of pain treatment, mitigate pain, and improve function and quality of life for
91 patients with pain, and reduce risks associated with opioid therapy, including opioid use disorder,
92 overdose, and death.

93 **Introduction**

94 **Background**

95 Pain is one of the most common reasons adults seek medical care in the United States
96 (Schappert & Burt, 2006). Acute pain, a nearly universal experience, is a physiologic response to noxious
97 stimuli that can become pathologic, is normally sudden in onset, time limited (<1 month), and often
98 caused by injury, trauma, or medical treatments such as surgery (Institute of Medicine Committee on
99 Advancing Pain Research Care and Education, 2011; Tighe et al., 2015). Chronic pain, defined in this
100 clinical practice guideline as pain that typically lasts greater than three months or past the time of
101 normal tissue healing, is often interlinked with acute pain (International Association for the Study of
102 Pain, 1986). Chronic pain can be the result of an underlying medical disease or condition, injury, medical

103 treatment, inflammation, or an unknown cause (Institute of Medicine Committee on Advancing Pain
104 Research Care and Education, 2011). It is estimated that approximately 1 in 5 U.S. adults had chronic
105 pain in 2019, and approximately 1 in 14 adults experienced “high-impact” chronic pain, defined as
106 having pain most days or every day in the past three months that limited life or work activities (Zelaya,
107 Dahlhamer, Lucas, & Connor, 2020). Pain, especially chronic pain, can impact almost every aspect of an
108 individual’s life, leading to impaired physical functioning, poor mental health, and reduced quality of life,
109 and contributes to substantial morbidity each year (U.S. Department of Health and Human Services,
110 2019b). In 2011, the economic costs of chronic pain were estimated to range from \$560 to \$635 billion
111 in annual direct medical costs, lost productivity, and disability (Institute of Medicine Committee on
112 Advancing Pain Research Care and Education, 2011).

113 Pain is a complex phenomenon that is influenced by multiple factors, including biological,
114 psychological, and social factors (Chou et al., April 2020). Given this complexity, there is substantial
115 heterogeneity in the effectiveness of various pain treatments depending on the type of underlying pain
116 or condition being treated (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al.,
117 December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). Patients may experience
118 persistent pain that is not well controlled (U.S. Department of Health and Human Services, 2019b). In
119 addition, chronic pain often co-occurs with behavioral health conditions, including mental and substance
120 use disorders (Hooten, 2016; Morasco et al., 2011); suicidal ideation also is common among patients
121 with chronic pain (Racine, 2018; M. T. Smith, Edwards, Robinson, & Dworkin, 2004). Data from death
122 investigations in 18 states between 2003 and 2014 indicate that at least 9% of suicide decedents had
123 evidence of having chronic pain at the time of their death, although this is likely an underestimate given
124 limitations of the underlying data sources used in the study (Petrosky et al., 2018). These factors and
125 potentially deleterious outcomes associated with chronic pain for some individuals add to the clinical
126 complexity and underscore the importance of adequately treating and caring for people with pain. Thus,

127 prevention, assessment, and treatment of pain is a persistent challenge for clinicians. Pain may go
128 unrecognized, and some individuals — in particular members of some marginalized racial and ethnic
129 groups, women, older persons, people with cognitive impairment, individuals with mental and
130 substance use disorders, and individuals with cancer and at the end-of-life or those with sickle cell
131 disease — can be at risk for inadequate pain treatment (Bazargan, Yazdanshenas, Gordon, & Orum,
132 2016; Becker et al., 2017; C Evans, Bazargan, Cobb, & Assari, 2019; Institute of Medicine Committee on
133 Advancing Pain Research Care and Education, 2011; Rupp & Delaney, 2004; Simon, Snow, & Wakeman,
134 2020; U.S. Department of Health and Human Services, 2019b; Yazdanshenas et al., 2016).

135 While there is significant opportunity for improvement in pain management broadly across the
136 United States, data underline particular opportunities for attending to specific, long-standing health
137 disparities (Joynt et al., 2013; Ly, 2019; Morden, Chyn, Wood, & Meara, 2021) in the treatment of pain.
138 For example, patients who identify as Black, Latino, and Asian have been found to receive fewer
139 postpartum pain assessments relative to White patients (Bazargan et al., 2016; C Evans et al., 2019; J. D.
140 Johnson et al., 2019; Rupp & Delaney, 2004; Simon et al., 2020; Yazdanshenas et al., 2016). Black (Goyal,
141 Kuppermann, Cleary, Teach, & Chamberlain, 2015; P. Lee et al., 2019) and Latino (P. Lee et al., 2019)
142 patients are less likely to receive analgesia for acute pain. Among Black and White patients receiving
143 opioids for pain, Black patients are less likely to be referred to a pain specialist and receive prescription
144 opioids at lower dosages than White patients (Hausmann, Gao, Lee, & Kwoh, 2013; Morden et al., 2021).
145 Racial/ethnic differences remain even after adjusting for access-related factors, as well as the needs and
146 preferences of patients, and the appropriateness of the intervention (Ly, 2019). These disparities appear
147 to be further magnified if patients from some racial and ethnic groups reside in socioeconomically
148 disadvantaged neighborhoods (Joynt et al., 2013). Women may be at higher risk for inadequate pain
149 management (Majedi et al., 2019) although they have higher opioid prescription fill rates (Schieber, Guy,
150 Seth, & Losby, 2020) than men at a population level. In addition, geographic disparities contribute to

151 increased use of opioids for conditions for which nonopioid treatment options may be preferred but
152 may be less available. For example, compared to adults living in nonrural areas, adults living in rural
153 areas are significantly more likely to be prescribed opioids for chronic nonmalignant pain (Prunuske et
154 al., 2014). Despite the fact that American Indian/Alaska Native, non-Hispanic and White, non-Hispanic
155 populations have experienced much higher rates of prescription opioid-related overdose deaths than
156 Black, non-Hispanic, Hispanic, or Asian/Pacific Islander, non-Hispanic populations (Wilson, Kariisa, Seth,
157 Smith IV, & Davis, 2020), there is evidence that application of safeguards in opioid prescribing are
158 disproportionately applied to Black patients. Black patients in one study were more likely than White
159 patients to receive regular office visits and have restricted early refills (Becker et al., 2011), and clinicians
160 in another study were substantially more likely to discontinue opioids given evidence of misuse when
161 patients were Black compared to when patients were White (Gaither et al., 2018). Pain being
162 differentially untreated or undertreated as a result of clinician biases persists and demands immediate
163 and sustained attention and action (Ghoshal, Shapiro, Todd, & Schatman, 2020; Nelson & Hackman,
164 2013; Pletcher, Kertesz, Kohn, & Gonzales, 2008; Soares, Knowles, & Friedmann, 2019).

165 Given the clinical, psychological, and social consequences associated with pain including
166 limitations in activities, lost work productivity, reduced quality of life, and pervasive stigma, it is
167 essential that clinicians have the training, education, guidance, and resources to provide appropriate,
168 holistic, and compassionate care for patients with pain (Institute of Medicine Committee on Advancing
169 Pain Research Care and Education, 2011; U.S. Department of Health and Human Services, 2019b). A key
170 aim of pain management is the provision of person-centered care, including the proper evaluation to
171 establish a diagnosis, with measurable outcomes that focus on optimizing function and quality of life,
172 that is built on a foundation of trust between patients and clinicians (U.S. Department of Health and
173 Human Services, 2019b). To achieve this aim, it is important that clinicians consider the full range of
174 pharmacological and nonpharmacological treatments for pain care, and health systems, payers, and

175 governmental programs and entities make the full spectrum of evidence-based treatments accessible to
176 patients with pain and their treating clinicians.

177 The range of therapeutic options that might benefit patients has historically been inaccessible to
178 many due to a variety of factors, including inadequate clinician education, training, and guidance,
179 unconscious bias, a shortage of pain management specialists, insufficient access to treatment modalities
180 such as behavioral therapy, siloed health systems, insurance coverage and reimbursement policies, and
181 lack of clarity around the evidence supporting different pain treatments (Becker et al., 2017; Benzing,
182 Bell, Derazin, Mack, & MacIntosh, 2020; Heyward et al., 2018; Jamison, Sheehan, Scanlan, Matthews, &
183 Ross, 2014; D. H. Lin et al., 2018; Sabin & Greenwald, 2012; Saluja & Bryant, 2021; U.S. Department of
184 Health and Human Services, 2019b). In part due to these factors affecting access to a wide range of
185 treatment modalities, for many years, medications such as prescription opioids have been the mainstay
186 to treat pain, despite very limited evidence to support their long-term (> 1 year) benefits, with most
187 placebo-controlled trials shorter than 6 weeks in duration (Chou et al., September 2014; Dahlhamer,
188 Connor, Bose, Lucas, & Zelaya, 2021; Institute of Medicine Committee on Advancing Pain Research Care
189 and Education, 2011; U.S. Department of Health and Human Services, 2019b).

190 While opioids can be essential medications for the management of pain, they carry significant
191 potential risk. A systematic review published in 2014 by the Agency for Healthcare Research and Quality
192 (AHRQ) found insufficient evidence to demonstrate long-term benefits of prescription opioid treatment
193 for chronic pain, and also that long-term prescription opioid use was associated with increased risk of
194 overdose and opioid misuse, among other risks, with some, such as overdose, being dose dependent
195 (Chou et al., September 2014). Based on accumulating evidence of potential risks for patients, in 2014
196 the U.S. Food and Drug Administration (FDA) required new safety labeling changes for extended-release
197 and long-acting opioids to include a boxed warning on the risks of addiction, abuse, and misuse which
198 can potentially lead to overdose and death, as well as the risk for neonatal opioid withdrawal syndrome

199 among patients receiving opioids during pregnancy (U.S. Food and Drug Administration, 2014a). These
200 warnings were subsequently added to the labels for immediate-release opioids in 2016 (U.S. Food and
201 Drug Administration, 2016).

202 In addition to the potential risks for patients prescribed opioids, these medications carry risks
203 due to their potential for diversion and nonmedical use among individuals to whom they were not
204 prescribed (Substance Abuse and Mental Health Services Administration, 2021a). In the United States,
205 opioid prescribing increased four-fold between 1999 and 2010, and this increase was paralleled by a
206 nearly four-fold increase in overdose deaths involving prescription opioids during the same time period
207 (Paulozzi, Jones, Mack, & Rudd, 2011) as well as increases in prescription opioid use disorder (Han,
208 Compton, Jones, & Cai, 2015). In addition to the overall volume of opioid prescriptions increasing during
209 this period, how opioids were prescribed also changed, with opioids increasingly prescribed at higher
210 dosages and for longer durations — prescribing behaviors associated with opioid use disorder and
211 overdose (Bohnert et al., 2011; Edlund et al., 2014). Thus, the limited evidence of long-term
212 effectiveness of opioids for chronic pain coupled with risks for patients and for people using prescription
213 opioids that were not prescribed to them underscored the importance of reducing inappropriate opioid
214 prescribing, while at the same time advancing evidence-based pain care to improve the lives of people
215 living with pain.

216 Recognizing the need for a national guideline on pain management that could improve
217 appropriate opioid prescribing while minimizing opioid-related risks, CDC released the CDC Guideline for
218 Prescribing Opioids for Chronic Pain in 2016 (referred to as the 2016 CDC Guideline hereafter). The 2016
219 CDC Guideline included 12 recommendations for the prescribing of opioids by primary care clinicians for
220 chronic pain in outpatient settings outside of active cancer treatment, palliative care, and end-of-life
221 care (Dowell et al., 2016). The recommendations in the 2016 CDC Guideline were based on a systematic
222 review of the best available evidence at the time, along with input from experts and from the public,

223 and review and deliberation by a federally chartered advisory committee. The ultimate goal of the 2016
224 CDC Guideline was: 1) to ensure that clinicians and patients considered safer and more effective pain
225 treatment, 2) improve patient outcomes such as reduced pain and improved function, and 3) reduce the
226 number of persons who developed opioid use disorder, overdose, or experienced other prescription
227 opioid-related adverse events (Dowell et al., 2016). To facilitate uptake of the 2016 CDC Guideline into
228 clinical practice, CDC employed a broad-reaching implementation strategy that included clinician
229 education and training, partnerships with health systems and payers, and multiple clinical tools and fact
230 sheets (Centers for Disease Control and Prevention, 2021b).

231 While the number of overall opioid prescriptions in the United States had been declining since
232 2012, the release of the 2016 CDC Guideline furthered these declines. The timing of its release was
233 associated with accelerated decreases in overall opioid prescribing and declines in high-risk prescribing
234 behaviors cautioned against in the 2016 CDC Guideline, such as high-dose opioid prescribing and the
235 concurrent prescribing of opioids and benzodiazepines (Bohnert, Guy, & Losby, 2018). Though not the
236 intent of the 2016 CDC Guideline, design and implementation of new laws, regulations, and policies also
237 drew from its recommendations. As one example since 2016, consistent with SUPPORT ACT
238 requirements, many state Medicaid programs have used the guideline as well as other resources in
239 creating opioid edits in their pharmacy programs (Centers for Medicare and Medicaid Services, 2019).
240 More than half of all states have passed legislation that limits initial opioid prescriptions for acute pain
241 to a seven day supply or less (National Conference of State Legislatures, June 30, 2019.), and many
242 insurers, pharmacy benefit managers, and pharmacies also have enacted similar policies (U.S.
243 Department of Health and Human Services, 2020). In addition, at least 17 states have passed laws that
244 require the co-prescription of naloxone when risk factors such as high doses of opioids or concomitant
245 opioids and benzodiazepines are prescribed (Haffajee, Cherney, & Smart, 2020).

246 While some laws, regulations, and policies that were derived from the 2016 CDC Guideline
247 might have had positive results for some patients, a central tenet of the 2016 CDC Guideline was that
248 the recommendations are voluntary and are intended to be flexible to support, not supplant,
249 individualized, patient-centered care. Of particular concern, some policies that were purportedly drawn
250 from the 2016 CDC Guideline have, in fact, been notably inconsistent with the 2016 CDC Guideline and
251 have gone well beyond its clinical recommendations (Dowell, Haegerich, & Chou, 2019; Kroenke et al.,
252 2019; U.S. Department of Health and Human Services, 2019b). Such misapplication includes extension of
253 the 2016 CDC Guideline to patient populations not covered in the 2016 CDC Guideline (e.g., cancer and
254 palliative care), opioid tapers and abrupt discontinuation without collaboration with patients, rigid
255 application of opioid dosage thresholds, application of the Guideline’s recommendations for opioid use
256 for pain to medications for opioid use disorder treatment (previously referred to as medication assisted
257 treatment), duration limits by insurers and by pharmacies, and patient dismissal and abandonment
258 (Dowell, Haegerich, et al., 2019; Kroenke et al., 2019; U.S. Food and Drug Administration, 2019c). These
259 actions are not consistent with the 2016 CDC Guideline and have contributed to patient harm, including
260 untreated and undertreated pain, serious withdrawal symptoms, worsening pain outcomes,
261 psychological distress, overdose, and suicidal ideation and behavior (Coffin et al., 2020; Demidenko et
262 al., 2017; Dowell, Haegerich, et al., 2019; Kroenke et al., 2019; Mark & Parish, 2019; U.S. Food and Drug
263 Administration, 2019c).

264 Rationale

265 New evidence on the risks and benefits of prescription opioids for both acute and chronic pain,
266 comparisons with nonopioid pain treatments, dosing strategies, opioid dose-response relationships, risk
267 mitigation strategies, and opioid tapering and discontinuation has emerged since release of the 2016
268 CDC Guideline (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al., December 2020;

269 McDonagh et al., April 2020; Skelly et al., April 2020). In particular, studies have been published on
270 misapplication of the 2016 CDC Guideline (Kroenke et al., 2019); benefits and risks of different tapering
271 strategies and rapid tapering associated with patient harm (K. S. Gordon et al., 2020; James et al., 2019;
272 Mark & Parish, 2019; U.S. Food and Drug Administration, 2019c); challenges in patient access to opioids
273 (U.S. Department of Health and Human Services, 2019b); patient abandonment and abrupt
274 discontinuation of opioids (U.S. Department of Health and Human Services, 2019b); a seminal
275 randomized clinical trial comparing prescription opioids to nonopioid medications on long-term pain
276 outcomes (E. E. Krebs et al., 2018); the association of characteristics of initial opioid prescriptions with
277 subsequent likelihood for long-term opioid use (Deyo et al., 2017; Shah, Hayes, & Martin, 2017); and
278 that many patients use a small proportion of opioids prescribed to them for postoperative pain (Hill,
279 McMahon, Stucke, & Barth, 2017; Hill, Stucke, McMahon, Beeman, & Barth, 2018; Howard, Waljee,
280 Brummett, Englesbe, & Lee, 2018).

281 Opioid prescribing has been declining since 2012, with the decline sharply accelerated after
282 release of the 2016 CDC Guideline; however, these medications remain a common treatment for pain. In
283 2015-2018, approximately 6% of U.S. adults reported use of one or more prescription opioids in the past
284 30 days (Hales, Martin, & Gu, 2020), and in 2020, approximately 143 million opioid prescriptions were
285 dispensed from pharmacies in the United States (Centers for Disease Control and Prevention, 2021c). In
286 addition, rates of opioid prescribing continue to vary across states, medical specialties, patient
287 demographics, and pain conditions in ways that cannot be explained by the underlying health status of
288 the population and are often discordant with the 2016 CDC Guideline recommendations (Guy & Zhang,
289 2018; Hill et al., 2017; Ly, 2019; Mikosz et al., 2020; Schieber et al., 2019). The prevalence of prescription
290 opioid misuse and opioid use disorder has also declined in recent years. Among people 12 and older in
291 the U.S. in 2019, 9.7 million reported misuse of prescription opioids in the past year (decreased from
292 12.5 million in 2015), and 1.4 million met criteria for a past-year prescription opioid use disorder

293 (decreased from 2.0 million in 2015) (Substance Abuse and Mental Health Services Administration,
294 2020); however, prescription opioids remain the most commonly misused prescription drug in the
295 United States in 2020 (Substance Abuse and Mental Health Services Administration, 2021a). Also in
296 2020, it is important to note that among those reporting misuse in the past year, 64.6% reported the
297 main reason for their most recent misuse was to “relieve physical pain” compared to 11.3% to “feel
298 good or get high” and 2.3% “because I am hooked or have to have it” (Substance Abuse and Mental
299 Health Services Administration, 2021a). Taken together, these factors underscore the need for an
300 updated clinical practice guideline on appropriate opioid prescribing and pain management.

301 This clinical practice guideline expands and updates the 2016 CDC Guideline for Prescribing
302 Opioids for Chronic Pain to provide evidence-based recommendations for the prescribing of opioid pain
303 medication for acute, subacute, and chronic pain by clinicians for outpatients aged ≥18 years outside of
304 sickle cell disease-related pain management, cancer pain treatment, palliative care, and end-of-life care.
305 This clinical practice guideline update leverages new data to expand content on prescription opioids for
306 acute and subacute pain throughout the recommendations. Importantly, the update also aims to clearly
307 delineate recommendations that apply to patients who are being considered for initial treatment with
308 prescription opioids and those who have already been receiving opioids as part of their ongoing pain
309 management treatment. CDC developed a draft clinical practice guideline based on five systematic
310 reviews of the best available evidence on the benefits and risks of prescription opioids, nonopioid
311 pharmacological treatments, and nonpharmacological treatments. As described in more detail below,
312 the draft clinical practice guideline was reviewed by an independent Federal Advisory Committee (CDC’s
313 Board of Scientific Counselors of the National Center for Injury Prevention and Control), peer reviewers,
314 and the public, and revised by CDC based on feedback from these reviews. In addition, insights from
315 patients, caregivers, and clinicians via conversations held in 2020 were incorporated during the clinical
316 practice guideline update.

317 This clinical practice guideline provides recommendations only. It does not replace clinical
318 judgment and individualized, patient-centered decision-making. The recommendations are based on
319 emerging evidence, including observational studies or randomized clinical trials with notable limitations,
320 and thus, when providing care, they should be considered in the context of the individual clinician-
321 patient relationship based on a shared understanding and a “whole-person approach” that considers
322 such factors as the patient’s physical and psychological functioning, support needs, expected health
323 outcomes and well-being, home environment, and home and work responsibilities. Flexibility for
324 clinicians and patients is paramount when making clinical treatment decisions based on individual
325 factors. The clinical practice guideline recommendations aim to improve communication between
326 clinicians and patients about the risks and benefits of prescription opioids and other pain treatment
327 strategies, improve the safety and effectiveness of pain treatment, improve pain, function, and quality
328 of life for people with pain, and reduce the risks associated with opioid pain treatment (including opioid
329 use disorder, overdose, and death) and with other pain treatment. Of utmost importance, this clinical
330 practice guideline provides voluntary clinical practice recommendations for clinicians that should not be
331 used as inflexible standards of care. The clinical practice guideline recommendations are also not
332 intended to be implemented as absolute limits of policy or practice across populations by organizations,
333 healthcare systems, or government entities.

334 **Scope and audience**

335 **This clinical practice guideline is intended for clinicians who are treating outpatients aged ≥18**
336 **years with acute (duration <1 month) pain, subacute (duration of 1-3 months) pain, or chronic**
337 **(duration of >3 months) pain outside of sickle cell disease-related pain management, cancer**
338 **treatment, palliative care, and end-of-life care. For the purposes of this clinical practice guideline,**
339 **“clinicians” refers to physicians, nurse practitioners, physician assistants, and oral health**

340 **practitioners. This clinical practice guideline update includes recommendations for primary care (e.g.,**
341 **internists, family physicians) and other (e.g., surgeons, emergency clinicians, occupational medicine**
342 **and physical medicine and rehabilitation clinicians, neurologists) clinicians (including physicians, nurse**
343 **practitioners, physician assistants, and oral health practitioners managing pain in outpatient settings.**
344 **Applicable settings include clinician offices, clinics, and urgent care centers. The recommendations do**
345 **not apply to inpatient care received while hospitalized or to care received while in an emergency**
346 **department or other observational setting from which a patient might be admitted to inpatient care**
347 **but do apply to prescribing for pain management upon discharge (from emergency departments,**
348 **hospitals, or other facilities).** As clinicians may work within team-based care, the recommendations
349 refer to and promote integrated pain management and collaborative working relationships with, for
350 example, behavioral health specialists, such as social workers or psychologists, and pharmacists.

351 In addition to updating recommendations based on new evidence regarding management of
352 chronic pain, this clinical practice guideline update is meant to assist clinicians in weighing benefits and
353 risks of prescribing opioid pain medication for painful acute conditions (e.g., low back pain, neck pain,
354 other musculoskeletal pain, neuropathic pain, dental pain, pain due to kidney stones, and acute episodic
355 migraines) and pain related to procedures (e.g., postoperative pain, pain from oral surgery). Several of
356 these indications were prioritized in 2020 by an ad hoc committee of the National Academies of
357 Sciences, Engineering, and Medicine (National Academies of Sciences Engineering and Medicine, 2020)
358 as those for which evidence-based clinical practice guidelines would help inform prescribing practices,
359 with the greatest potential impact on public health. The clinical practice guideline has additionally been
360 updated to include content on management of subacute painful conditions — when duration falls
361 between that typically considered acute (defined as <1 month in this clinical practice guideline) and
362 chronic (generally considered as >3 months). Note that the durations used to define acute, subacute,
363 and chronic pain might imply more specificity than is found in real-life patient experience, when pain

364 often gradually transitions from acute to chronic pain. These time-bound definitions are not meant to be
365 absolute, but instead to provide approximate guides to facilitate consideration and practical use of
366 recommendations by clinicians and patients.

367 The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain focused on recommendations
368 for primary care physicians. This clinical practice guideline expands the scope of the 2016 CDC Guideline
369 to additional clinicians. While primary care physicians prescribe approximately 37% of all opioid
370 prescriptions, other clinicians, including pain medicine clinicians (8.9%) and dentists (8.6%), account for
371 significant proportions of prescriptions. Pain medicine and physical medicine and rehabilitation clinicians
372 prescribe opioids at the highest rates, followed by orthopedic and family medicine clinicians (Guy &
373 Zhang, 2018). Thus, expanding the clinical practice guideline's scope to outpatient opioid prescribing can
374 provide evidence-based advice for many additional clinicians, including dentists and other oral health
375 providers, clinicians managing postoperative pain in outpatients, and clinicians providing pain
376 management for patients being discharged from emergency departments.

377 Many principles of pain management are similar whether or not the treating clinician is a pain
378 management specialist, and many of the recommendations might be relevant for pain management
379 specialists. In addition, many pain management specialists already follow principles outlined in this
380 clinical practice guideline. However, use by pain management specialists is not the focus of this clinical
381 practice guideline. Pain management specialists often have extensive training and expertise in pain
382 management modalities that other clinicians do not, and they might see patients with clinical situations
383 that are more complex, less prevalent, and not well-addressed by the available evidence; thus, the
384 balance of benefits and risks to patients might differ when the treating clinician is a pain management
385 specialist treating patients with complex pain conditions.

386 In addition, the recommendations address the use of opioid pain medication in certain special
387 populations (e.g., older adults and pregnant people) and in populations with conditions posing special
388 risks (e.g., a history of substance use disorder). The recommendations do not address the use of opioid
389 pain medication in children or adolescents aged <18 years. The available evidence concerning the
390 benefits and risks of long-term opioid therapy in children and adolescents remains limited, and few
391 opioid medications provide information in the labeling regarding safety and effectiveness in pediatric
392 patients. Guidelines and recommendations are available for pain management in children with sickle cell
393 disease (Brandow et al., 2020) and undergoing surgical procedures (Michigan Opioid Prescribing
394 Engagement Network), and for palliative care in adolescent and young adult patients with cancer
395 (National Comprehensive Cancer Network).

396 While some principles in this clinical practice guideline might be helpful in the management of
397 pain in sickle cell disease, cancer, palliative care, and end-of-life care, some recommendations might not
398 be relevant for patients with these conditions and receiving care in these settings. Thus, this clinical
399 practice guideline does not apply to patients experiencing pain associated with these conditions or
400 settings. Other guidelines more specifically address pain management for patients with these conditions
401 (Brandow et al., 2020; Denlinger, Sanft, & Armenian; National Comprehensive Cancer Network; Paice et
402 al., 2016; Swarm et al., 2019). This does not imply that any other types of pain are more or less worthy
403 of effective treatment – only that they are not covered by this clinical practice guideline. This clinical
404 practice guideline follows the Institute of Medicine’s definition of palliative care as care that provides
405 relief from pain and other symptoms, supports quality of life, and is focused on patients with serious
406 advanced illness (Committee on Approaching Death: Addressing Key End of Life Issues & Institute of
407 Medicine, 2015). Palliative care can begin early in the course of treatment for any serious illness that
408 requires advanced management of pain or other distressing symptoms (Committee on Approaching
409 Death: Addressing Key End of Life Issues & Institute of Medicine, 2015). End-of-life care is defined as

410 care for persons in hospice care and others with a terminal illness or at high risk of dying in the near
411 future in hospitals, receiving long-term services and supports (including institutional care, and home and
412 community-based services), or at home. This clinical practice guideline does not apply to patients
413 undergoing cancer treatment, palliative care, or end-of-life care because of the unique therapeutic
414 goals, ethical considerations, opportunities for medical supervision, and balance of risks and benefits
415 with opioid therapy in such care. Readers are referred to the National Comprehensive Cancer Network
416 (NCCN) Clinical Practice Guidelines in Oncology: Adult Cancer Pain (Swarm et al., 2019), NCCN Clinical
417 Practice Guidelines in Oncology: Survivorship (Denlinger et al.), and Management of Chronic Pain in
418 Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline (Paice et al.,
419 2016) for recommendations on pain management for patients with cancer and patients who have
420 survived cancer. In addition, given unique considerations in management of pain related to sickle cell
421 disease, which can change the balance of benefits and risks for the use of opioids, clinicians should refer
422 to specific guidelines for pain management for patients facing painful complications of sickle cell disease
423 and are referred to the American Society of Hematology 2020 Guidelines for Sickle Cell Disease:
424 Management of Acute and Chronic pain (Brandow et al., 2020). In 2018, the National Comprehensive
425 Cancer Network and the American Society of Clinical Oncology convened and led a meeting including
426 representatives and guideline authors from the National Comprehensive Cancer Network, American
427 Society of Clinical Oncology, American Society of Hematology, and Centers for Disease Control and
428 Prevention to review existing pain management guidelines (Denlinger et al.; Dowell et al., 2016; Paice et
429 al., 2016; Swarm et al., 2019) and guidelines then in development (Brandow et al., 2020) from these
430 organizations. Meeting participants noted that these guidelines applied to different patient populations
431 and target audiences, but found no disagreement among recommendations when applied to the
432 appropriate patient and clinical situation (Schatz et al., 2020).

433 While this clinical practice guideline update includes content on pain management for patients
434 with opioid use disorder, and one recommendation focuses on management of opioid use disorder as a
435 complication of opioid use, recommendations on opioids used specifically as medications for opioid use
436 disorder are not the focus of this clinical practice guideline. Readers are referred to *The ASAM National*
437 *Practice Guideline for the Treatment of Opioid Use Disorder: 2020 Focused Update* (American Society of
438 Addiction Medicine, 2020) for more detailed recommendations on management of patients with opioid
439 use disorder.



440 **Methods for clinical practice guideline development**

441 **Methods for conducting systematic reviews**

442 **Sources of evidence**

443 The 2016 CDC Guideline was based on a systematic clinical evidence review sponsored by AHRQ
444 on the effectiveness and risks of long-term opioid therapy for chronic pain (Chou et al., September 2014;
445 Chou et al., 2015), supplemented by a CDC update to the AHRQ-sponsored review and additional
446 contextual questions (Dowell et al., 2016). The AHRQ-sponsored systematic review addressed the
447 effectiveness of long-term opioid therapy for outcomes related to pain, function, and quality of life; the
448 comparative effectiveness of different methods for initiating and titrating opioids; the harms and
449 adverse events associated with opioids; and the accuracy of risk-prediction instruments and
450 effectiveness of risk mitigation strategies on outcomes related to overdose, opioid use disorder, illicit
451 drug use, and/or prescription opioid misuse. The CDC update to the AHRQ-sponsored review included
452 more recently published literature (published during or after 2015) and an additional question on the
453 association between opioid therapy for acute pain and long-term use. The contextual evidence review
454 addressed effectiveness of nonpharmacologic and nonopioid pharmacologic treatments, clinician and
455 patient values and preferences, and information regarding resource allocation.

456 For this CDC update to the 2016 CDC Guideline, CDC funded AHRQ in 2018 and 2019 to conduct
457 five systematic reviews (Chou et al., April 2020; Chou et al., December 2020; Halker Singh et al.,
458 December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). AHRQ’s Evidence-based Practice
459 Centers completed these reviews, which include new evidence related to the treatment of chronic and
460 acute pain. The AHRQ review of opioids for chronic pain updated the evidence addressed in the prior
461 (2016) CDC review and expanded upon it, by including studies on shorter term (1 to 12 month)
462 outcomes of therapy involving opioids, effects of opioid plus nonopioid combination therapy, effects of
463 tramadol, effects of naloxone co-prescription, risks of co-prescribed benzodiazepines, risks of co-
464 prescribed gabapentinoids, and effects of concurrent use of cannabis (Chou et al., April 2020). The
465 systematic clinical evidence review on opioids for chronic pain (Chou et al., April 2020) also included
466 Contextual Questions on clinician and patient values and preferences and costs and cost-effectiveness of
467 opioid therapy and risk mitigation strategies. In addition, CDC used four new, complementary AHRQ
468 reviews on the benefits and harms of nonpharmacologic treatments for chronic pain (Skelly et al., April
469 2020), nonopioid pharmacologic treatments for chronic pain (McDonagh et al., April 2020), treatments
470 for acute episodic migraine (Halker Singh et al., December 2020), and treatment for acute (non-
471 migraine) pain (Chou et al., December 2020). A question on management of acute pain in the 2016 CDC
472 review on opioids for chronic pain was moved to the new review on therapies for acute pain (Chou et
473 al., December 2020). CDC also reviewed AHRQ-sponsored surveillance reports conducted in follow-up to
474 the five systematic reviews for any new evidence that could potentially change systematic review
475 conclusions (Chou R et al., 2022). To supplement the clinical evidence reviews, CDC sponsored a
476 contextual evidence review on clinician and patient values and preferences and resource allocation
477 (costs) for the areas addressed in the four new reviews (Chou et al., December 2020; Halker Singh et al.,
478 December 2020; McDonagh et al., April 2020; Skelly et al., April 2020).

479 **Primary clinical questions guiding the systematic reviews**

480 Across reviews, the main outcomes were pain, function, and quality of life. Harms varied
481 depending on the therapy evaluated but included serious adverse events when reported; for opioids,
482 key harms included overdose and harms related to opioid use disorder. The reviews of therapies for
483 chronic pain assessed outcomes at short- (1 to <6 months), intermediate- (6 to <12 months), and long-
484 term follow-up (≥ 12 months). The reviews of therapies for acute pain assessed outcomes at < 1 day; 1
485 day to <1 week; 1 week to <2 weeks; and 2 weeks to 4 weeks; the review of treatments for acute non-
486 migraine pain also evaluated outcomes at ≥ 4 weeks. All reviews included key questions (KQs) or sub-
487 questions on how benefits and harms varied according to demographic (age, sex, race), clinical (severity
488 and duration of pain, medical and psychiatric comorbidities, concomitant medications), and intervention
489 (dose, duration, intensity) characteristics.

490 The systematic clinical evidence reviews addressed questions in the following topic areas
491 (details including questions available in the full AHRQ reports [Chou et al., April 2020; Chou et al.,
492 December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April
493 2020]):

494 **Opioids for chronic pain**

- 495 • The effectiveness and comparative effectiveness (benefits, [KQ] 1 and harms, [KQ 2]) of
496 long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy.
- 497 • The comparative effectiveness of various opioid dosing strategies (KQ3):
 - 498 ○ Different methods for initiating and titrating opioids
 - 499 ○ Short-acting versus long-acting/extended-release opioids
 - 500 ○ Different long-acting opioids
 - 501 ○ Short- plus long-acting versus long-acting opioid alone

- 502 ○ Scheduled, continuous versus as-needed dosing
- 503 ○ Opioid dose escalation versus dose maintenance or use of dose thresholds
- 504 ○ Opioid rotation versus maintenance
- 505 ○ Different strategies for treating acute exacerbations of chronic pain
- 506 ○ Decreasing opioid doses or tapering off opioids versus continuation of opioids
- 507 ○ Different tapering protocols and strategies
- 508 ○ Different opioid dosages and durations of therapy
- 509 • The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or
- 510 misuse; the effectiveness of risk prediction instruments; the effectiveness of various risk
- 511 mitigation strategies; and comparative effectiveness of strategies for managing patients
- 512 with opioid use disorder (KQ 4). The risk mitigation strategies are:
- 513 ○ Opioid management plans
- 514 ○ Patient education
- 515 ○ Urine drug screening
- 516 ○ Use of prescription drug monitoring program (PDMP) data
- 517 ○ Use of monitoring instruments in patients prescribed opioids
- 518 ○ More frequent monitoring intervals
- 519 ○ Pill counts
- 520 ○ Use of abuse-deterrent formulations

- 521 ○ Consultation with mental health specialists when mental health conditions are
- 522 present or suspected
- 523 ○ Avoidance of co-prescribing of sedative hypnotics
- 524 ○ Co-prescribing of naloxone

525 **Noninvasive nonpharmacological treatments for chronic pain**

- 526 • The effectiveness and comparative effectiveness (benefits and harms) of noninvasive
- 527 nonpharmacological treatments (exercise, mind-body practices, psychological
- 528 interventions, multidisciplinary rehabilitation, mindfulness practices, musculoskeletal
- 529 manipulation, physical modalities, and acupuncture) versus inactive treatments, usual
- 530 care, no treatment, pharmacological therapy, or selected active treatments (exercise
- 531 [chronic pain conditions other than headache] or biofeedback [headache]), for the
- 532 following conditions:

- 533 ○ Chronic low back pain (KQ 1)
- 534 ○ Chronic neck pain (KQ 2)
- 535 ○ Osteoarthritis (knee, hip, hand) (KQ 3)
- 536 ○ Fibromyalgia (KQ 4)
- 537 ○ Chronic tension headache (KQ 5)

538 **Nonopioid pharmacologic treatments for chronic pain**

- 539 • Effectiveness and comparative effectiveness (benefits [KQ 1] and harms [KQ 2]) of
- 540 nonopioid pharmacologic agents (non-steroidal anti-inflammatory drugs [NSAIDs],
- 541 antidepressants, anticonvulsants, acetaminophen, muscle relaxants, memantine, topical
- 542 agents, and cannabis) versus placebo or other nonopioid pharmacologic agents.

543 **Treatments for acute pain**

544 • Effectiveness and comparative effectiveness (benefits and harms) of opioid therapy
545 versus nonopioid pharmacologic therapy (acetaminophen, NSAIDs, skeletal muscle
546 relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabis) or
547 nonpharmacologic therapy (exercise, cognitive behavioral therapy, meditation,
548 relaxation, music therapy, virtual reality, acupuncture, massage,
549 manipulation/mobilization, physical modalities); nonopioid pharmacologic therapy
550 versus other nonopioid pharmacologic treatments or nonpharmacologic therapy; and
551 nonpharmacologic therapy versus inactive treatments or usual care, for the following
552 conditions:

- 553 ○ Acute back pain (including back pain with radiculopathy) (KQ 1)
- 554 ○ Acute neck pain (including neck pain with radiculopathy) (KQ 2)
- 555 ○ Musculoskeletal pain not otherwise included in KQ 1 or KQ 2 (including
556 fractures) (KQ 3)
- 557 ○ Peripheral neuropathic pain (related to herpes zoster and trigeminal neuralgia)
558 (KQ 4)
- 559 ○ Postoperative pain (excluding inpatient management of pain following major
560 surgical procedures) (KQ 5)
- 561 ○ Dental pain (KQ 6)
- 562 ○ Kidney stones (including inpatient management) (KQ 7)
- 563 ○ Sickle cell crisis (episodic pain) (KQ 8)

564 **Treatments for acute episodic migraine**

565 • Effectiveness and comparative effectiveness (benefits and harms) of:

- 566 ○ Opioid therapy versus nonopioid pharmacologic therapy (acetaminophen,
567 NSAIDs, triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-
568 nausea medications, cannabis, or others [e.g., gepants]) or nonpharmacologic
569 therapy (exercise, cognitive behavioral therapy, acupuncture, or others) (KQ 1)
- 570 ○ Nonopioid pharmacologic therapy versus a different nonopioid pharmacologic
571 therapy or nonpharmacologic therapy (KQ 2)
- 572 ○ Nonpharmacologic therapy versus inactive treatments, usual care, or no
573 treatment (KQ 3)



574
575 **Search protocols**

576 Complete methods and data, including detailed search protocols and inclusion and exclusion
577 criteria, for the five AHRQ reports summarized here have been published (Chou et al., April 2020; Chou
578 et al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al.,
579 April 2020). Briefly, study authors developed the search protocols using a standardized process with
580 input from experts and the public. The review protocols were submitted for registration in the
581 PROSPERO database prior to conducting the reviews. For each review, research librarians conducted
582 searches on multiple electronic databases. For all reviews, searches were conducted on MEDLINE,
583 Cochrane CENTRAL, and the Cochrane Database of Systematic Reviews; other databases that were
584 utilized for one or more reviews (depending on the topic) were Embase PsycINFO, CINAHL, Scopus, and
585 others. The searches were supplemented by a review of reference lists (including prior AHRQ and CDC
586 reviews on these topics) (Chou et al., September 2014; Dowell et al., 2016; Skelly et al., 2018) and gray
587 literature sources. Searches were conducted in August or September 2019 for the chronic pain reviews
588 and in July or August 2020 for the acute pain reviews.

589

Summarizing the evidence

590 The reviews categorized magnitude of effects for pain and function using the same system as
591 prior AHRQ reviews (Chou et al., 2017; Skelly et al., 2018). A small effect was defined for pain as a mean
592 between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating
593 scale (NRS) or visual analog scale (VAS) and for function as a standardized mean difference (SMD) of 0.2
594 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI)
595 (Fairbank & Pynsent, 2000), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire
596 (RDQ) (Roland & Morris, 1983), or equivalent. A moderate effect was defined for pain as a mean
597 difference of 10 to 20 points on a 0- to 100-point VAS (1 to 2 points on a 0- to 10-point NRS) and for
598 function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the
599 RDQ, or equivalent (Chou et al., 2017; Skelly et al., 2018). Large/substantial effects were defined as
600 greater than moderate. We applied similar thresholds to other outcomes measured. Small effects using
601 this system may not meet proposed thresholds for clinically meaningful effects (Ostelo et al., 2008).
602 However, there is variability in estimated minimum clinically important differences across studies, and
603 the clinical relevance of effects classified as small might vary for individual patients depending on
604 preferences, baseline symptom severity, harms, cost, and other factors (Jayadevappa, Cook, & Chhatre,
605 2017; Keurentjes, Van Tol, Fiocco, Schoones, & Nelissen, 2012). The reviews also evaluated results based
606 on dichotomous outcomes (e.g., likelihood of experiencing clinically meaningful improvement in pain or
607 function, often defined as >30% or >50% improvement from baseline).

608

Evaluating quality of the evidence: the AHRQ method

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The reviews used the AHRQ approach to synthesize and grade the strength of evidence
(Berkman et al., 2015). The AHRQ approach is based on a systematic review of the evidence and
provides an overall strength of evidence indicating the level of certainty (high, moderate, low, or

614 insufficient), based on similar factors considered in the CDC Advisory Committee on Immunization
615 Practices (ACIP) adapted (Ahmed, Temte, Campos-Outcalt, & Schünemann, 2011; G. Lee & Carr, 2018)
616 GRADE (Guyatt et al., 2008) approach (study limitations/risk of bias, consistency, directness, precision,
617 reporting bias, and other factors [large strength of association, dose response, and plausible
618 confounders strengthening observed findings]).

619 **Evaluating the quality of the evidence: the ACIP-adapted GRADE method**

620
621 Predicated on a systematic review of scientific evidence, the GRADE approach provides a
622 transparent framework for grading the quality of evidence and strength of recommendations based on
623 the evidence. GRADE has been adapted by the ACIP, (Ahmed et al., 2011; G. Lee & Carr, 2018) and CDC
624 used the ACIP adaptation of the GRADE framework in this clinical practice guideline. Applying the ACIP
625 GRADE framework, each body of evidence is initially categorized using a hierarchy that reflects the
626 degree of confidence in the effect of a clinical action on health outcomes. The categories in the
627 hierarchy ([Box 2](#)) are: type 1 evidence (randomized clinical trials or overwhelming evidence from
628 observational studies), type 2 evidence (randomized clinical trials with important limitations, or
629 exceptionally strong evidence from observational studies), type 3 evidence (observational studies or
630 randomized clinical trials with notable limitations), and type 4 evidence (clinical experience and
631 observations, observational studies with important limitations, or randomized clinical trials with several
632 major limitations). The evidence is downgraded if issues are identified with regard to risk of bias,
633 inconsistency, indirectness, imprecision, or publication bias; observational studies may be upgraded in
634 certain situations (large strength of association, presence of dose response, or plausible effects of
635 confounding would strengthen findings). That is, if it is likely that confounding would provide results
636 opposite to the observed findings, it strengthens the confidence that the observed association is
637 present. Based on these considerations, a final evidence type is assigned. Type 1 evidence indicates high
638 confidence that the true effect is close to the estimate of the effect; type 2 evidence means that the

639 true effect is likely to be close to the estimate of the effect, but there is some uncertainty; type 3
640 evidence means that confidence in the effect estimate is limited (moderate uncertainty), and the true
641 effect could differ substantially from the estimate of the effect; and type 4 evidence indicates that one
642 has very little confidence in the effect estimate (high uncertainty), and the likelihood that the true effect
643 differs from the estimate of the effect is high (Ahmed et al., 2011; Balshem et al., 2011). When no
644 studies are available or the evidence is too limited to estimate effects, evidence is considered
645 insufficient.

646 **Evaluating the quality of the evidence: converting the AHRQ quality rating to the ACIP-adapted GRADE** 647 **rating** 648

649 The AHRQ approach uses a different method and terminology (high, moderate, low, or
650 insufficient) to grade the strength of evidence (SOE) than the ACIP-adapted GRADE approach (evidence
651 types 1, 2, 3, or 4) (Berkman et al., 2015). However, the underlying principles are similar, enabling
652 translation from the AHRQ to CDC grades. A methodologist translated the AHRQ strength of evidence
653 grades to CDC evidence types based on the information provided in the summary of evidence tables in
654 the AHRQ reviews. Tables with GRADE clinical evidence review ratings of the evidence for the key clinical
655 questions are available (<http://stacks.cdc.gov/XXXXX> link TBD). Evidence was categorized into the
656 following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies;
657 generally equivalent to AHRQ high strength of evidence), type 2 (randomized clinical trials with
658 important limitations, or exceptionally strong evidence from observational studies; generally equivalent
659 to AHRQ moderate strength of evidence), type 3 (observational studies, or randomized clinical trials with
660 notable limitations; generally equivalent to most AHRQ low strength of evidence ratings), or type 4
661 (clinical experience and observations, observational studies with important limitations, or randomized
662 clinical trials with several major limitations; equivalent to AHRQ low strength of evidence with serious
663 limitations). When no studies were available or the evidence was too limited to estimate effects,

664 evidence was assessed as insufficient. Results from meta-analyses conducted for the AHRQ reviews
665 were reported when available; otherwise, the evidence was synthesized qualitatively.

666 **Methods to develop the recommendations**

667 CDC developed this clinical practice guideline using the approach developed by the GRADE
668 working group (<https://www.gradeworkinggroup.org/>). Recommendations are based on the reviewed
669 evidence. In the ACIP adapted GRADE framework, recommendations are assigned one of two categories
670 (category A or B). Four major factors determine the category of the recommendation: the quality of
671 evidence, the balance between desirable and undesirable effects, values and preferences, and resource
672 allocation (e.g., costs to patients or health systems) (Andrews et al., 2013). Other considerations include
673 feasibility and acceptability, and impact on equity (Welch et al., 2017). Recommendations are more
674 likely to be category A when the evidence is higher quality, there is a greater balance of desirable
675 relative to undesirable effects, resources and costs are lower, and when recommendations are less
676 sensitive to differences in values and preferences. Category A recommendations generally apply to all
677 persons in the group addressed in the recommendation and indicate a course of action that can be
678 followed in most circumstances. Category B recommendations indicate that the recommendation may
679 not apply to all persons in the group addressed in the recommendation; therefore, different choices will
680 be appropriate for different patients and decisions should be individualized based on the individual
681 patient's circumstances. For category B recommendations, clinicians must help patients arrive at a
682 decision consistent with patient values and preferences, and specific clinical situations (shared decision-
683 making) (Ahmed, 2013). In the GRADE approach, a particular quality of evidence does not necessarily
684 result in a particular strength of recommendation (Andrews et al., 2013; Balshem et al., 2011; Guyatt et
685 al., 2008). Although it is desirable for category A recommendations to be based on type 1 or type 2
686 evidence, category A recommendations can be made based on type 3 or type 4 evidence when the
687 advantages of a clinical action are assessed as clearly outweighing the disadvantages based on a

688 consideration of benefits and harms, values and preferences, and costs, despite uncertainty in effect
689 estimates (Andrews et al., 2013). The GRADE Working Group has presented several “paradigmatic”
690 situations in which strong (category A) recommendations may be justified despite low quality evidence,
691 for example, when high quality evidence suggests equivalence of two alternatives and low quality
692 evidence suggests harm in one alternative, or when high quality evidence suggests modest benefits and
693 low/very low quality evidence suggests possibility of catastrophic harm (Andrews et al., 2013). Category
694 B recommendations are made when the advantages and disadvantages of a clinical action are more
695 balanced or when there is more uncertainty with regard to whether benefits clearly outweigh harms.

696 In accordance with the ACIP adapted GRADE process, CDC drafted recommendations based on
697 the clinical and contextual evidence (including benefits and harms, values and preferences, resource
698 allocation). Draft recommendations focused on determining whether or not to initiate opioids for pain;
699 opioid selection and dosage; opioid duration and follow-up; and assessing risk and addressing potential
700 harms of opioid use. To help assure the draft guideline’s integrity and credibility, CDC then began a
701 multistep review process described in detail below.

Federal Advisory Committee review and recommendation

702 CDC sought recommendations on the draft updated clinical practice guideline from one of its
703 federal advisory committees, the Board of Scientific Counselors of the National Center for Injury
704 Prevention and Control (BSC/NCIPC). The BSC/NCIPC advises the Secretary of the Department of Health
705 and Human Services (HHS), the Director of CDC, and the Director of NCIPC, and makes recommendations
706 regarding scientific, programmatic, and research policies, strategies, objectives, projects, and priorities.
707 The BSC/NCIPC also reviews progress toward injury and violence prevention. BSC/NCIPC members are
708 special government employees appointed by the Secretary, HHS, or their designee, as CDC advisory
709 committee members. Members are required to complete the Office of Government Ethics Form 450
710

711 annually to disclose relevant interests and report on their disclosures during meetings. Disclosures for
712 the BSC/NCIPC are reported in this clinical practice guideline.

713 On December 4-5, 2019, CDC held a public meeting of the BSC/NCIPC (announced via *Federal*
714 *Register* 84 FR 57021; 84 FR 65159) and provided a presentation on the background for updating the
715 clinical practice guideline. CDC then requested the formation of an Opioid Workgroup (OWG), under the
716 parent BSC, whose primary purpose would be to review a draft updated clinical practice guideline and to
717 develop a report of their observations for the BSC/NCIPC (Centers for Disease Control and Prevention,
718 2021a). After considering CDC's presentations, the proposed OWG Terms of Reference, and public
719 comments, the BSC/NCIPC voted unanimously to establish an OWG that reports to the BSC/NCIPC. CDC
720 then held a public nomination process for prospective OWG members (Centers for Disease Control and
721 Prevention, 2021a).

722 To provide background to the BSC/NCIPC for informing the creation of the OWG with a balance
723 of perspectives, CDC identified audiences that would be: 1) directly affected by the clinical practice
724 guideline, 2) directly involved with implementing or integrating recommendations into current practice,
725 and 3) qualified to represent a specific discipline or expertise in alignment with the tasks of the
726 workgroup for consideration by the BSC/NCIPC. Identified groups with perspectives that would support
727 the workgroup's capacity included, but were not limited to, patients living with pain, family members
728 and caregivers, clinicians, public health practitioners, and research scientists. CDC announced the call for
729 nominations at the December 4-5, 2019, public meeting and heard recommendations from the public
730 during the public comment opportunities, as well as from BSC/NCIPC members regarding
731 recommendations for nominations. People interested in being considered for the workgroup were
732 encouraged to submit self-nominations from December 4, 2019, through February 4, 2020. CDC's
733 BSC/NCIPC received 255 nominations for the OWG.

734 After carefully reviewing clinical expertise, professional credentials, and diversity in perspectives
735 of all nominees (including sex, race/ethnicity, geographic region, institutional affiliations, and personal
736 experiences relevant to pain management and caring for patients with pain), the OWG's Designated
737 Federal Officer (DFO) created a list of prospective workgroup members and sent invitations to
738 participate along with conflict-of-interest disclosure forms. The OWG's DFO and the BSC/NCIPC's DFO
739 reviewed conflict of interest disclosure forms. CDC's Strategic Business Initiatives Unit (SBIU), which
740 oversees the Federal Advisory Committee Act program, also reviewed the OWG Terms of Reference,
741 prospective OWG roster, curricula vitae, and conflict of interest disclosure forms and determined all
742 reported financial or other conflicts of interest were not present or non-significant before finalizing
743 selection. OWG members disclosed any potential topical conflicts of interest related to OWG meeting
744 agenda items prior to each meeting. Disclosures of the OWG are reported in the clinical practice
745 guideline.

746 The OWG had 23 members (Centers for Disease Control and Prevention, 2020d). In accordance
747 with CDC guidance (Centers for Disease Control and Prevention, 2008, 2020c) that at least two
748 BSC/NCIPC members must serve on the OWG, and one of the two members must serve as the
749 workgroup chair, the OWG included a total of three BSC/NCIPC members, with one BSC/NCIPC member
750 serving as the OWG chair. A NCIPC subject matter expert served as the OWG's DFO. OWG members
751 included patients with pain, caregivers, and family members of patients with pain. The OWG also
752 comprised clinicians and subject matter experts, with the following perspectives represented: primary
753 care, pain medicine, public health, behavioral health, pharmacy, emergency medicine, medical
754 toxicology, obstetrics/gynecology, bioethics, orthopedic surgery, plastic surgery, dentistry, sickle cell
755 disease, substance use disorder treatment, and research. OWG members were diverse in regard to sex,
756 race/ethnicity, geographic region, institutional affiliation, subject matter expertise, and personal

757 experiences. The CDC NCIPC OWG DFO presented the OWG roster and reviewed the Terms of Reference
758 at the publicly held BSC/NCIPC meeting on July 22, 2020 (*Federal Register* 85 FR 30709; 85 FR 40290).

759 The OWG had a total of 11 meetings from October 2020 through June 2021. Before receiving
760 the draft updated clinical practice guideline, the OWG held meetings to review and discuss the 2016 CDC
761 Guideline, CDC's community engagement activities with patients, caregivers, and clinicians, and GRADE
762 methodology. CDC NCIPC staff provided the OWG with the evidence reviews, public comments from
763 BSC/NCIPC meetings, and summaries of community engagements for review before providing the OWG
764 with the draft updated clinical practice guideline in March 2021. The OWG held 7 meetings to review
765 and discuss the draft clinical practice guideline and develop a report summarizing their expert
766 observations and findings for the BSC/NCIPC. The OWG report (BSC/NCIPC Opioid Workgroup Members,
767 2021) provided overall observations on overarching themes and draft clinical practice guideline
768 recommendations. In addition, many members of the OWG developed a document entitled *OWG*
769 *Guiding Principles* that was included as an appendix in the OWG report; this document outlines the
770 "general process and principles by which the OWG approached their assigned tasks." These *Guiding*
771 *Principles* included: minimize bias, scientific integrity, enhance inclusivity, patient and clinician centered,
772 and historical context.

773 The OWG chair presented the OWG report at a public BSC/NCIPC meeting held on July 16, 2021
774 (*Federal Register* 86 FR 30048). After hearing additional CDC presentations on the process and progress
775 of the draft clinical practice guideline, discussion of the OWG report, and a two-hour public comment
776 period, the BSC/NCIPC voted unanimously that CDC adopt the OWG report, while considering ideas and
777 suggestions raised by the BSC/NCIPC and public during the meeting, and that the OWG's work be
778 considered complete and the OWG sunsetted. After the meeting, the BSC/NCIPC provided their
779 recommendations to HHS and CDC. CDC carefully considered the OWG's observations, BSC/NCIPC
780 recommendations, and public comments when revising the draft updated clinical practice guideline.

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Federal partner engagement

The BSC/NCIPC invited federal partners to serve as ex-officio members of the OWG, which comprised representatives from the National Institute on Drug Abuse (NIDA) at the National Institutes of Health (NIH), the Substance Abuse and Mental Health Services Administration (SAMHSA), FDA, and the Indian Health Service (IHS). The BSC/NCIPC comprised ex-officio members from the Administration for Children and Families, the Administration on Aging in the Administration for Community Living, the National Institute for Occupational Safety and Health and the National Center for Health Statistics at the CDC, the Health Resources and Services Administration, IHS, SAMHSA, and the National Institute on Aging, the National Institute of Child Health and Human Development, NIDA, and the National Institute of Mental Health at the NIH. Additional federal partners were engaged throughout the clinical practice guideline update process. Federal partners reviewed the full draft clinical practice guideline as part of CDC’s agency clearance process.

Public comment and community engagement

CDC garnered input through *Federal Register* notices to better understand community members’ lived experiences and perspectives related to pain and pain management options before drafting the updated clinical practice guideline. Through the *Federal Register* notice (85 FR 21441) posted from April 17, 2020, through June 16, 2020, CDC invited input specifically on topics focused on using or prescribing opioid pain medications, nonopioid medications, or nonpharmacological treatments and received 5,392 public comments. Public comments were synthesized into common themes, utilizing a CDC-funded analysis contract.

In addition, the Lab at the US Office of Personnel Management (OPM) worked with CDC to design and implement community engagement opportunities to gain additional insight into the values and preferences of patients, caregivers, and clinicians. For these opportunities, key groups included patients with acute or chronic pain, patients’ family members and/or caregivers, and clinicians who care

805 for patients with pain or conditions that can complicate pain management (e.g., opioid use disorder or
806 overdose).

807 CDC planned to have individual conversations with patients, caregivers, and clinicians in person
808 but pivoted to holding conversations with individuals in a virtual format due to the COVID-19 pandemic.
809 CDC posted a companion *Federal Register* notice (85 FR 44303) from July 22, 2020, through August 21,
810 2020, to solicit input from patients, caregivers, and clinicians interested in participating in individual
811 conversations. After the *Federal Register* notice closed, CDC and OPM randomly selected participants
812 within each group (i.e., patients, caregivers, clinicians) from a total of 973 respondents. They also
813 developed a randomly-selected waitlist of participants that they used to fill conversation appointments
814 that were missed or cancelled by participants. The community engagement was authorized under the
815 Generic Clearance for the Collection of Qualitative Feedback on Agency Service Delivery (OMB Control
816 Number: 0920-1050) approval for the Paperwork Reduction Act. CDC and OPM conducted telephone
817 and video conversations throughout September 2020 and spoke with 106 individuals, which included 42
818 patients, 21 caregivers, and 43 clinicians. Participating individuals lived and worked all over the United
819 States and had diverse experiences with opioids. Participants provided verbal consent for their
820 conversations to be recorded. A transcription service reviewed the conversation recordings to develop
821 anonymized transcripts. CDC and OPM reviewed the anonymized transcripts to develop thematic
822 summaries.

823 CDC and OPM also held two human-centered co-design workshops with staff from CDC and
824 Centers for Medicare and Medicaid Services (CMS). Workshop topics included framing priority needs for
825 public input, objectives for individual conversations, and synthesizing engagement strategies based on
826 insights from public comments and conversations with patients, caregivers, and clinicians. Workshop
827 participants included patients, caregivers, clinicians, clinical practice guideline authors, and other subject
828 matter experts.

829 CDC also garnered input through oral and written public comment opportunities at and in
830 conjunction with public BSC/NCIPC meetings. These public comment opportunities were announced
831 through Federal Register notices (*Federal Register* 84 FR 57021; 84 FR 65159; 85 FR 30709; 85 FR 40290;
832 86 FR 1502; 86 FR 30048) and partner newsletters.

833 CDC reviewed thematic summaries of public comments, individual conversations, and the
834 workshops to learn more about the values and preferences of patients, caregivers, clinicians, and
835 experts before drafting the updated clinical practice guideline. After incorporating observations and
836 comments on the draft clinical practice guideline from the BSC/NCIPC and agency clearance process,
837 CDC will post the revised full draft clinical practice guideline in the Federal Register for public comment.
838 The public comment period is anticipated to be open for 60 days. CDC will review and carefully consider
839 all comments when revising the updated clinical practice guideline.

840 **Peer review**

841 This clinical practice guideline provides influential scientific information that could have a clear
842 and substantial impact on public- and private-sector decisions. Therefore, peer review of the draft
843 clinical practice guideline is required per the final information quality bulletin for peer review
844 (<https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf>).

845 **Note: at the time of developing this revision of the draft updated clinical practice guideline, the**
846 **peer review process is ongoing. This information will be updated once peer review is complete.**

847 CDC selected peer reviewers based on scientific and subject-matter expertise, racial/ethnic
848 diversity, diversity of experiences and perspectives, independence from the clinical practice guideline
849 development process, and consideration of conflicts of interest. Specific effort was made to identify
850 subject matter experts with knowledge and experience in topics such as chronic and acute pain
851 management; clinical practice; health equity; mental health and well-being; opioids and opioid
852 therapies; opioid tapering; opioid use disorder treatment; pharmacological and non-pharmacological

853 pain management; and surgical pain management. CDC assessed potential conflicts of interest with the
854 same conflict of interest disclosure form used for selection of BSC/NCIPC OWG members. Conflict of
855 interest forms will be reviewed by the NCIPC Associate Director for Science and confirmed by SBIU
856 before finalizing selection. Any disclosures of the peer reviewers will be reported in the final published
857 clinical practice guideline. After the peer reviewers have completed their reviews, CDC will post the
858 names of peer reviewers on the CDC and the NCIPC Peer Review Agenda websites that are used to
859 provide information about the peer review of influential government scientific documents. Peer
860 reviewers will independently review the draft clinical practice guideline to determine the
861 reasonableness and strength of recommendations; the clarity with which scientific uncertainties were
862 clearly identified; and the rationale, importance, clarity, and ease of implementation of the
863 recommendations. CDC will review and carefully consider peer review comments when revising the
864 draft clinical practice guideline.

866 **Summary of findings for clinical questions**

867 **Opioids for chronic pain**

868 The AHRQ systematic clinical evidence review on opioids for chronic pain (Chou et al., April
869 2020) updated the 2014 AHRQ report (Chou et al., September 2014) and 2016 CDC update (Dowell et al.,
870 2016) and expanded upon the prior reviews by adding evidence from randomized trials reporting short-
871 term outcomes, including tramadol as an opioid intervention, addressing risks of co-prescribing
872 benzodiazepines or gabapentin, and addressing effects of co-use of cannabis.

873 **Effectiveness (benefits and harms)**

874 For short-term (1 to <6 month) outcomes, based on over 70 placebo-controlled trials (evidence
875 type 1), opioids were associated with beneficial effects versus placebo, but mean differences were

876 small: for pain, <1 point on a 0 to 10 scale and for function, a SMD of 0.22 (or <1 point on the 0 to 10
877 Brief Pain Inventory [BPI]) (Cleeland & Ryan, 1994) interference scale and <1 point on the 0 to 24
878 Roland-Morris Disability Questionnaire [RDQ]). Opioids were associated with a number of patients
879 needed to treat (NNT) of approximately 6.7 to achieve one additional case of short-term pain relief (e.g.,
880 $\geq 30\%$ improvement in pain). Analyses based on a combination of head-to-head (within study)
881 comparisons as well as a meta-regression of placebo-controlled trials indicated an association between
882 higher opioid dose and greater short-term effects on pain which appeared to plateau at around 50 mg
883 morphine equivalent dose (MME)/day (evidence type 2). Evidence also indicated that effects of opioids
884 dissipate with longer duration of therapy. Opioids were associated with a small mean improvement in
885 short-term sleep quality (evidence type 2) versus placebo and a small mean short-term improvement in
886 Short-Form 36-item (SF-36) (Ware & Sherbourne, 1992) mental health status (evidence type 1). Effects
887 of opioids on short-term outcomes were generally consistent across opioid types (opioid agonist, partial
888 agonist, or mixed medication agent). Effects on pain were somewhat greater for neuropathic than
889 musculoskeletal pain (effects on pain about 0.5 point greater for neuropathic versus musculoskeletal
890 pain on a 0 to 10 scale). Use of a crossover or enriched enrollment randomized withdrawal (EERW)
891 design (a type of trial in which potential participants receive the study drug for a period of time in a
892 prerandomization phase, and only those who benefit from the drug and can tolerate the side effects
893 continue in the trial, randomly assigned to continue on the study drug or placebo [Furlan, Chaparro,
894 Irvin, & Mailis-Gagnon, 2011]) was associated with greater effects on pain than parallel group or non-
895 EERW studies.

896 Opioids were associated with increased risk versus placebo of discontinuation due to adverse
897 events (number of patients treated to cause one adverse event [number needed to harm, NNH 10], and
898 increased risk of gastrointestinal events [NNH 7.1 for nausea, 14.3 for vomiting, and 7.1 for
899 constipation], somnolence [NNH 11.1], dizziness [NNH 12.5], and pruritus [NNH 14.3]) (evidence type 1).

900 There were few serious adverse events and no difference between opioids versus placebo in risk in the
901 short-term trials (evidence type 2), but serious adverse events were not well-defined by the trials, the
902 trials excluded higher risk patients (e.g., those with history of substance use disorder), and the trials
903 were not designed to assess serious but less common harms such as overdose, opioid use disorder
904 mortality, cardiovascular events, and fractures. EERW studies tended to report lower risk with opioids of
905 discontinuation due to adverse events and gastrointestinal adverse events than non-EERW studies.
906 Uncontrolled studies (studies without a non-opioid control group) were not included in the AHRQ
907 review, though a recent systematic review with such studies found that rates of misuse ranged from 21
908 to 29% (range, 95% confidence interval [CI], 13 to 38%) and rates of addiction ranged from 8 to
909 12%(range, 95% CI, 3 to 17%), based on higher quality observational evidence (Vowles et al., 2015).

910 As in the 2014 AHRQ report and 2016 CDC update, the clinical evidence review identified no
911 long-term (>1 year) randomized controlled trials (RCTs) of opioid therapy versus placebo. One new
912 cohort study found long-term opioid therapy was not associated with improved pain, function or other
913 outcomes versus no opioids (Veiga et al., 2019). New observational studies included in the new AHRQ
914 review were consistent with the 2014 AHRQ report in finding an association between use of prescription
915 opioids and risk of addiction, overdose, fractures, falls, and cardiovascular events (evidence type 3); a
916 new study also found an association between opioid use and risk of all-cause mortality (Ray, Chung,
917 Murray, Hall, & Stein, 2016) (evidence type 4). New observational studies were also consistent with the
918 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose,
919 addiction, and endocrinological adverse events; new studies also found an association between higher
920 dose and increased risk of incident or refractory depression (Scherrer, Salas, Copeland, et al., 2016;
921 Scherrer, Salas, Sullivan, et al., 2016). Observational studies also indicated an association between co-
922 prescription of gabapentinoids (Gomes et al., 2018; Gomes et al., 2017; Peckham, Fairman, & Sclar,
923 2018) or benzodiazepines (Dunn et al., 2010; Hernandez, He, Brooks, & Zhang, 2018; E. C. Sun et al.,

947 strategy versus maintenance of current doses in pain, function, or discontinuation due to opioid misuse,
948 but the difference in opioid doses between arms was small (52 vs. 40 mg MMD/day) (Naliboff et al.,
949 2011) (evidence type 3). There were no clear differences between short- versus long-acting opioids
950 (evidence type 3) or between different long-acting opioids (evidence type 2) in pain or function, but in
951 most trials, doses were titrated to achieve adequate pain control. Evidence on comparative risks of
952 methadone versus other opioids and risk of overdose remains limited and inconsistent. Evidence on the
953 benefits and harms of different methods for initiating and titrating opioids, scheduled and continuous
954 versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing
955 patients off opioids remains insufficient. The 2014 AHRQ report found buccal or intranasal fentanyl
956 more effective than placebo or oral opioids for treatment of exacerbations of chronic pain, based on
957 immediate effects (up to 2 hours after administration). None of the trials of buccal or intranasal fentanyl
958 were designed to assess longer-term benefits or harms, and no new trials were identified for the 2020
959 systematic review. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths
960 and other life-threatening adverse effects in patients prescribed buccal fentanyl (U.S. Food and Drug
961 Administration, 2007).

962 **Risk mitigation strategies**

963 New evidence on the accuracy of risk prediction instruments was consistent with the 2014
964 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological
965 limitations and few studies of risk assessment instruments other than the Opioid Risk Tool (L. R. Webster
966 & Webster, 2005) and Screening and Opioid Assessment for Patients with Pain-Revised instrument
967 (Butler, Fernandez, Benoit, Budman, & Jamison, 2008) (evidence type 3). Evidence on the effectiveness
968 of risk mitigation strategies also remains very limited. One new observational study found provision of
969 naloxone to patients prescribed opioids in primary care clinics was associated with decreased likelihood
970 of emergency department visits, but no difference in overdose risk (evidence type 3) (Coffin et al.,

971 2016). Evidence on opioid tapering was largely limited to a trial that found a taper support intervention
972 associated with better functional outcomes and a trend towards lower opioid doses versus usual opioid
973 care (Sullivan et al., 2017) (evidence type 2). A cohort study found discontinuation of opioid therapy was
974 associated with increased risk of overdose mortality versus continuation, but there was no statistically
975 significant difference in risk of all-cause mortality (James et al., 2019). Findings should be interpreted
976 with caution, because of potential confounding related to the reason for discontinuation.

977 No trial compared different rates of opioid tapering, though one observational study found an
978 association between longer time to opioid discontinuation in patients on long-term, high-dose opioid
979 therapy and decreased risk of opioid-related emergency department visit or hospitalization (Mark &
980 Parish, 2019) (evidence type 3). The review did not identify any study that evaluated the effectiveness of
981 risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient
982 education, urine drug screening, PDMP data review, monitoring instruments in patients prescribed
983 opioids, more frequent monitoring intervals, pill counts, abuse-deterrent formulations, or avoidance of
984 co-prescribing of benzodiazepines on risk of overdose, addiction, abuse or misuse.

985 Evidence on the effectiveness of interventions for opioid use disorder in patients with
986 prescription opioid dependence or opioid use disorder was highly limited due to methodological
987 shortcomings (small sample sizes, high attrition or crossover) and/or exclusion of patients with chronic
988 pain.

989 **Noninvasive nonpharmacologic treatment for chronic pain**

990 The AHRQ systematic clinical evidence review (Skelly et al., April 2020) focused on commonly
991 encountered pain conditions and frequently used interventions; selection of conditions for review was
992 informed by stakeholder input.

993 **Benefits**

994 Chronic low back pain: The review found psychological therapies associated with small
995 improvements versus usual care or an attention control for function and pain at short-, intermediate-,
996 and long-term follow-up (evidence type 2). Exercise, low-level laser therapy, spinal manipulation,
997 massage, yoga, acupuncture, and multidisciplinary rehabilitation were associated with improvements in
998 function at short and/or intermediate term follow-up versus usual care, placebo, wait list, or inactive
999 therapies; effects on pain were small for all therapies except yoga, for which benefits were moderate
1000 (evidence type 2 at short term for exercise, massage, and yoga; evidence type 3 for others). Massage,
1001 mindfulness-based stress reduction, acupuncture, and multidisciplinary rehabilitation were associated
1002 with small short-term improvement in pain versus control (evidence type 2); exercise, low-level laser
1003 therapy, and yoga were also associated with small to moderate short-term improvement in pain, though
1004 evidence was not as strong (evidence type 3). At intermediate term, spinal manipulation, yoga,
1005 multidisciplinary rehabilitation (evidence type 2) and exercise and mindfulness-based stress reduction
1006 (evidence type 3) were associated with improved pain versus sham, usual care, or attention control;
1007 effects were small for all therapies except for yoga, for which effects were moderate. Compared with
1008 exercise, multidisciplinary rehabilitation was associated with small improvements in function and pain at
1009 short and intermediate terms (evidence type 2).

1010 Chronic neck pain: The AHRQ systematic clinical evidence review found low-level laser therapy
1011 (evidence type 2) and massage (evidence type 3) associated with improved short-term function and pain
1012 for chronic neck pain. The magnitude of effect was moderate for low-level laser therapy and small for
1013 massage. Exercise was associated with small improvement in long-term function versus attention
1014 control (evidence type 3) and combination exercise was associated with improved short- and long-term
1015 function and short-term pain versus wait list or attention control (evidence type 3). Acupuncture was
1016 associated with small improvements in short- and intermediate-term function versus sham, placebo, or
1017 usual care, but there were no differences in pain versus sham acupuncture, an intervention meant to

1018 mimic acupuncture but without acupuncture effects (e.g., needles into non-acupuncture point, or non-
1019 penetrating needles/pressure on acupuncture points) (evidence type 3). Pilates was associated with
1020 improved short-term function (small effect) and pain (large effect) versus acetaminophen (evidence type
1021 3).

1022 Osteoarthritis pain: The AHRQ systematic clinical evidence review found that for knee
1023 osteoarthritis, exercise was associated with small improvements in short- and long-term function and
1024 pain versus usual care, no treatment, or sham (evidence type 2 for short-term and type 3 for long-term),
1025 and moderate improvement in intermediate-term pain and function (evidence type 3). For hip
1026 osteoarthritis, exercise was associated with small improvement in short-term function and pain versus
1027 usual care (evidence type 3). Functional improvement persisted at intermediate-term follow-up, but
1028 pain improvement did not (evidence type 3).

1029 Fibromyalgia: The AHRQ systematic clinical evidence review found exercise, mind-body
1030 practices, and multidisciplinary rehabilitation, and acupuncture associated with small improvement in
1031 short-term function versus usual care or inactive treatments for fibromyalgia (evidence type 2 for
1032 acupuncture and evidence type 3 for others). At intermediate term, exercise, acupuncture, cognitive-
1033 behavioral therapy (CBT), mindfulness-based stress reduction, myofascial release, and multidisciplinary
1034 rehabilitation were associated with improvements in function versus inactive treatments, usual care, or
1035 waitlist (evidence type 2 for exercise and acupuncture and evidence type 3 for others). Effects on
1036 intermediate-term function were moderate for CBT and small for the other therapies. At long term,
1037 multidisciplinary rehabilitation was associated with persistent small improvement in function versus
1038 usual care, but not for pain (evidence type 3). Tai chi was associated with small improvement in function
1039 versus exercise at short- to intermediate-term follow-up (evidence type 3). Therapies associated with
1040 improved pain versus usual care, waitlist, no treatment, or inactive treatments were exercise (small
1041 effect, short and intermediate term; evidence type 2), CBT (small, short-term; evidence type 3),

1042 mindfulness practices (small, intermediate-term; evidence type 3), and multidisciplinary rehabilitation
1043 (small, intermediate-term; evidence type 3).

1044 Chronic tension headache: The AHRQ systematic clinical evidence review found spinal
1045 manipulation was associated with moderate improvement in short-term pain and small improvement in
1046 function versus usual care for chronic tension headache (evidence type 3). For other interventions,
1047 evidence was sparse, and the majority of trials had serious methodological limitations.

1048 **Harms**

1049 Across conditions, data on harms of nonpharmacological therapies was limited, but no evidence
1050 suggested serious harms. Although reporting on harms was suboptimal, among studies that reported
1051 data, non-serious treatment-related adverse events (e.g., discomfort, soreness, bruising, increased pain,
1052 and worsening of symptoms) were infrequently reported, there were few withdrawals from
1053 nonpharmacological therapies due to adverse events, and there were no differences between
1054 comparison groups (either usual care/no nonpharmacological therapy or another therapy) in the
1055 frequency of intervention-related adverse events or withdrawals (evidence type 2 or 3).

1056 **Nonopioid pharmacologic treatments for chronic pain**

1057 **Benefits**

1058 For neuropathic pain, the AHRQ systematic clinical evidence review (McDonagh et al., April
1059 2020) found anticonvulsants (gabapentin, pregabalin, and oxcarbazepine) were associated with small
1060 short-term improvement in pain versus placebo (evidence type 2), with no difference between
1061 pregabalin versus gabapentin enacarbil (evidence type 3). The antidepressant duloxetine was associated
1062 with small improvements in short-term pain, function, and quality of life versus placebo in patients with
1063 diabetic peripheral neuropathy (evidence type 2 for pain and quality of life and type 3 for function).

1064 Tetrahydrocannabinol (THC) and cannabidiol (CBD) oral spray had inconsistent effects on pain in
1065 patients with multiple sclerosis or with allodynia (evidence type 3). Topical capsaicin was not associated
1066 with significant effects on pain versus placebo, or effects were below the threshold for a small effect
1067 (evidence type 2).

1068 For fibromyalgia, the serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants
1069 milnacipran and duloxetine were associated with small, short- and intermediate-term improvements in
1070 pain and quality of life versus placebo; a small beneficial effect on function was only observed at short-
1071 term (evidence type 2). The anticonvulsants pregabalin and gabapentin were associated with small
1072 short-term improvements in pain and function versus placebo; there were no effects on quality of life
1073 (evidence type 2). Memantine was associated with moderate intermediate-term improvements in pain,
1074 function, and quality of life versus placebo (evidence type 3).

1075 For osteoarthritis, NSAIDs were associated with small short-term improvement in pain (evidence
1076 type 2) and function (evidence type 1). Topical diclofenac was associated with small improvement in
1077 short-term pain (evidence type 2) and function (evidence type 3) versus placebo. Duloxetine was
1078 associated with small improvement in pain severity, function and quality of life; and moderate
1079 improvement in likelihood of a pain response (evidence type 1). Acetaminophen was not associated
1080 with improvement in pain or function versus placebo (evidence type 3).

1081 For inflammatory arthritis, NSAIDs were associated with small improvements in short-term pain
1082 and function versus placebo (evidence type 2); effects on pain and function were small at intermediate-
1083 term follow-up (evidence type 3). At long-term follow-up effects on pain were large, with no effects on
1084 function (evidence type 3).

1085 For low back pain, duloxetine was associated with a small short-term improvement in pain
1086 intensity and likelihood of a pain response versus placebo, but improvements in function and quality of
1087 life did not meet the threshold for small improvement (evidence type 2).

1088 Harms

1089 Across all classes of nonopioid therapies, the AHRQ systematic clinical evidence review found
1090 that the incidence of serious adverse events (SAE) was low; however, the trials were not designed to
1091 assess SAEs and there were few SAEs (evidence type 3).

1092 Antidepressants were associated with increased risk of withdrawal due to adverse events (WAE)
1093 versus placebo. SNRI antidepressants were associated with moderate to large increases in risk of nausea
1094 and excessive sweating (evidence type 2 or 3). Duloxetine was associated with a large, dose-dependent,
1095 increase in sedation versus placebo (evidence type 2 or 3).

1096 With regard to anticonvulsants, oxcarbazepine was associated with a large increase in risk of
1097 WAEs versus placebo (evidence type 2). Pregabalin and gabapentin were associated with moderate
1098 increased risk of WAEs (evidence type 2), with an association between higher doses of pregabalin and
1099 increased risk. Pregabalin and gabapentin were associated with large increases in blurred vision,
1100 dizziness, weight gain, and cognitive effects (e.g., confusion) (evidence type 2). Additionally, pregabalin
1101 was associated with large increases in risk of peripheral edema and sedation (evidence type 2).

1102 NSAIDs were associated with increased risk of WAEs versus placebo; the magnitude was small
1103 for ibuprofen and diclofenac and moderate for naproxen (evidence type 2). The risk of any
1104 cardiovascular event was not significantly elevated for NSAIDs as a group, but diclofenac was associated
1105 with small increase in risk, particularly in the first 6 months, and with higher doses (evidence type 2).
1106 Versus placebo, the risk of major coronary events was elevated with diclofenac and celecoxib (moderate
1107 effect) and with ibuprofen (large effect). For every 3000 patients treated with diclofenac or celecoxib,

1108 there were an estimated 3 additional major coronary events. There was no difference in cardiovascular
1109 events between celecoxib versus nonselective NSAIDs in the intermediate or long term (evidence type
1110 2). The risk of serious upper gastrointestinal events was increased with diclofenac (moderate effect) and
1111 ibuprofen or naproxen (large increase), particularly in the first 6 months of treatment (evidence type 1
1112 to 2). In the intermediate term, diclofenac and naproxen were associated with large increase in risk of
1113 hepatic harms (evidence type 1 to 2).

1114 Acetaminophen was not associated with increased risk of short- or intermediate-term WAEs
1115 versus placebo (evidence type 3). Capsaicin was associated with large increase in risk of application site
1116 pain (evidence type 2) and a small increased risk of erythema (evidence type 3). Cannabis as oral
1117 dronabinol solution was associated with large increase in risk of dizziness, and as
1118 tetrahydrocannabinol/cannabidiol was associated with large increase in risk of WAEs, dizziness, and
1119 nausea (evidence type 3).

1120 **Treatments for acute pain**

1121 The AHRQ systematic clinical evidence review (Chou et al., December 2020) found that most
1122 trials of treatments for acute pain focused on effects on pain at short-term (up to 1 week) follow-up.
1123 Evidence was somewhat stronger for pharmacological than nonpharmacological therapies.

1124 For acute surgical dental pain (evidence type 3) and kidney stone pain (evidence type 2), the
1125 AHRQ systematic clinical evidence review found that opioids were associated with small to moderate
1126 increases in pain or need for rescue medication use versus NSAIDs. Findings for postoperative pain were
1127 somewhat inconsistent. Although opioids were associated with increased likelihood of repeat or rescue
1128 medication use at 1 day to 1 week (evidence type 3), evidence on pain intensity was insufficient due to
1129 inconsistency. Results for postoperative pain were based on a small number of trials and pain related to
1130 a limited set of surgical procedures (most commonly cesarean section, anterior cruciate ligament (ACL)

1131 reconstruction, knee arthroplasty, and cholecystectomy), limiting generalizability to other surgical
1132 procedures. Opioids were associated with increased risk of adverse events such as nausea, dizziness,
1133 and sedation versus nonopioid pharmacologic therapies (evidence type 2 or 3). The trials were not
1134 designed to assess SAEs, and few such events were reported. Evidence on opioids versus acetaminophen
1135 was somewhat mixed: for dental pain, the systematic clinical evidence review found opioids were
1136 associated with small improvement in pain outcomes on some measures (evidence type 2), but for
1137 kidney stone pain, opioids were associated with small increase in pain (evidence type 2). Evidence on
1138 NSAIDs versus acetaminophen was also somewhat mixed: for dental pain, evidence indicated that
1139 NSAIDs were associated with moderate to large decrease in pain (evidence type 2), but for kidney stone
1140 pain, evidence was insufficient. Evidence on nonopioid pharmacologic therapies other than NSAIDs or
1141 acetaminophen was very limited.

1142 Evidence on nonpharmacological therapies for acute pain was limited. For low back pain, the
1143 AHRQ systematic clinical evidence review found heat therapy was associated with a moderate decrease
1144 in pain versus usual care or placebo at 1 day to <1 week and at 2 to <4 weeks (evidence type 2 to 3).
1145 There may be no difference between spinal manipulation versus inactive controls for non-radicular low
1146 back pain (evidence type 2 to 3), though one trial of patients with radiculopathy found manipulation was
1147 associated with increased likelihood of improvement in pain at 2 to <4 weeks, and at ≥ 4 weeks
1148 (evidence type 3) (Santilli, Beghi, & Finucci, 2006). Acupuncture was associated with moderate
1149 improvement in pain and function versus an NSAID for low back pain, but findings were based on one
1150 trial that evaluated one session of acupuncture and a single dose of an NSAID (evidence type 3) (Shin et
1151 al., 2013). For postoperative pain, there was type 3 evidence that massage might have some
1152 effectiveness, with likely no difference between cold therapy versus no cold therapy, with the possible
1153 exception of decreased pain medication use at <1 week. There was also limited evidence supporting
1154 effectiveness of acupressure for acute musculoskeletal pain (evidence type 3). Reporting of harms for

1178 favored antiemetics versus placebo or no antiemetic but was more limited (evidence type 3). Newer
1179 treatments (calcitonin gene-related peptide [CGRP] antagonists [gepants] and the 5-HT_{1F} receptor
1180 antagonist lasmiditan) were associated with reduced pain and improved function versus placebo
1181 (evidence type 2 or 3). However, lasmiditan was associated with increased risk of severe adverse events
1182 (most commonly, dizziness; evidence type 3); evidence on serious adverse events of CGRP antagonists
1183 was insufficient.

1184 Evidence on nonpharmacological therapy for acute episodic migraine was sparse. There was
1185 moderate evidence (evidence type 2) supporting remote electrical neuromodulation. More limited
1186 evidence (evidence type 3) supported acupuncture, chamomile oil, external trigeminal nerve
1187 stimulation, and eye movement desensitization reprocessing. There was insufficient evidence to
1188 determine risk of serious adverse events with nonpharmacological therapies for acute episodic
1189 migraine.

1190 **Contextual evidence reviews**

1191 **Patient and clinician values and preferences**

1192 **Opioids for chronic pain**

1193 A Contextual Evidence Review conducted for the 2016 CDC Guideline (Dowell et al., 2016) found
1194 data indicating that physicians frequently lacked confidence in their ability to safely prescribe opioids,
1195 predict or identify prescription medication misuse or opioid use disorder, or discuss these issues with
1196 their patients. Clinicians reported favorable beliefs and attitudes about effects of opioids on pain and
1197 quality of life; however, they also had concerns about risk of opioid use disorder and overdose, yet did
1198 not consistently utilize risk mitigation strategies (e.g., use of PDMP data, urine toxicology testing, and/or
1199 opioid treatment agreements). Evidence on patient values and preferences was limited but indicated

1200 unfamiliarity with some terms (“opioids”), more familiarity with the term “narcotics” but an association
1201 between “narcotics” and “addiction” or “abuse,” and concerns about addiction and abuse. Side effects
1202 such as nausea, constipation, and somnolence (rather than pain relief) accounted for most of the
1203 variation in patient preferences regarding use of opioids. Patients prescribed high dose opioids reported
1204 reliance on opioids, and ambivalence or uncertainty about benefits and side effects.

1205 The AHRQ review identified some new information on preferences and values. A survey of 961
1206 clinicians found that 82% were reluctant to prescribe opioids and less than half (47%) expressed
1207 confidence in caring for patients with chronic noncancer pain (Ebbert et al., 2018). Sixty-seven percent
1208 were aware of the 2016 CDC guideline and 55% were enrolled in the state PDMP; 2% always or
1209 frequently prescribed naloxone to patients on opioids, although results are difficult to interpret as the
1210 study did not specify whether patients met 2016 CDC Guideline criteria for naloxone. Guideline
1211 awareness was associated with increased confidence in caring for patients with chronic pain. Other
1212 surveys found negative attitudes or concerns regarding prescription opioid use disorder, but beliefs in
1213 potential effectiveness of opioids for treating pain and support for policies and guidelines aimed at
1214 mitigating risks, with increased confidence when following “best practices” (Kennedy-Hendricks et al.,
1215 2016; D. H. Lin et al., 2017; Razouki, Khokhar, Philpot, & Ebbert, 2019).

1216 Regarding patient preferences and values, a new systematic review found that among various
1217 opioid-related outcomes (effects), patients ranked pain relief, nausea, and vomiting as most important,
1218 followed by constipation (Goshua et al., 2018). “Addiction” was only evaluated in two studies and rated
1219 as less important than pain relief. An online (non-peer reviewed) survey of over 3000 patients 1 year
1220 after the release of the 2016 CDC Guideline found that 84% reported more pain and worse quality of life
1221 and 42% said they had considered suicide; however, the survey did not attempt to sample patients with
1222 chronic pain using a rigorous methodological approach (Pain News Network, 2017).

1223

Noninvasive nonpharmacological treatments for chronic pain

1224 The Contextual Evidence Review found that evidence on patient values and preferences related
1225 to noninvasive nonpharmacological treatments for chronic pain was limited. A Gallup poll found that
1226 78% of Americans preferred nonpharmacological therapies (e.g., physical therapy and chiropractic care)
1227 to address pain over prescribed pain medication (Rosenberg et al., 2008). Another survey indicated
1228 frequent use of complementary and integrative therapies for chronic pain (Francois, Lanier, Marich,
1229 Wallendorf, & Van Dillen, 2018).

1230 Clinicians generally agreed with use of guideline-supported therapies and therapies supported
1231 by evidence, including nonpharmacological therapies; clinicians also felt that treatments should be
1232 credible and individualized to the patient (Cottrell, Foster, Porcheret, Rathod, & Roddy, 2017; Dima et
1233 al., 2013). Clinician concerns regarding nonpharmacological treatments included costs and safety
1234 (Cottrell et al., 2017). Surveys indicated high support for use of exercise therapy, complementary
1235 medicine therapies, and psychological therapies (Cottrell, Roddy, & Foster, 2010; Cowell et al., 2018;
1236 Driver, Kean, Oprescu, & Lovell, 2017); clinicians also supported chronic pain management informed by
1237 a biopsychosocial framework or using a multidimensional approach (Holden, Nicholls, Young, Hay, &
1238 Foster, 2009). Some barriers to use of therapies included lack of knowledge or expertise and uncertainty
1239 regarding potential benefits (Cottrell et al., 2010; Cowell et al., 2018; Dima et al., 2013; Heyward et al.,
1240 2018; Holden et al., 2009; Sierpina, Levine, Astin, & Tan, 2007).

1241

Nonopioid pharmacological treatments for chronic pain

1242 The Contextual Evidence Review found limited evidence on clinician and patient values and
1243 preferences related to nonopioid pharmacological treatments. Evidence described variability in patient
1244 preferences regarding nonopioid pharmacological treatments, interest in medical cannabis, cost as an
1245 important consideration, high priority on pain reduction as well as side effects and harms (including risk

1246 of OUD), and high value for having alternatives to opioids (Mühlbacher et al., 2015; Patel et al., 2016;
1247 Turk et al., 2020). A survey of pharmacists in Canada found that 38% agreed that non-prescription
1248 analgesics should be first line for chronic low back pain and 79% agreed that tricyclic antidepressants are
1249 effective for peripheral diabetic neuropathy (R. C. Wielage, Bansal, Andrews, Klein, & Happich, 2013).

1250 **Treatments for acute pain**

1251 The Contextual Evidence Review found limited evidence suggesting variability in patient values
1252 and preferences regarding treatments for acute pain (Fullen et al., 2008; Hallway et al., 2019), with
1253 some evidence of high satisfaction when postoperative pain was managed using an opioid-sparing
1254 pathway (Swenson, Prashar, Mangino, Thode, & Singer, 2019). There was also variability in clinician
1255 values and preferences regarding acute pain treatments that were impacted by clinical specialty,
1256 knowledge regarding effectiveness, and costs; negative attitudes towards acute pain conditions were
1257 associated with less likelihood of using or re-dosing opioids (Cherkin, Deyo, Wheeler, & Ciol, 1995; Fullen
1258 et al., 2009; Glassberg et al., 2013; Green, Wheeler, & LaPorte, 2003; Mikhail, Korner-Bitensky,
1259 Rossignol, & Dumas, 2005). A systematic review found inconsistent evidence that education increased
1260 clinician adherence with acute low back pain guideline recommendations in terms of referral rates to
1261 physiotherapy (C. C. Lin et al., 2018).

1262 **Treatments for acute episodic migraine**

1263 The Contextual Evidence Review found very limited evidence on clinician and patient values and
1264 preferences related to treatments for acute episodic migraine. One survey found that patients with
1265 headaches (primarily episodic or chronic migraine) prioritized efficacy of treatment over the safety or
1266 route of administration and preferred oral over parenteral medications (Adelman & Belsey, 2003). A
1267 survey of Canadian pharmacists found that 42% agreed that migraine patients should try non-

1268 prescription prior to prescription medications and 53% agreed that triptans should be reserved until
1269 failure of at least two other prescription medications (R. C. Wielage et al., 2013).

1270 **Costs and cost-effectiveness**

1271 **Opioid therapy for chronic pain**

1272 The Contextual Evidence Review conducted for the 2016 CDC Guideline estimated (based on
1273 studies published after 2010) yearly direct and indirect costs related to prescription opioids at \$53.4
1274 billion for nonmedical use of prescription opioids; \$55.7 billion for abuse, dependence (i.e., opioid use
1275 disorder), and misuse of prescription opioids; and \$20.4 billion for opioid-related overdoses (Birnbaum
1276 et al., 2011; Hansen, Oster, Edelsberg, Woody, & Sullivan, 2011; Inocencio, Carroll, Read, & Holdford,
1277 2013). In 2012, total expenses for outpatient prescription opioids were estimated at \$9.0 billion, an
1278 increase of 120% from 2002 (Stagnitti, 2001). Based on a large national sample of 2008 claims data,
1279 direct costs of opioids in patients with osteoarthritis were estimated at \$287.4 per patient, but there
1280 was wide variability in estimates (SD \$1,652.1) (Gore, Tai, Sadosky, Leslie, & Stacey, 2012). One study
1281 estimated costs of urine toxicology testing (including screening and confirmatory tests) at \$211 to \$363
1282 per test (Laffer et al., 2011).

1283 The AHRQ report included data that estimated the total economic burden of fatal overdose,
1284 abuse, and dependence of prescription opioids in 2013 at \$78.5 billion, with \$28.9 billion related to
1285 increased healthcare and substance use disorder treatment costs (Florence, Zhou, Luo, & Xu, 2016).
1286 More recent data indicate that spending on opioid prescriptions peaked at \$1.6 billion in 2009, with a
1287 decrease to \$1.2 billion in 2016 (Cox, Rae, & Sawyer, 2018). However, costs of treatment for opioid use
1288 disorder and overdose increased (\$646 million in 2009 and \$2.6 billion in 2016). Data also indicate that
1289 Medicaid spending on opioids has declined since 2014, though spending on buprenorphine (a partial

1290 opioid agonist often used to treat opioid use disorder) has increased (Young, 2019), likely because of
1291 greater numbers of individuals accessing medication and treatment for opioid use disorder (MOUD).

1292 No study was identified that formally evaluated the cost-effectiveness of opioid therapy versus
1293 no opioid therapy or nonopioid pharmacological therapy for noncancer pain. A modeling study that
1294 estimated 80% of opioid overdose deaths to be attributable to illicit opioids projected that interventions
1295 targeting prescription opioid misuse such as prescription monitoring programs would decrease the
1296 number of opioid overdose deaths by 3.0% to 5.3% (Chen et al., 2019). There were also no cost-
1297 effectiveness analyses of risk mitigation strategies in persons prescribed opioids for chronic pain. A
1298 systematic review that included 43 economic evaluation studies of treatments for opioid use disorder
1299 found evidence supporting the cost-effectiveness of methadone therapy, with less evidence for other
1300 opioid use disorder therapies (Murphy & Polsky, 2016). Additional analyses from the UK and California
1301 also found treatment for opioid use disorder to be cost-effective or cost saving (Kenworthy et al., 2017;
1302 E. Krebs et al., 2018).

1303 **Noninvasive nonpharmacological treatments for chronic pain**

1304 The Contextual Evidence Review found that for nonpharmacological treatments covered by
1305 commercial insurers, out-of-pocket costs ranged from \$25 to \$60 per visit (\$150 to \$720 for a 6- to 12-
1306 visit course of therapy) (Heyward et al., 2018). Studies found that a number of nonpharmacologic
1307 therapies were cost-effective for various chronic pain conditions. For osteoarthritis, cost-effective
1308 interventions (relative to a comparison such as no therapy or usual care) included exercise, acupuncture,
1309 and transcutaneous electrical nerve stimulation (Center for Health Information and Analysis, 2015;
1310 Coupe et al., 2007; Dagenais, Caro, & Haldeman, 2008; Hurley et al., 2007; Jessep, Walsh, Ratcliffe, &
1311 Hurley, 2009; MacPherson et al., 2017; Oppong et al., 2015; Sevick et al., 2000; Sevick, Miller, Loeser,
1312 Williamson, & Messier, 2009). For low back pain, cost-effective interventions included interdisciplinary

1313 rehabilitation, exercise, yoga, acupuncture, spinal manipulation, cognitive behavioral therapy,
1314 mindfulness based stress reduction, biofeedback, and multidisciplinary rehabilitation (Aboagye,
1315 Karlsson, Hagberg, & Jensen, 2015; Andronis et al., 2017; Driessen, Lin, & van Tulder, 2012; Haines &
1316 Bowles, 2017; Herman et al., 2017; Herman, Lavelle, Sorbero, Hurwitz, & Coulter, 2019; C. W. Lin, Haas,
1317 Maher, Machado, & van Tulder, 2011; Suni et al., 2018; Tsertsvadze et al., 2014). For neck pain, cost-
1318 effective interventions included manual therapy, physiotherapy, acupuncture, exercise, and spinal
1319 manipulative therapy (Essex et al., 2017; Herman et al., 2019; Miyamoto, Lin, Cabral, van Dongen, & van
1320 Tulder, 2019; R. L. Robinson & Jones, 2006; van der Velde et al., 2016; Willich et al., 2006). For
1321 fibromyalgia, cost-effectiveness analyses of nonpharmacological therapies was very limited (Luciano et
1322 al., 2014), but some evidence suggested that cognitive behavioral therapy dominated (associated with
1323 cost savings and greater benefits) pharmacological therapy or usual care (Hsiao & Fraenkel, 2019).

1324 **Nonopioid pharmacologic treatments for chronic pain**

1325 The Contextual Evidence Review found some evidence indicating that nonopioid
1326 pharmacological therapies are cost-effective for chronic pain. For osteoarthritis and low back pain, there
1327 was some evidence that nonopioid pharmacological therapies (NSAIDs, duloxetine) are cost-effective
1328 versus opioids (Huelin, Pokora, Foster, & Mould, 2012; Ivanova, Birnbaum, Kantor, Schiller, & Swindle,
1329 2012; R. Wielage, Bansal, Wilson, Klein, & Happich, 2013); studies also found NSAIDs, duloxetine, and
1330 pregabalin cost-effective versus usual care or no treatment (Huelin et al., 2012; Ivanova, Birnbaum,
1331 Kantor, Schiller, & Swindle, 2014; Morera-Dominguez, Ceberio-Balda, Florez-Garcia, Masramon, &
1332 Lopez-Gomez, 2010; O'Connor, 2009). For neuropathic pain, cost-effective treatments included tricyclic
1333 antidepressants, duloxetine, pregabalin, and topical capsaicin or lidocaine (Armstrong, Malone,
1334 McCarberg, Panarites, & Pham, 2011; Beard et al., 2011; Cepeda & Farrar, 2006; Darba et al., 2014; de
1335 Salas-Cansado, Perez, Saldana, Navarro, & Rejas, 2012; J. Gordon et al., 2012; Kirson et al., 2010;
1336 Liedgens et al., 2008; Mankowski, Patel, Trueman, Bentley, & Poole, 2016; Parker, Huelin, Khankhel,

1337 Wasiak, & Mould, 2015; Tarride, Gordon, Vera-Llonch, Dukes, & Rousseau, 2006; E. Q. Wu et al., 2006;
1338 N. Wu, Chen, Boulanger, Rao, & Zhao, 2011; Zhao et al., 2010). For fibromyalgia, cost-effective
1339 treatments included duloxetine, pregabalin, and amitriptyline, though analyses of relative cost-
1340 effectiveness among these therapies were inconsistent (Burke et al., 2012; Gan et al., 2004; Gore, Tai,
1341 Chandran, Zlateva, & Leslie, 2012; Harnett et al., 2011; Kleinman et al., 2011; Lloyd, Boomershine, Choy,
1342 Chandran, & Zlateva, 2012; P. Sun et al., 2014; Zhao, Sun, & Watson, 2011).

1343 **Treatments for acute pain**

1344 The Contextual Evidence Review found limited evidence exercise was cost-effective for acute
1345 low back pain and interdisciplinary rehabilitation cost-effective for low back pain that was identified as
1346 high risk for becoming chronic (Essex et al., 2017; Rogerson, Gatchel, & Bierner, 2010; Seferlis, Lindholm,
1347 & Nemeth, 2000). There was limited evidence that acetaminophen and spinal manipulation were not
1348 cost-effective for acute low back pain (the acetaminophen analysis was based on a randomized trial that
1349 found acetaminophen to be ineffective for acute low back pain and the spinal manipulation analysis was
1350 based on a cohort study that found that manipulation for acute low back pain did not reduce follow-up
1351 visits or days of sick leave for low back pain) (C. C. Lin et al., 2018; Walker, Mertens, Schmidt, & Chenot,
1352 2017). One cohort study of patients with postsurgical pain found use of long-acting opioids within 30
1353 days associated with greater costs of services (\$11,900 vs. \$8,400, $p < 0.0001$) (Gold, Strassels, & Hansen,
1354 2016).

1355 **Treatments for acute episodic migraine**

1356 The Contextual Evidence Review found that studies on costs and cost-effectiveness of
1357 treatments for acute episodic migraine focused almost exclusively on triptans. Triptans were
1358 consistently found to be associated with low costs per pain-free episode and other outcomes (e.g.,
1359 migraine-disability days averted) (Asseburg et al., 2012; Belsey, 2004; Cady, Sheftell, Lipton, Kwong, &

1360 O'Quinn, 2001; Kelman & Von Seggern, 2006; Lofland et al., 2001; Lofland & Nash, 2005; Mullins,
1361 Subedi, Healey, & Sanchez, 2007; Perfetto, Weis, Mullins, Subedi, & Healey, 2005; P. Williams & Reeder,
1362 2004). Triptans were dominant (more effective and less costly) over fixed-dose combination of
1363 ergotamine tartrate plus caffeine (Zhang & Hay, 2005).

1364 **Recommendations**

1365 This clinical practice guideline includes 12 recommendations ([Box 1](#)) for clinicians who are
1366 prescribing opioids for outpatients aged ≥ 18 years with acute (duration < 1 month) pain, subacute
1367 (duration of 1-3 months) pain, or chronic (duration of > 3 months) pain outside of sickle cell disease-
1368 related pain management, cancer pain treatment, palliative care, and end-of-life care. Refer to the
1369 earlier section on scope and audience for further details on clinicians and patients and on definitions of
1370 acute, subacute, and chronic pain. In accordance with the ACIP adapted GRADE process, CDC based the
1371 recommendations on consideration of clinical evidence, contextual evidence (including benefits and
1372 harms, values and preferences, resource allocation), and expert opinion. Expert input is reflected within
1373 the recommendation rationales. For each recommendation statement, CDC notes the recommendation
1374 category (A or B) and the type of the evidence (1, 2, 3, or 4) supporting the statement ([Box 2](#)).

1375 Category A recommendations indicate that most patients should receive the recommended
1376 course of action; category B recommendations indicate that different choices will be appropriate for
1377 different patients, requiring clinicians to help patients arrive at a decision consistent with patient values
1378 and preferences and specific clinical situations. Consistent with the ACIP (Ahmed, 2013; Centers for
1379 Disease Control and Prevention, 2018a) and GRADE process (Balshem et al., 2011), category A
1380 recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that
1381 the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of
1382 benefits and harms, values and preferences, and resource allocation. Category B recommendations

1383 were made when there was broad agreement that the advantages and disadvantages of a clinical action
1384 were more balanced, but advantages were significant enough to warrant a recommendation.
1385 Recommendations were associated with a range of evidence types, from type 1 to type 4.

1386 In summary, the categorization of recommendations was based on the following assessment:

- 1387 • A number of nonpharmacological treatments and a number of nonopioid medications are
1388 associated with improvements in pain and/or function that are reportedly comparable to
1389 improvements associated with opioid use.
- 1390 • There is evidence that several noninvasive, nonpharmacologic interventions improve chronic
1391 pain and function, with small to moderate effects in specific pain conditions, and are not
1392 associated with serious harms. Compared with medication treatment, for which benefits are
1393 anticipated while patients are taking the medication but are not usually expected to persist
1394 following completion of treatment (once patients stop taking the medication), several
1395 noninvasive, nonpharmacologic interventions are associated with improvements in pain and/or
1396 function that are sustained following treatment.
- 1397 • Nonopioid drugs, including SNRI antidepressants, pregabalin/gabapentin, and NSAIDs, are
1398 associated with small to moderate improvements in chronic pain and function. Drug class-
1399 specific adverse events include serious cardiovascular, gastrointestinal, or renal effects with
1400 NSAIDs and sedation with anticonvulsants.
- 1401 • Opioid therapy is associated with similar or decreased effectiveness for pain and function versus
1402 NSAIDs across several acute pain conditions, with small improvements in short-term (1 to <6
1403 months) pain and function compared with placebo, with increased short-term harms compared
1404 with placebo, and with evidence of attenuated pain reduction over time (between 3 and 6
1405 months versus between 1 and 3 months). There is evidence from observational studies of an
1406 association between opioid use for acute pain and long-term opioid use. Evidence on long-term

1407 effectiveness of opioids remains very limited; a long-term (12 months) randomized trial of
1408 stepped therapy for chronic musculoskeletal pain found no difference in function and higher
1409 pain intensity after starting with opioid therapy compared to starting with nonopioid therapy.
1410 There is evidence of increased risk of serious harms (including opioid use disorder and overdose)
1411 with long-term opioid therapy that appears to increase with increase in opioid dosage, without a
1412 clear threshold below which there is no risk. There is no validated, reliable way to predict which
1413 patients will suffer serious harm from opioid therapy and no reliable way to predict which
1414 patients will benefit from opioid therapy.

- 1415 • It can be very challenging for clinicians and patients to discontinue opioids after extended
1416 periods of continuous opioid use. Tapering or discontinuing opioids in patients who have taken
1417 them long-term can be associated with significant risks (U.S. Food and Drug Administration,
1418 2019c), particularly if opioids are tapered rapidly or patients do not receive effective support.
- 1419 • Patients, caregivers, and clinicians responded to CDC with invited input regarding their lived
1420 experiences and perspectives related to pain and pain management options. Key themes
1421 expressed included strained patient-provider relationships and the need for patients and
1422 providers to make shared decisions, the impact of misapplication of the 2016 CDC Guideline,
1423 inconsistent access to effective pain management solutions, and achieving reduced prescription
1424 opioid use through diverse approaches.

1425 Each of the 12 recommendations is followed by a rationale for the recommendation, with
1426 considerations for implementation noted immediately below the recommendation statement. These
1427 bulleted implementation considerations offer practical insights meant to further inform clinician-patient
1428 decision-making for the respective recommendation and are not meant to be rigidly or inflexibly
1429 followed. The recommendations are grouped into four areas for consideration:

- 1430 • Determining whether or not to initiate opioids for pain

- |
- 1431 • Opioid selection and dosage
 - 1432 • Opioid duration and follow-up
 - 1433 • Assessing risk and addressing potential harms of opioid use

1434 In addition, these five guiding principles should broadly inform implementation across
1435 recommendations:

- 1436 1. Acute, subacute, and chronic pain need to be appropriately and effectively treated independent
1437 of whether opioids are part of a treatment regimen.
- 1438 2. Recommendations are voluntary and are intended to support, not supplant, individualized,
1439 person-centered care. Flexibility to meet the care needs and the clinical circumstances of a
1440 specific patient are paramount.
- 1441 3. A multimodal and multidisciplinary approach to pain management attending to the physical
1442 health, behavioral health, long-term services and supports, and expected health outcomes and
1443 well-being of each person is critical.
- 1444 4. Special attention should be given to avoid misapplying this updated clinical practice guideline
1445 beyond its intended use or implementing policies purportedly derived from it that might lead to
1446 unintended consequences for patients.
- 1447 5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities,
1448 provide culturally and linguistically appropriate communication (Office of Minority Health,
1449 2021), including communication that is accessible to persons with disabilities, and ensure access
1450 to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and
1451 pharmacologic pain management regimen for all persons.

1452 **Determining whether or not to initiate opioids for pain**

1453 All patients with pain should receive treatment that provides the greatest benefits relative to
1454 risks. See Recommendation 1 for determining whether to initiate opioids for acute pain (i.e., with a
1455 duration of less than one month) and Recommendation 2 for determining whether or not to initiate
1456 opioids for subacute (i.e., with a duration of at least one month and less than three months) or chronic
1457 pain (i.e., with a duration of three months or more).

1458
1459 **1. Nonopioid therapies are effective for many common types of acute pain. Clinicians should only**
1460 **consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient**
1461 **(recommendation category: B, evidence type: 3).**

1462 Implementation considerations:

- 1463 • *There is an important role for opioid therapy for acute pain related to severe traumatic injuries*
1464 *(including crush injuries and burns), invasive surgeries typically associated with moderate to*
1465 *severe postoperative pain, and other severe acute pain when NSAIDs and other therapies are*
1466 *contraindicated or likely to be ineffective.*
- 1467 • *Opioids are not first-line therapy for many common acute pain conditions, including low back*
1468 *pain, neck pain, pain related to other musculoskeletal injuries (such as sprains, strains,*
1469 *tendonitis, bursitis), pain related to minor surgeries typically associated with minimal tissue*
1470 *injury and only mild postoperative pain (e.g., dental extraction), dental pain, kidney stone pain,*
1471 *and headaches including episodic migraine.*
- 1472 • *When diagnosis and severity of acute pain are reasonably assumed to warrant the use of*
1473 *opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the*
1474 *lowest dose to achieve expected effects (see Recommendation 4) and for no longer than the*
1475 *expected duration of pain severe enough to require opioids (see Recommendation 6).*
- 1476 • *Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs and/or acetaminophen)*
1477 *and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or exercise) therapies*
1478 *as appropriate for the specific condition and continue these therapies as needed once opioids are*
1479 *discontinued.*
- 1480 • *Clinicians should prescribe and advise opioid use only as needed (e.g., hydrocodone 5*
1481 *mg/acetaminophen 325mg, one tablet not more frequently than every 4 hours as needed for*
1482 *pain) rather than on a scheduled basis (e.g., one tablet every 4 hours) and encourage and include*
1483 *an opioid taper if opioids will be taken around the clock for more than a few days (see*
1484 *Recommendation 6).*
- 1485 • *If patients already receiving opioids in a long-term fashion require additional medication for*
1486 *acute pain, nonopioid medications should be used when possible, and if additional opioids are*

1487 *required (e.g., for superimposed severe acute pain), they should be continued only for the*
1488 *duration of pain severe enough to require additional opioids, returning to the patient’s baseline*
1489 *opioid dosage as soon as possible, including a taper to baseline dosage if additional opioids were*
1490 *used around the clock for more than a few days (see Recommendation 6).*

- 1491 • *Clinicians should ensure that patients are aware of expected benefits of, common and serious*
1492 *risks of, and alternatives to opioids before starting or continuing opioid therapy and should*
1493 *involve patients meaningfully in decisions about whether to start opioid therapy.*

1494 *Supporting Rationale*

1495 Evaluation of the patient is critical in order to inform appropriate management. Evaluation can
1496 identify reversible causes of pain and underlying etiologies with potentially serious sequelae that require
1497 urgent action. To guide patient-specific selection of therapy, clinicians should evaluate patients and
1498 establish or confirm the diagnosis. Diagnosis can help identify interventions to reverse, ameliorate, or
1499 prevent worsening of pain and improve function; for example, surgical intervention to repair structure
1500 and function following certain traumatic injuries, bracing to prevent recurrence of acute ankle sprain,
1501 fracture immobilization, ice or elevation to reduce swelling, and early mobilization to maintain function
1502 (Doherty, Bleakley, Delahunt, & Holden, 2017).

1503 **Noninvasive, nonpharmacologic approaches to acute pain**

1504 Noninvasive, nonpharmacologic approaches have the potential to improve pain and function
1505 without risk of serious harms (Chou et al., December 2020). The clinical evidence reviews found that
1506 some nonpharmacologic treatments were likely effective for acute pain (e.g., heat therapy will probably
1507 be effective for acute low back pain, spinal manipulation might be effective for acute back pain with
1508 radiculopathy, a cervical collar or exercise might be effective for acute neck pain with radiculopathy,
1509 acupuncture might be effective for acute musculoskeletal pain, massage might be effective for
1510 postoperative pain (Chou et al., December 2020), and remote electrical neuromodulation might improve
1511 acute pain related to episodic migraine (Halker Singh et al., December 2020)). Some nonpharmacologic
1512

1513 therapies are relatively low cost and available without a clinician appointment (e.g., heat for low back
1514 pain) (Chou et al., December 2020).

1515 The American College of Physicians recommends nonpharmacologic treatment with superficial
1516 heat, massage, acupuncture, or spinal manipulation as a cornerstone of treatment for acute low back
1517 pain (Qaseem, Wilt, McLean, & Forciea, 2017). The American College of Physicians and American
1518 Academy of Family Physicians suggest acupuncture to improve pain and function and transcutaneous
1519 electrical nerve stimulation to reduce pain in patients with acute musculoskeletal injuries (Qaseem et
1520 al., 2020).

1521 Despite evidence supporting their use, noninvasive, nonpharmacologic therapies are not always
1522 or fully covered by insurance (Heyward et al., 2018), and access and cost can be barriers for patients,
1523 particularly for patients who are uninsured, individuals with limited income, and for people with
1524 transportation challenges or living in rural areas. Experts expressed concern about limited access to non-
1525 opioid pain management modalities, in part due to lack of availability or lack of coverage by payers, and
1526 emphasized improving access to non-opioid pain management modalities as a priority. To improve pain
1527 management and reduce medication use and associated risks, health insurers and health systems should
1528 increase access to noninvasive, nonpharmacologic therapies with evidence of effectiveness.

1529 Noninvasive, nonpharmacologic approaches should be used as appropriate to alleviate acute pain,
1530 including ice and elevation to reduce swelling and discomfort from musculoskeletal injuries, heat to
1531 alleviate low back pain, and other modalities depending on the cause of the acute pain.

1532
1533 **Nonopioid medications for acute pain**

1534 Many acute pain conditions can often be managed most effectively with nonopioid medications
1535 (Chou et al., December 2020). NSAIDs are probably more effective than opioids for surgical dental pain
1536 and for kidney stone pain and similarly effective to opioids for low back pain (Chou et al., December
1537 2020). There is limited evidence on comparative effectiveness of therapies for acute neuropathic pain,

1538 neck pain, and postoperative pain (Chou et al., December 2020). For episodic migraine, triptans, NSAIDs,
1539 antiemetics, dihydroergotamine, CGRP antagonists, and lasmiditan are associated with improved pain
1540 and function with generally mild and transient adverse events (Halker Singh et al., December 2020).

1541 The American College of Physicians recommends NSAIDs or skeletal muscle relaxants if
1542 pharmacologic treatment is desired to treat low back pain (Qaseem et al., 2017). For acute
1543 musculoskeletal injuries other than low back pain, the American College of Physicians and American
1544 Academy of Family Physicians recommend topical NSAIDs with or without menthol gel as first-line
1545 therapy and suggest oral NSAIDs to improve function, or oral acetaminophen to reduce pain (Qaseem et
1546 al., 2020). The American Dental Association recommends NSAIDs as first-line treatment for acute dental
1547 pain management (American Dental Association, 2020). For pain management for women in the
1548 postpartum period, the American College of Obstetricians and Gynecologists (ACOG) recommends a
1549 stepwise, multimodal approach. After vaginal delivery, ACOG recommends acetaminophen or NSAIDs,
1550 and if needed, escalating to an opioid; after caesarian delivery, ACOG recommends standard oral and
1551 parenteral medications such as acetaminophen, NSAIDs, and/or low-dose, low-potency, short-acting
1552 opioids with duration of opioid use limited to the shortest reasonable course expected for treating acute
1553 pain (The American College of Obstetricians and Gynecologists, 2021). ACOG recommends counseling
1554 individuals who are prescribed opioids about the risk of central nervous system depression in the
1555 individual and in the breastfed infant (The American College of Obstetricians and Gynecologists, 2021).
1556 For acute kidney stone pain, NSAIDs are at least as effective as opioids (Cordell et al., 1994; Cordell et
1557 al., 1996; Teichman, 2004; Udén, Rentzhog, & Berger, 1983), can decrease the ureteral smooth muscle
1558 tone and ureteral spasm (Cole, Fry, & Shuttleworth, 1988) causing kidney stone pain, and are preferred
1559 for kidney stone pain if not contraindicated. Triptans, NSAIDs, combined triptans with NSAIDs, as well as
1560 antiemetics, dihydroergotamine, and acetaminophen are established acute treatments for migraine
1561 (Halker Singh et al., December 2020). The 5-HT_{1F} receptor antagonist lasmiditan and the gepant

1562 ubrogepant were approved by the FDA in 2019 for the treatment of migraine (U.S. Food and Drug
1563 Administration, 2019a); another gepant, rimegepant, was approved in 2020. Lasmiditan and the gepants
1564 were more effective than placebo in providing pain relief at 2 hours, 1 day, and at 1 week (Halker Singh
1565 et al., December 2020). Adverse events related to these newer medications require further study, but
1566 given their mechanisms of action, are believed to be nonvasoconstrictive (Shapiro et al., 2019), and
1567 potentially carry lower risks than vasoactive medications in patients with cardiovascular risk factors
1568 (Halker Singh et al., December 2020).

1569 When not contraindicated, NSAIDs should be used for low back pain, painful musculoskeletal
1570 injuries (including minor pain related to fractures), dental pain, postoperative pain, and kidney stones;
1571 triptans, NSAIDs, or their combinations should be used along with antiemetics as needed for acute pain
1572 related to episodic migraine. NSAID use has been associated with serious gastrointestinal events and
1573 major coronary events (McDonagh et al., April 2020), particularly in patients with cardiovascular or
1574 gastrointestinal co-morbidities, and clinicians should weigh risks and benefits of use, dose, and duration
1575 of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart
1576 failure, or those with risk for peptic ulcer disease or cardiovascular disease. Vasoactive effects of triptans
1577 and ergot alkaloids might preclude their use in patients with migraine who also have cardiovascular risk
1578 factors (Buse, Reed, Fanning, Kurth, & Lipton, 2017; Halker Singh et al., December 2020; Lipton, Reed,
1579 Kurth, Fanning, & Buse, 2017). Clinicians should review FDA-approved labeling, including boxed
1580 warnings before initiating treatment with any pharmacologic therapy.

1581

1582 **Opioid medication for acute pain**

1583 The evidence review (Chou et al., December 2020) found that opioids might not be more
1584 effective than nonopioid therapies for some acute pain conditions (Chang, Bijur, Esses, Barnaby, & Baer,
1585 2017; Friedman et al., 2015; Lewis et al., 2015; Moore & Hersh, 2013; Pathan, Mitra, & Cameron, 2018),

1586 and use of opioids might negatively affect recovery and function (Franklin, Stover, Turner, Fulton-Kehoe,
1587 & Wickizer, 2008; B. S. Webster, Verma, & Gatchel, 2007). The review found that opioids were probably
1588 less effective than NSAIDs for surgical dental pain and kidney stones, less effective than acetaminophen
1589 for kidney stone pain, and similarly effective as NSAIDs for low back pain (Chou et al., December 2020).
1590 For postoperative pain, effects of opioids on pain intensity were inconsistent, and opioids were
1591 associated with increased likelihood of repeat or rescue analgesic use (Chou et al., December 2020).
1592 There was some evidence that opioids might be more effective than gabapentin for acute neuropathic
1593 pain (Chou et al., December 2020). There was insufficient evidence for opioids in treatment of episodic
1594 migraine (Halker Singh et al., December 2020). Compared with NSAIDs or acetaminophen, opioids were
1595 associated with increased risk of short-term adverse events, including any adverse event, nausea,
1596 dizziness, and somnolence (Chou et al., December 2020). Observational studies found opioid use for
1597 acute low back pain or postoperative pain was associated with increased likelihood of long-term opioid
1598 use (Chou et al., December 2020). Proportions of adults with new long-term opioid use at follow-up
1599 after initiation for short-term use for post-operative pain have ranged from <1% to 13% (Brummett et
1600 al., 2017; Deyo et al., 2018; Goesling et al., 2016; S. P. Johnson et al., 2016; J. S. Lee et al., 2017; E. C.
1601 Sun, Darnall, Baker, & Mackey, 2016). Odds of long-term opioid use at follow-up after initiation for
1602 short-term use for acute pain might be greater with higher dose and duration of exposure. For example,
1603 one study found that compared with no early opioid use for acute low back pain, the adjusted odds ratio
1604 was 2.08 (95% CI 1.55 to 2.78) for an early prescription totaling 1 to 140 MME/day and increased to 6.14
1605 (95% CI 4.92 to 7.66) for an early prescription totaling ≥ 450 MME/day (B. S. Webster et al., 2007). In
1606 episodic migraine, opioids as well as butalbital-containing medications were associated with a two-fold
1607 higher risk of development of medication overuse headache compared with simple analgesics and
1608 triptans (Halker Singh et al., December 2020; Katsarava et al., 2004). Serious adverse events were

1609 uncommon for opioids as well as for other medications, but studies were not designed to assess risk of
1610 overdose, opioid use disorder, or long-term harms (Chou et al., December 2020).

1611 For acute low back pain, the American College of Physicians found insufficient evidence for
1612 effectiveness of opioids and recommends nonopioid medications (see **Nonopioid medications for acute**
1613 **pain**) if choosing pharmacologic treatment (Qaseem et al., 2017). The American College of Physicians
1614 and American Academy of Family Physicians suggest against treating patients with acute pain from
1615 musculoskeletal injuries with opioids, including tramadol (Qaseem et al., 2020). The American Dental
1616 Association recommends NSAIDs as the first-line therapy for acute pain management (see **Nonopioid**
1617 **medications for acute pain**) (American Dental Association, 2020). The American College of Obstetricians
1618 and Gynecologists recommends a shared decision-making approach to postpartum discharge pain
1619 management, incorporating pharmacologic treatments that may include opioids, limiting duration of
1620 opioid use to the shortest reasonable course expected for treating acute pain, noting that if a codeine-
1621 containing medication is selected, duration of therapy and neonatal signs of toxicity should be reviewed
1622 with individuals and their families (The American College of Obstetricians and Gynecologists, 2021).
1623 Multiple guidelines addressing prescribing for postoperative pain include both nonopioid and opioid
1624 treatment options and have emphasized multimodal analgesia, incorporating around the clock
1625 nonopioid analgesics and nonpharmacologic therapies and noting that systemic opioids are often
1626 needed postoperatively but are not required in all patients (Chou et al., 2016; Hill, Stucke, Billmeier,
1627 Kelly, & Barth, 2018; Overton et al., 2018). The American Headache Society recommends against
1628 prescribing opioid or butalbital-containing medications as first-line treatment for recurrent headache
1629 disorders (Loder, Weizenbaum, Frishberg, & Silberstein, 2013), and the American Academy of Neurology
1630 recommends against use of these medications for treatment of migraine, except as a last resort (Langer-
1631 Gould et al., 2013).

1632 Given equivalent or lesser effectiveness for pain relief compared with NSAIDs and risks of long-
1633 term opioid use after using opioids for acute pain, opioids are not recommended as first-line therapy for
1634 many common acute pain conditions, including low back pain, neck pain, pain related to other
1635 musculoskeletal injuries (such as sprains, strains, tendonitis, bursitis), pain related to minor surgeries
1636 typically associated with minimal tissue injury and only mild postoperative pain (e.g., dental extraction),
1637 dental pain, kidney stone pain, and headaches including episodic migraine. There is an important role
1638 for opioid therapy for acute pain related to severe traumatic injuries (including crush injuries and burns),
1639 invasive surgeries typically associated with moderate to severe postoperative pain, and other severe
1640 acute pain when NSAIDs and other therapies are contraindicated or likely to be ineffective.

1641 When diagnosis and severity of acute pain are reasonably assumed to warrant the use of
1642 opioids, clinicians should prescribe immediate-release opioids (see Recommendation 3) at the lowest
1643 dose to achieve expected effects (see Recommendation 4) and for no longer than the expected duration
1644 of pain severe enough to require opioids (see Recommendation 6) to minimize unintentional initiation
1645 of long-term opioid use. Clinicians should maximize use of nonopioid pharmacologic (e.g., NSAIDs
1646 and/or acetaminophen) and nonpharmacologic (e.g., ice, heat, elevation, rest, immobilization and/or
1647 exercise) therapies as appropriate for the specific condition and continue these therapies as needed
1648 once opioids are discontinued. Clinicians should work with patients to prevent prolonged opioid use,
1649 prescribe and advise opioid use only as needed (e.g., hydrocodone 5 mg/acetaminophen 325mg, one
1650 tablet not more frequently than every 4 hours as needed for pain) rather than on a scheduled basis (e.g.,
1651 one tablet every 4 hours), and encourage and include an opioid taper if opioids will be taken around the
1652 clock for more than a few days (see Recommendation 6). Clinicians should consider concurrent medical
1653 conditions, including sleep apnea, pregnancy, renal or hepatic insufficiency, mental health conditions,
1654 and substance use disorder, in assessing risks of opioid therapy (see Recommendation 8), offer naloxone
1655 if the patient or a household member has risk factors for opioid overdose (see Recommendation 8), use

1656 extreme caution when prescribing benzodiazepines or other sedating medications with opioids (see
1657 Recommendation 11), and check the PDMP database to ensure a new opioid prescription will not
1658 contribute to cumulative opioid dosages or medication combinations that put the patient at risk for
1659 overdose (see Recommendation 9). If there are signs of opioid use disorder, clinicians should address
1660 concerns with the patient, should offer or arrange medication treatment for patients who meet criteria
1661 for opioid use disorder, and should use nonpharmacologic and pharmacologic treatments as appropriate
1662 to manage the patient’s pain (see Recommendation 12 and The ASAM National Practice Guideline for
1663 the Treatment of Opioid Use Disorder: 2020 Focused Update (American Society of Addiction Medicine,
1664 2020)).

1665 Although findings regarding risks of new long-term opioid use after use for acute pain (Chou et
1666 al., December 2020) relate specifically to patients who were previously opioid-naïve, there might also be
1667 risks associated with dose escalation (see Recommendation 4) if patients already treated with long-term
1668 opioids are prescribed additional opioid medication for new acute pain superimposed on chronic pain.
1669 Therefore, strategies that minimize opioid use should be implemented for both opioid-naïve and opioid-
1670 tolerant patients with acute pain when possible. If patients already receiving long-term opioids require
1671 additional medication for acute pain, nonopioid medications should be used when possible, and if
1672 additional opioids are required (e.g., for superimposed severe acute pain), they should be continued
1673 only for the duration of pain severe enough to require additional opioids, returning to the patient’s
1674 baseline opioid dosage as soon as possible, including an appropriate taper to baseline dosage if
1675 additional opioids were used around the clock for more than a few days (see Recommendation 6).

1676 Patient education and discussion before starting outpatient opioid therapy are critical so that
1677 patient preferences and values can be understood and inform clinical decisions. Clinicians should ensure
1678 that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids
1679 before starting or continuing opioid therapy and should involve patients in decisions about whether to

1680 start opioid therapy. Essential elements for communication and discussion with patients before starting
1681 outpatient opioid therapy for acute pain include the following:

- 1682 • Advise patients that short-term opioid use can lead to unintended long-term opioid use and the
1683 importance of working toward planned discontinuation of opioid use as soon as feasible,
1684 including a plan to appropriately taper opioids as pain resolves if opioids have been used around
1685 the clock for more than a few days (see Recommendation 6).
- 1686 • Review communication mechanisms and protocols patients can use to inform clinicians of
1687 severe or uncontrolled pain and to arrange for timely reassessment and management.
- 1688 • Advise patients about serious adverse effects of opioids, including potentially fatal respiratory
1689 depression and development of a potentially serious lifelong opioid use disorder (see
1690 Recommendation 12) that can cause distress and inability to fulfill major role obligations at
1691 work, school, or home.
- 1692 • Advise patients about common effects of opioids, such as constipation, dry mouth, nausea,
1693 vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms
1694 when stopping opioids. To prevent constipation associated with opioid use, advise patients to
1695 increase hydration and fiber intake and to maintain or increase physical activity as they are able.
1696 A cathartic (e.g., senna) with or without a stool softener or a laxative might be needed if opioids
1697 are used for more than a few days. To minimize withdrawal symptoms, clinicians should provide
1698 and discuss an opioid tapering plan when opioids will be used around the clock for more than a
1699 few days (see Recommendation 6). Limiting opioid use to the minimum needed to manage pain
1700 (e.g., taking the opioid only when needed if needed less frequently than every 4 hours and the
1701 prescription is written for every 4 hours as needed for pain) can help limit development of
1702 tolerance and therefore of withdrawal once opioids are discontinued.

- |
- 1703 • If formulations are prescribed that combine opioids with acetaminophen, advise patients of the
1704 risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen
1705 can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic
1706 alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological
1707 Management of Persistent Pain in Older Persons, 2009).
 - 1708 • To help patients assess when a dose of opioids is needed, explain that the goal is to reduce pain
1709 to make it manageable rather than to eliminate pain.
 - 1710 • Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery,
1711 particularly when opioids are initiated or when other central nervous system depressants, such
1712 as benzodiazepines or alcohol, are used concurrently.
 - 1713 • Discuss increased risks for opioid use disorder, respiratory depression, and death at higher
1714 dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not
1715 taking more opioids or taking them more often.
 - 1716 • Review increased risks for respiratory depression when opioids are taken with benzodiazepines,
1717 other sedatives, alcohol, non-prescribed or illicit drugs such as heroin, or other opioids (see
1718 Recommendations 8, 11).
 - 1719 • Discuss risks to household members and other individuals if opioids are intentionally or
1720 unintentionally shared with others for whom they are not prescribed, including the possibility
1721 that others might experience overdose at the same or at lower dosage than prescribed for the
1722 patient, and that young children and pets are susceptible to unintentional ingestion. Discuss
1723 storage of opioids in a secure, preferably locked location and options for safe disposal of unused
1724 opioids (U.S. Food and Drug Administration, 2020a).

- 1725 • Discuss planned use of precautions to reduce risks, including naloxone for overdose reversal
1726 (see Recommendation 8), and clinician use of prescription drug monitoring program information
1727 (see Recommendation 9).

1728
1729 **2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider**
1730 **initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh**
1731 **risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should**
1732 **discuss with patients the known risks and realistic benefits of opioid therapy, should work with**
1733 **patients to establish treatment goals for pain and function, and should consider how opioid**
1734 **therapy will be discontinued if benefits do not outweigh risks (recommendation category: A,**
1735 **evidence type: 2).**

1736 Implementation considerations:

- 1737 • *To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or*
1738 *confirm the diagnosis.*
- 1739 • *Clinicians should use appropriate noninvasive, nonpharmacologic approaches to help manage*
1740 *chronic pain, such as exercise (aerobic, aquatic, and/or resistance exercises) or exercise therapy*
1741 *(a prominent modality in physical therapy) for back pain, fibromyalgia, and hip or knee*
1742 *osteoarthritis; weight loss for knee osteoarthritis; manual therapies for hip osteoarthritis;*
1743 *psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based*
1744 *stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back pain; mind-*
1745 *body practices (yoga, tai chi, qigong), massage, and acupuncture for neck pain; CBT, myofascial*
1746 *release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary*
1747 *rehabilitation for fibromyalgia; and spinal manipulation for tension headache.*
- 1748 • *Low-cost options to integrate exercise include walking in public spaces or use of public recreation*
1749 *facilities for group exercise. Physical therapy can be helpful, particularly for patients who have*
1750 *limited access to safe public spaces or public recreation facilities for exercise or have not*
1751 *improved with low-intensity physical exercise.*
- 1752 • *To improve pain management and reduce medication use and associated risks, health insurers*
1753 *and health systems should increase access to noninvasive, nonpharmacologic therapies with*
1754 *evidence for effectiveness.*
- 1755 • *Clinicians should review FDA-approved labeling including boxed warnings and weigh benefits*
1756 *and risks before initiating treatment with any pharmacologic therapy.*

- 1757 • *When patients affected by osteoarthritis have an insufficient response to nonpharmacologic*
 1758 *interventions such as exercise for arthritis pain, topical NSAIDs can be used in patients with a*
 1759 *single or few joints near the surface of the skin (e.g., knee). In patients with osteoarthritis pain in*
 1760 *multiple joints or incompletely controlled with topical NSAIDs, duloxetine or systemic NSAIDs can*
 1761 *be considered.*
- 1762 • *NSAIDs should be used at the lowest dose and duration needed and should be used with caution,*
 1763 *particularly in patients with cardiovascular comorbidities, chronic renal failure, or previous*
 1764 *gastrointestinal bleeding.*
- 1765 • *When patients with chronic low back pain have had an insufficient response to*
 1766 *nonpharmacologic approaches such as exercise, clinicians can consider NSAIDs or duloxetine for*
 1767 *patients without contraindications.*
- 1768 • *Tricyclic, tetracyclic, and SNRI antidepressants, selected anticonvulsants (pregabalin, gabapentin*
 1769 *enacarbil, oxcarbazepine), and capsaicin and lidocaine patches can be considered for*
 1770 *neuropathic pain.*
- 1771 • *Duloxetine and pregabalin are FDA-approved for the treatment of diabetic peripheral*
 1772 *neuropathy, and pregabalin and gabapentin are FDA-approved for treatment of post-herpetic*
 1773 *neuralgia.*
- 1774 • *In patients with fibromyalgia, tricyclic (amitriptyline) and SNRI antidepressants (duloxetine and*
 1775 *milnacipran), NSAIDs (topical diclofenac), and specific anticonvulsants (pregabalin and*
 1776 *gabapentin) are used to improve pain, function, and quality of life. Duloxetine, milnacipran, and*
 1777 *pregabalin are FDA-approved for the treatment of fibromyalgia.*
- 1778 • *Patients with co-occurring pain and depression might be especially likely to benefit from*
 1779 *antidepressant medication (see Recommendation 8).*
- 1780 • *Opioids should not be considered first-line or routine therapy for subacute or chronic pain. This*
 1781 *does not mean that patients should be required to sequentially “fail” nonpharmacologic and*
 1782 *nonopioid pharmacologic therapy or be required to use any specific therapy before proceeding to*
 1783 *opioid therapy. Rather, expected benefits specific to the clinical context should be weighed*
 1784 *against risks before initiating therapy. In some clinical contexts (e.g., serious illness in a patient*
 1785 *with poor prognosis for return to previous level of function, contraindications to other therapies,*
 1786 *and clinician and patient agreement that the overriding goal is patient comfort), opioids might*
 1787 *be appropriate regardless of previous therapies used. In other situations, (e.g., headache or*
 1788 *fibromyalgia), expected benefits of initiating opioids are unlikely to outweigh risks regardless of*
 1789 *previous nonpharmacologic and nonopioid pharmacologic therapies used.*
- 1790 • *Opioid therapy should not be initiated without consideration by the clinician and patient of an*
 1791 *“exit strategy” to be used if opioid therapy is unsuccessful.*
- 1792 • *Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine jointly*
 1793 *with patients how effectiveness will be evaluated and establish treatment goals.*

- 1794 • *Clinicians seeing new patients already receiving opioids should establish treatment goals for*
1795 *continued opioid therapy. Clinicians should avoid rapid tapering or abrupt discontinuation of*
1796 *opioids (see Recommendation 5).*
- 1797 • *Patient education and discussion before starting opioid therapy are critical so that patient*
1798 *preferences and values can be understood and used to inform clinical decisions.*
- 1799 • *Clinicians should review available low-cost options for pain management for all patients, and*
1800 *particularly for low-income, underinsured and uninsured patients.*
- 1801 • *Clinicians should ensure that patients are aware of expected benefits of, common and serious*
1802 *risks of, and alternatives to opioids before starting or continuing opioid therapy and should*
1803 *involve patients in decisions about whether to start opioid therapy.*

1804 *Supporting Rationale*

1805 To guide patient-specific selection of therapy, clinicians should evaluate patients and establish
1806 or confirm the diagnosis. Detailed recommendations on diagnosis are provided in other guidelines
1807 (American College of Occupational and Environmental Medicine, 2017; Chou et al., 2007; Federation of
1808 State Medical Boards, 2017; Hooten et al., 2013; U.S. Department of Veterans Affairs and Department of
1809 Defense, 2017), but evaluation should generally include a focused history, including history and
1810 characteristics of pain and potential contributing factors (e.g., function, psychosocial stressors, sleep)
1811 and physical exam, with imaging or other diagnostic testing only if indicated (e.g., if severe or
1812 progressive neurologic deficits are present or if serious underlying conditions are suspected [Chou et al.,
1813 2007; Hooten et al., 2013]). For complex pain syndromes, pain specialty consultation can be considered
1814 to assist with diagnosis as well as management.

1815 Diagnosis can help identify disease-specific interventions to reverse, ameliorate, or prevent
1816 worsening of pain and improve function; for example, improving glucose control to prevent progression
1817 of diabetic neuropathy; immune-modulating agents for rheumatoid arthritis; physical or occupational
1818 therapy to address posture, muscle weakness, or repetitive occupational motions that contribute to
1819 musculoskeletal pain; or surgical intervention to relieve mechanical/compressive pain (Hooten et al.,
1820 2013). The underlying mechanism for most pain syndromes can be categorized as neuropathic (e.g.,

1821 diabetic neuropathy, postherpetic neuralgia, fibromyalgia), or nociceptive (e.g., osteoarthritis, muscular
1822 back pain). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic
1823 pain treatment with medication. For example, there is limited evidence for improved pain or function, or
1824 evidence of worse outcomes, with long-term use of opioids for several chronic pain conditions for which
1825 opioids are commonly prescribed, such as osteoarthritis (Bannuru et al., 2019), low back pain (Chaparro
1826 et al., 2014; Qaseem et al., 2017), headache (Loder et al., 2013), and fibromyalgia (Gaskell, Moore,
1827 Derry, & Stannard, 2014; Goldenberg, Clauw, Palmer, & Clair, 2016). For moderate to severe chronic
1828 back pain or hip or knee osteoarthritis pain, a nonopioid strategy starting with acetaminophen or
1829 NSAIDs results in significantly improved pain intensity compared to a strategy starting with opioids (E. E.
1830 Krebs et al., 2018). Tricyclic antidepressants, SNRI antidepressants, selected anticonvulsants, or
1831 transdermal lidocaine are recommended for neuropathic pain syndromes (e.g., diabetic neuropathy,
1832 postherpetic neuralgia [American College of Occupational and Environmental Medicine, 2017]).

1833 In addition, review of the patient’s history and context beyond the presenting pain syndrome is
1834 helpful in selection of pain treatments. In particular, medications should be used only after assessment
1835 and determination that expected benefits outweigh risks given patient-specific factors. For example,
1836 clinicians should consider fall risk when selecting and dosing potentially sedating medications such as
1837 tricyclics, anticonvulsants, and opioids, and should weigh risks and benefits of use, dose, and duration of
1838 NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart
1839 failure, or those with risk for peptic ulcer disease or cardiovascular disease. Some guidelines recommend
1840 topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged
1841 ≥ 75 years to minimize systemic effects (Hochberg et al., 2012). See Recommendation 8 for additional
1842 considerations for assessing risks of opioid therapy.

1843
1844 **Noninvasive, nonpharmacologic approaches to subacute and chronic pain**

1845 Many noninvasive, nonpharmacologic approaches, including physical therapy, weight loss for
1846 knee osteoarthritis, and psychological therapies such as CBT, and mindfulness-based stress reduction
1847 can improve pain and function without risk for serious harms (Skelly et al., April 2020). There is high-
1848 quality evidence that exercise therapy (a prominent modality in physical therapy) for back pain,
1849 fibromyalgia, and hip or knee osteoarthritis reduces pain and improves function immediately after
1850 treatment and that the improvements are sustained for at least 2–6 months (Busch, Barber, Overend,
1851 Peloso, & Schachter, 2007; Fransen et al., 2015; Fransen, McConnell, Hernandez-Molina, & Reichenbach,
1852 2014; Hayden, van Tulder, Malmivaara, & Koes, 2005; Skelly et al., April 2020). Previous guidelines have
1853 recommended aerobic, aquatic, and/or resistance exercises for people with chronic pain, including
1854 osteoarthritis of the knee or hip, back pain, and fibromyalgia (American College of Occupational and
1855 Environmental Medicine, 2017; Hochberg et al., 2012; Macfarlane et al., 2017; Qaseem et al., 2017; U.S.
1856 Department of Veterans Affairs and Department of Defense, 2017). Other noninvasive,
1857 nonpharmacologic therapies that improve pain and/or function for at least one month after delivery
1858 without apparent risk for serious harm include CBT for knee osteoarthritis; manual therapies for hip
1859 osteoarthritis; psychological therapy, spinal manipulation, low-level laser therapy, massage,
1860 mindfulness-based stress reduction, yoga, acupuncture, and multidisciplinary rehabilitation for low back
1861 pain; mind-body practices (e.g., yoga, tai chi, qigong), massage, and acupuncture for neck pain; CBT,
1862 myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, and multidisciplinary
1863 rehabilitation for fibromyalgia; and spinal manipulation for tension headache (Skelly et al., April 2020).
1864 For temporomandibular disorder pain, patient education and self-care can be effective, as can occlusal
1865 splints for some patients and biobehavioral therapy for prevention of disabling symptoms (List &
1866 Axelsson, 2010; Michelotti, Iodice, Vollaro, Steenks, & Farella, 2012). Exercise, mind-body interventions,
1867 and psychological treatments (including CBT and mindfulness practices) can encourage active patient
1868 participation in the care plan and address the effects of pain in the patient’s life; these more “active”

1869 therapies have somewhat more robust evidence for sustained improvements in pain and function than
1870 more “passive” treatments (e.g., massage), particularly at longer-term follow-up (Skelly et al., April
1871 2020). Active approaches that engage the patient should be used, when possible, with a supplementary
1872 role for more passive approaches, to reduce pain and improve function.

1873 Despite their favorable benefit-to-risk profile, noninvasive, nonpharmacologic therapies are not
1874 always or fully covered by insurance (Heyward et al., 2018). Access and cost can be barriers for patients,
1875 particularly people who are low-income, uninsured, underinsured, or living in rural areas or with
1876 transportation challenges. To improve pain management and reduce medication use and associated
1877 risks, health insurers and health systems should increase access to noninvasive, nonpharmacologic
1878 therapies with evidence for effectiveness. In addition, for many patients, aspects of these approaches
1879 can be used even when there is limited access to specialty care. For example, previous guidelines have
1880 strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of
1881 the knee or hip (Hochberg et al., 2012) and maintenance of physical activity, including normal daily
1882 activities, for patients with low back pain (Chou et al., 2007). A randomized trial found no difference in
1883 reduced chronic low back pain intensity, frequency or disability between patients assigned to relatively
1884 low-cost group aerobics and individual physiotherapy or muscle reconditioning sessions (Mannion,
1885 Müntener, Taimela, & Dvorak, 1999). Low-cost options to integrate exercise include walking in public
1886 spaces or use of public recreation facilities for group exercise. Physical therapy can be helpful,
1887 particularly for patients who have limited access to safe public spaces or public recreation facilities for
1888 exercise or have not improved with low-intensity physical exercise. A randomized trial found a stepped
1889 exercise program, in which patients were initially offered an internet-based exercise program and
1890 progressively advanced to biweekly coaching calls and then to in-person physical therapy if not
1891 improved at previous steps, successfully improved symptomatic knee osteoarthritis, with 35% of
1892 patients ultimately requiring in-person physical therapy (Allen et al., 2020). In addition, primary care

1893 clinicians can integrate elements of psychosocial therapies such as CBT, which addresses psychosocial
1894 contributors to pain and improves function (A. C. Williams, Eccleston, & Morley, 2012), by encouraging
1895 patients to take an active role in the care plan, by supporting patients in engaging activities such as
1896 exercise that are generally beneficial but that might initially be associated with fear of exacerbating pain
1897 (Hooten et al., 2013), or by providing education in relaxation techniques and coping strategies. In many
1898 locations, there are free or low-cost patient support, self-help, and educational community-based or
1899 employer-sponsored programs that can provide stress reduction and other mental health benefits.
1900 Clinicians should be familiar with such options within their communities so they can refer patients to
1901 low-cost services. Patients with higher levels of anxiety or fear related to pain, or other significant
1902 psychological distress, can be referred for treatment with a mental health specialist (e.g., psychologist,
1903 psychiatrist, clinical social worker).

1904

1905 **Nonopioid medications for subacute and chronic pain**

1906 Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected
1907 antidepressants and anticonvulsants) are used for painful symptoms in chronic pain conditions.
1908 Nonopioid pharmacologic therapies are associated with risks, particularly in older adults, pregnant
1909 patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and
1910 liver disease. For example, NSAID use has been associated with serious gastrointestinal events and
1911 major coronary events (McDonagh et al., April 2020). Increases in non-serious adverse events have been
1912 found with the anticonvulsants pregabalin (blurred vision, cognitive effects, sedation, weight gain,
1913 dizziness and peripheral edema) and gabapentin (blurred vision, cognitive effects, sedation, and weight
1914 gain), with cannabis (nausea and dizziness), and with the SNRIs duloxetine (nausea, sedation) and
1915 milnacipran (nausea); dose reductions reduced the risk of some adverse events with SNRI

1916 antidepressants (McDonagh et al., April 2020). Clinicians should review FDA-approved labeling including
1917 boxed warnings before initiating treatment with any pharmacologic therapy.

1918 For osteoarthritis, NSAIDs including topical NSAIDs (diclofenac) and the SNRI duloxetine have
1919 small to moderate benefits for pain and function at short-term assessment (3 to 6 months), with
1920 intermediate-term (6 to 12 months) evidence for some medications (celecoxib and duloxetine), and
1921 some evidence that duloxetine is more effective in older (>65 years) compared to younger patients and
1922 in patients with knee osteoarthritis (McDonagh et al., April 2020). Acetaminophen has limited evidence
1923 for effectiveness (McDonagh et al., April 2020) and is no longer considered a first-line treatment for
1924 osteoarthritis (Bannuru et al., 2019). When patients have an insufficient response to nonpharmacologic
1925 interventions such as exercise for arthritis pain and if a single or a few joints near the surface of the skin
1926 (e.g., knee) are affected by osteoarthritis, use of topical NSAIDs is recommended (Bannuru et al., 2019).
1927 In patients with osteoarthritis pain in multiple joints or incompletely controlled with topical NSAIDs,
1928 systemic NSAIDs or duloxetine can be used. However, systemic NSAIDs should be used at the lowest
1929 dose and duration needed as risks may increase with longer use and at higher doses (U.S. Food and Drug
1930 Administration, 2015b). NSAIDs should be used with caution particularly in patients with cardiovascular
1931 comorbidities, chronic renal failure, or previous gastrointestinal bleeding. In patients with
1932 gastrointestinal comorbidities but without current or previous gastrointestinal bleeding,
1933 cyclooxygenase-2 (COX-2) inhibitors or NSAIDs with proton pump inhibitors can be used to minimize risk
1934 compared to risk with use of NSAIDs alone (Bannuru et al., 2019). Moderate-quality evidence shows
1935 small improvements in chronic low back pain with NSAIDs (Qaseem et al., 2017) and with duloxetine
1936 (McDonagh et al., April 2020). When patients have had an insufficient response to nonpharmacologic
1937 approaches such as exercise, clinicians can consider NSAIDs or duloxetine (Qaseem et al., 2017) for
1938 patients without contraindications. For temporomandibular disorder pain that is not sufficiently
1939 improved with nonpharmacologic interventions, NSAIDs can be effective (Kulkarni, Thambar, & Arora,

1940 2020; Mujakperuo, Watson, Morrison, & Macfarlane, 2010). Tricyclic, tetracyclic, and SNRI
1941 antidepressants, selected anticonvulsants, and capsaicin and lidocaine patches are recommended for
1942 neuropathic pain (American College of Occupational and Environmental Medicine, 2017). However,
1943 evidence on topical lidocaine and capsaicin is limited (McDonagh et al., April 2020). The SNRI
1944 antidepressant duloxetine and selected anticonvulsants (pregabalin, gabapentin, and carbamazepine,
1945 oxcarbazepine) are associated with small improvements in neuropathic pain (mainly diabetic
1946 neuropathy and post-herpetic neuralgia) (McDonagh et al., April 2020). Duloxetine and pregabalin are
1947 FDA-approved for the treatment of diabetic neuropathy, and pregabalin and gabapentin are FDA-
1948 approved for treatment of post-herpetic neuralgia. In patients with fibromyalgia, several medications
1949 have been shown to be associated with small to moderate improvements in pain, function, and quality
1950 of life, including SNRI antidepressants (duloxetine and milnacipran), NSAIDs (topical diclofenac), and
1951 specific anticonvulsants (pregabalin and gabapentin) (McDonagh et al., April 2020). Tricyclics and SNRIs
1952 can also relieve fibromyalgia symptoms. Duloxetine, milnacipran, and pregabalin are FDA-approved for
1953 and are recommended for the treatment of fibromyalgia (American College of Occupational and
1954 Environmental Medicine, 2017). The tricyclic antidepressant amitriptyline is often used and
1955 recommended in patients with fibromyalgia (American College of Occupational and Environmental
1956 Medicine, 2017), although evidence on its effectiveness is limited (McDonagh et al., April 2020). Because
1957 patients with chronic pain might experience concurrent depression (Howe & Sullivan, 2014), and
1958 depression can exacerbate physical symptoms including pain (Sullivan, Edlund, Zhang, Unützer, & Wells,
1959 2006), patients with co-occurring pain and depression might be especially likely to benefit from
1960 antidepressant medication (see Recommendation 8). Evidence on effectiveness of cannabis for painful
1961 conditions is limited, inconsistent across studies, and some studies have reported adverse events such
1962 as dizziness, nausea, and sedation (Banerjee & McCormack, 2019; McDonagh et al., April 2020).
1963

1964 **Opioid medication for subacute and chronic pain**

1965 The clinical evidence reviews found insufficient evidence to determine long-term benefits of
1966 opioid therapy for chronic pain and found an increased risk for serious harms related to long-term
1967 opioid therapy that appears to be dose-dependent (Chou et al., April 2020). Compared with no opioid
1968 use, opioid use was associated with increased risk of opioid use disorder, overdose, all-cause mortality,
1969 fractures, falls, and myocardial infarction (Chou et al., April 2020). Opioids were also associated with
1970 increased risk of discontinuation due to gastrointestinal adverse events, somnolence, dizziness, and
1971 pruritus (Chou et al., April 2020). Compared with placebo, at short-term (1 - <6 months) follow-up,
1972 opioids were associated with small mean improvements in pain intensity (mean difference -0.79 point
1973 on a 0 to 10 scale, 95% confidence interval [CI], -0.93 to -0.67, I²=71%) and function (Chou et al., April
1974 2020). There was some evidence that improvement in pain is reduced with longer duration of opioid
1975 therapy; from a mean improvement of 1 on a 0 to 10 scale at 1 to 3 months to about 0.5 at 3 to 6
1976 months (Chou et al., April 2020). No placebo-controlled trial evaluated effectiveness of opioids at
1977 intermediate (6 - <12 months) or long-term (≥12 months) follow-up (Chou et al., April 2020). Compared
1978 with nonopioid treatments at short-term follow-up, there were no differences in mean pain
1979 improvement (mean difference -0.29 on a 0 to 10 scale, 95% CI, -0.61 to 0.03) or functional
1980 improvement. No trials compared opioids with nonopioid therapies at intermediate or long-term follow-
1981 up, with the exception of one trial which found stepped therapy starting with opioids associated with
1982 higher pain intensity than stepped therapy starting with nonopioids (4.0 vs. 3.5, mean difference 0.5,
1983 95% CI, 0.0 to 1.0) at 12-months (Chou et al., April 2020; E. E. Krebs et al., 2018).

1984 The clinical evidence reviews identified an observational study (Edlund et al., 2014) finding long-
1985 term (>90 days' supply) opioid prescription to be associated with significantly increased risk of a new
1986 opioid use disorder diagnosis for all dosages of long-term (>90 days' supply) opioids prescribed, with
1987 adjusted odds ratios of 15, 29, and 122 at low (1 to 36 MME/day), medium (36 to 120 MME/day) and

1988 high (≥ 120 MME/day) opioid dosages, respectively). Compared with no opioid use, opioid use was
1989 associated with increased risk of opioid use disorder, overdose, all-cause mortality, fractures, falls, and
1990 myocardial infarction (Chou et al., April 2020).

1991 Several experts from the Opioid Workgroup appreciated the importance of highlighting both
1992 pain and function, of clinicians being realistic “upfront” with patients, and of attention to tapering and
1993 exit strategies. While some experts felt the recommendation statement could state nonopioid therapies
1994 “may be preferred” or “may be effective” for chronic pain, others agreed with language that nonopioid
1995 therapies “are preferred” for chronic pain, given opioid therapies are associated with small short-term
1996 benefits compared with placebo, comparable or reduced short-term benefits compared with nonopioid
1997 therapies, uncertain long-term benefits, and potential for serious harms.

1998 ***Opioids should not be considered first-line or routine therapy for subacute or chronic pain.***

1999 Although evidence on long-term benefits of nonopioid therapies is also limited, these therapies are also
2000 associated with short-term benefits, there is no evidence for attenuated benefit over time or difficulty
2001 stopping therapy when benefits do not outweigh risks, and risks for serious harms are usually lower.

2002 ***This does not mean that patients should be required to sequentially “fail” nonpharmacologic and***
2003 ***nonopioid pharmacologic therapy or be required to use any specific therapy before proceeding to***
2004 ***opioid therapy.*** Rather, expected benefits specific to the clinical context should be weighed against risks
2005 before initiating therapy. ***In some clinical contexts (e.g., serious illness in a patient with poor prognosis***
2006 ***for return to previous level of function, contraindications to other therapies, and clinician and patient***
2007 ***agreement that the overriding goal is patient comfort), opioids might be appropriate regardless of***
2008 ***previous therapies used. In other situations (e.g., headache or fibromyalgia), expected benefits of***
2009 ***initiating opioids are unlikely to outweigh risks regardless of previous nonpharmacologic and***
2010 ***nonopioid pharmacologic therapies used.***

2011 The clinical evidence reviews found no instrument with high accuracy for predicting opioid-
2012 related harms such as overdose or opioid use disorder (Chou et al., April 2020). It can be very
2013 challenging for clinicians to predict whether benefits of opioids for chronic pain will outweigh risks of
2014 ongoing treatment for individual patients. **Therefore, opioid therapy should not be initiated without**
2015 **consideration by the clinician and patient of an “exit strategy” that could be used if opioid therapy is**
2016 **unsuccessful.** Before opioid therapy is initiated for subacute or chronic pain, clinicians should determine
2017 with patients how effectiveness will be evaluated and establish treatment goals. Some patients have
2018 reported treatment goals are effective in increasing motivation and functioning (Chou et al., April 2020).
2019 Goals ideally include improvement in pain relief, function (including social and emotional as well as
2020 physical dimensions), and quality of life. Goals can be tailored to individual patient and clinical
2021 circumstances. For example, for some patients with diseases typically associated with progressive
2022 functional impairment or catastrophic injuries such as spinal cord trauma, reductions in pain without
2023 improvement in physical function might be more realistic. Clinicians can assess and then follow (see
2024 Recommendation 7) function, pain control, and quality of life using tools such as the three-item “Pain
2025 average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment
2026 Scale (Krebs et al., 2009). Clinically meaningful improvement has been defined as a 30% improvement in
2027 scores for both pain and function (Ostelo et al., 2008). Clinicians can ask patients about functional goals
2028 that have meaning for them (e.g., walking the dog or walking around the block, returning to part-time
2029 work, attending family sports or recreational activities), and then use these goals in assessing benefits of
2030 opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy
2031 (see Recommendation 7). Clinicians seeing new patients already using opioid medication should
2032 establish treatment goals for continued opioid therapy. Clinicians should avoid rapid tapering or abrupt
2033 discontinuation of opioids (see Recommendation 5). Although the clinical evidence reviews did not find
2034 studies evaluating the effectiveness of written agreements or treatment plans (Chou et al., April 2020),

2035 clinicians and patients who set a treatment plan in advance of prescribing will clarify expectations
2036 regarding how opioids will be prescribed and monitored with an aim to improve patient safety, health,
2037 and well-being.

2038 Patient education and discussion before starting opioid therapy are critical so that patient
2039 preferences and values can be understood and used to inform clinical decisions. Clinicians should ensure
2040 that patients are aware of expected benefits of, common and serious risks of, and alternatives to opioids
2041 before starting or continuing opioid therapy and should involve patients in decisions about whether to
2042 start opioid therapy. Many patients rank pain relief, nausea, vomiting, and constipation as significant
2043 effects (Chou et al., April 2020). Essential elements for communication and discussion with patients
2044 before starting opioid therapy include the following:

- 2045 • Review available low-cost options for pain management for all patients, and particularly for low-
2046 income, underinsured, and uninsured patients. Review considerations related to access to care
2047 given the clinical oversight needed to initiate and continue opioid therapy and other treatments
2048 for pain.
- 2049 • Be explicit and realistic about expected benefits of opioids, explaining that there is not robust
2050 evidence that opioids improve pain or function with long-term use, and that complete
2051 elimination of pain is unlikely.
- 2052 • Emphasize improvement in function as a primary goal and that function can improve even when
2053 pain is not completely eliminated.
- 2054 • Advise patients about serious adverse effects of opioids, including potentially fatal respiratory
2055 depression and development of a potentially serious lifelong opioid use disorder that can cause
2056 distress and inability to fulfill major role obligations at work, school, or home.
- 2057 • Advise patients about common effects of opioids, such as constipation, dry mouth, nausea,
2058 vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms

2059 when stopping opioids. To prevent constipation associated with opioid use, advise patients to
2060 increase hydration and fiber intake and to maintain or increase physical activity. A cathartic
2061 (e.g., senna) with or without a stool softener or a laxative might be needed.

- 2062 • If formulations are prescribed that combine opioids with acetaminophen, advise patients of the
2063 risks of taking additional over-the-counter products containing acetaminophen. Acetaminophen
2064 can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic
2065 alcohol use or liver disease (American Geriatrics Society Panel on the Pharmacological
2066 Management of Persistent Pain in Older Persons, 2009).
- 2067 • Discuss effects that opioids might have on ability to safely operate a vehicle or other machinery,
2068 particularly when opioids are initiated, when dosages are increased, or when other central
2069 nervous system depressants, such as benzodiazepines or alcohol, are used concurrently.
- 2070 • Discuss increased risks for opioid use disorder, respiratory depression, and death at higher
2071 dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not
2072 taking more opioids or taking them more often.
- 2073 • Review increased risks for respiratory depression when opioids are taken with benzodiazepines,
2074 other sedatives, alcohol, non-prescribed drugs such as heroin, or other opioids.
- 2075 • Discuss risks to household members and other individuals if opioids are intentionally or
2076 unintentionally shared with others for whom they are not prescribed, including the possibility
2077 that others might experience overdose at the same or at lower dosage than prescribed for the
2078 patient, and that young children are susceptible to unintentional ingestion. Discuss storage of
2079 opioids in a secure, preferably locked location and options for safe disposal of unused opioids
2080 (U.S. Food and Drug Administration, 2020a).
- 2081 • Discuss the importance of periodic reassessment to ensure that opioids are helping to meet
2082 patient goals and to allow opportunities for opioid dosage reduction and/or discontinuation and

2083 consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if
2084 opioids are not effective or are harmful.

2085 • Discuss expectations for clinician and patient responsibilities to mitigate risks of opioid therapy
2086 and planned use of precautions to reduce risks, including naloxone for overdose reversal (see
2087 Recommendation 8), and clinician use of prescription drug monitoring program information (see
2088 Recommendation 9) and toxicology screening (see Recommendation 10).

2089 • Consider whether cognitive status might interfere with management of opioid therapy and, if
2090 so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the
2091 importance of reassessing medication use over time with both the patient and caregiver (as
2092 appropriate).

2093
2094 Given the possibility that benefits of opioid therapy might diminish or that risks might become
2095 more prominent over time, it is important that clinicians elicit patients' experiences and preferences and
2096 review expected benefits and risks of continued opioid therapy with patients periodically (see
2097 Recommendation 7).

2098
2099 **Interventional approaches to subacute and chronic pain**

2100 Interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for
2101 pain associated with rheumatoid arthritis (Wallen & Gillies, 2006) or osteoarthritis (Bellamy et al., 2006)
2102 and subacromial corticosteroid injection for rotator cuff disease (Buchbinder, Green, & Youd, 2003) can
2103 provide short-term improvement in pain and function. Evidence is insufficient to determine the extent
2104 to which repeated glucocorticoid injection increases potential risks such as articular cartilage changes (in
2105 osteoarthritis) and sepsis (Bellamy et al., 2006). Interventional pain management specialists offer
2106 additional interventions that can alleviate pain as part of a comprehensive pain management approach

2107 (U.S. Department of Health and Human Services, 2019b), including epidural steroid injections (for
2108 lumbar radiculopathy with herniated disc), nerve ablation procedures (e.g., radiofrequency denervation
2109 for low back pain), and neurostimulation procedures (e.g., peripheral nerve stimulation, spinal cord
2110 stimulation). Evidence is limited for many of these procedures, and additional research is needed to
2111 establish the clinical benefits of specific interventional procedures for specific pain conditions (Chou et
2112 al., 2021; U.S. Department of Health and Human Services, 2019b). Rare, serious adverse events have
2113 been reported with epidural injection (U.S. Food and Drug Administration, 2014c).

2114

2115 **Multimodal therapy for subacute and chronic pain**

2116 Integrated pain management requires coordination of medical, psychological, and social aspects
2117 of healthcare and includes primary care, mental and behavioral healthcare, and specialist services when
2118 needed (The Interagency Pain Research Coordinating Committee, 2015). Multimodal therapies and
2119 multidisciplinary biopsychosocial rehabilitation-combining approaches (e.g., psychological therapies
2120 with exercise) can reduce long-term pain and disability compared with usual care and compared with
2121 physical treatments (e.g., exercise) alone. Nonpharmacologic therapies can also provide synergistic
2122 benefits when nonopioid or opioid pain medications are used (U.S. Department of Health and Human
2123 Services, 2019b). When needed, medications should ideally be combined with nonpharmacologic
2124 therapy to provide greater benefits to patients in improving pain and function. Multimodal therapies are
2125 not always available or reimbursed by insurance and can be time-consuming and costly for patients, and
2126 disparities for being able to access multimodal care exist. There is evidence that less-intensive
2127 multidisciplinary rehabilitation can be similarly effective to high-intensity multidisciplinary rehabilitation
2128 (Skelly et al., April 2020). Multimodal therapies should be considered for patients not responding to
2129 single-modality therapy, and combinations should be tailored depending on patient needs, cost,
2130 convenience, and other individual factors.

2131 Depending on patient co-morbidities and benefit-to-risk ratio in individual patients,
2132 combinations of medications (for example, two nonopioid medications with different mechanisms of
2133 action or a nonopioid with an opioid medication) might also be used. In some cases, medication
2134 combinations might provide complementary or synergistic benefits and/or facilitate lower dosing of
2135 individual medications (Chou et al., April 2020), as has been demonstrated in trials of patients with
2136 neuropathic pain (Chou et al., April 2020). However, caution should be used to avoid synergistic risks of
2137 medications. For example, combinations of medications that depress the central nervous system and
2138 cause sedation (see Recommendation 11), such as an opioid with gabapentin, have been associated with
2139 increased risk of overdose compared with either medication alone (Chou et al., April 2020).

2140 **Opioid selection and dosage**

2141 **3. When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe**
2142 **immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids**
2143 **(recommendation category: A, evidence type: 4).**

2144 Implementation considerations:

- 2145 • *Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for*
2146 *subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for*
2147 *intermittent or as needed use.*

- 2148 • *ER/LA opioids should be reserved for severe, continuous pain. Some ER/LA opioids should be*
2149 *considered only for patients who have received certain dosages of opioids (e.g., 60 mg daily of*
2150 *oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) of*
2151 *immediate-release opioids daily for at least 1 week.*

- 2152 • *When changing to an ER/LA opioid for a patient previously receiving a different immediate-*
2153 *release opioid, clinicians should consult product labeling and reduce total daily dosage to*
2154 *account for incomplete opioid cross-tolerance.*

- 2155 • *Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval*
2156 *when prescribing to patients with renal or hepatic dysfunction because decreased clearance of*
2157 *medications among these patients can lead to accumulation of drugs to toxic levels and*
2158 *persistence in the body for longer durations.*

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- *Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given the potential increased risk for adverse events, including respiratory depression and overdose.*
- 2164
- 2165
- 2166
- 2167
- *Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone’s unique risk profile and who are prepared to educate and closely monitor their patients, including assessing risk for QT prolongation and considering electrocardiographic monitoring, should consider prescribing methadone for pain.*
- 2168
- 2169
- 2170
- *Only clinicians who are familiar with the dosing and absorption properties of the ER/LA opioid transdermal fentanyl and are prepared to educate their patients about its use should consider prescribing it.*

2171

2172 *Supporting Rationale*

2173 ER/LA opioids include methadone, transdermal fentanyl, and extended-release versions of

2174 opioids such as oxycodone, hydromorphone, hydrocodone, and morphine. The clinical evidence reviews

2175 found effects of opioids on short-term pain and function were generally consistent across duration of

2176 action (short- or long-acting) and opioid type (opioid agonist, partial agonist, or mixed mechanism [with

2177 mixed opioid and nonopioid mechanisms of action] agent), although 5 trials directly comparing different

2178 types of opioids found a mixed mechanism agent associated with greater pain relief versus a pure opioid

2179 agonist, with fewer nonserious adverse events (Chou et al., April 2020). A fair-quality study showed a

2180 higher risk for overdose among patients treated with ER/LA opioids than among those treated with

2181 immediate-release opioids, especially within the first 2 weeks of therapy, with relative risk decreasing

2182 with longer duration of exposure (Chou et al., April 2020; Miller et al., 2015). The clinical evidence

2183 reviews did not find evidence that continuous, time-scheduled use of ER/LA opioids is more effective or

2184 safer than intermittent use of immediate-release opioids or that time-scheduled use of ER/ LA opioids

2185 reduces risks for opioid use disorder (Chou et al., April 2020). In 2014, the FDA modified the labeling for

2186 ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved

2187 for “management of pain severe enough to require daily, around-the-clock, long-term opioid treatment”
2188 when “alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are
2189 ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain”
2190 and not used as “as needed” pain relievers (U.S. Food and Drug Administration, 2013). FDA has also
2191 noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients
2192 who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral
2193 oxycodone, or equianalgesic dosages of other opioids) for at least 1 week (U.S. Food and Drug
2194 Administration, 2014b). Time-scheduled opioid use can be associated with greater total average daily
2195 opioid dosage compared with intermittent, as-needed opioid use (Von Korff et al., 2011). Abuse-
2196 deterrent technologies have been employed to prevent manipulation intended to defeat extended-
2197 release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration,
2198 such as intravenous injection of oral opioids. As indicated in FDA guidance for industry on evaluation and
2199 labeling of abuse-deterrent opioids (U.S. Food and Drug Administration, 2015a), although abuse-
2200 deterrent technologies are expected to make manipulation of opioids more difficult or to reduce the
2201 potent effects of manipulation, they do not prevent opioid misuse or overdose through oral intake the
2202 most common route of opioid misuse — and can still be misused by nonoral routes. The “abuse-
2203 deterrent” label does not indicate that there is no risk for misuse or opioid use disorder. No studies
2204 were found in the clinical evidence reviews assessing the effectiveness of abuse-deterrent technologies
2205 as a risk mitigation strategy for deterring or preventing opioid misuse, use disorder, or overdose (Chou
2206 et al., April 2020). Experts agreed with the recommendation for clinicians to initiate opioid treatment
2207 with immediate-release opioids instead of with extended-release/long-acting (ER/LA) opioids and
2208 appreciated discussion of the lack of evidence for “abuse-deterrent” formulations.

2209 In comparing different ER/LA formulations, the clinical evidence reviews found inconsistent
2210 results for overdose risk with methadone versus other ER/LA opioids used for chronic pain, with two

2211 cohort studies of Medicaid beneficiaries finding methadone associated with increased risk of overdose
2212 or all-cause mortality versus morphine and one cohort study of Veterans Affairs patients finding
2213 methadone associated with decreased risk (Chou et al., April 2020). Methadone has been associated
2214 with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed
2215 for pain (Paulozzi, Mack, & Jones, 2012). In addition, methadone is associated with cardiac arrhythmias
2216 along with QT prolongation on the electrocardiogram, and it has complicated pharmacokinetics and
2217 pharmacodynamics, including a long and variable half-life and peak respiratory depressant effect
2218 occurring later and lasting longer than peak analgesic effect (Grissinger, 2011; Lugo, Satterfield, & Kern,
2219 2005; Stringer, Welsh, & Tommasello, 2009). In regard to other ER/LA opioid formulations, the
2220 absorption and pharmacodynamics of transdermal fentanyl are also complex, with gradually increasing
2221 serum concentration during the first part of the 72-hour dosing interval, as well as variable absorption
2222 based on factors such as external heat. In addition, the dosing of transdermal fentanyl is in mcg/hour,
2223 which is not typical for a drug used by outpatients and can be confusing. These complexities might
2224 increase the risk for fatal overdose when methadone or transdermal fentanyl is prescribed.

2225 ***Clinicians should not treat acute pain with ER/LA opioids or initiate opioid treatment for***
2226 ***subacute or chronic pain with ER/LA opioids, and clinicians should not prescribe ER/LA opioids for***
2227 ***intermittent use.*** Given longer half-lives and longer duration of effects (e.g., respiratory depression)
2228 with ER/LA opioids such as methadone, fentanyl patches, or extended-release versions of opioids such
2229 as oxycodone, hydromorphone, hydrocodone, or morphine, clinicians should not prescribe ER/LA
2230 opioids for the treatment of acute pain. ER/LA opioids should be reserved for severe, continuous pain
2231 and should be considered only for patients who have received certain dosages of immediate-release
2232 opioids daily (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic
2233 dosages of other opioids) for at least 1 week. When changing to an ER/LA opioid for a patient previously
2234 receiving a different immediate-release opioid, clinicians should consult product labeling and reduce

2235 total daily dosage to account for incomplete opioid cross-tolerance. Clinicians should use additional
2236 caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal
2237 or hepatic dysfunction because decreased clearance of medications among these patients can lead to
2238 accumulation of medications to toxic levels and persistence in the body for longer durations. Although
2239 there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids
2240 together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily
2241 using lower dosages of both or in patients with opioid use disorder treated and stabilized on methadone
2242 who need short-acting opioids for acute pain), in general, avoiding the use of immediate-release opioids
2243 in combination with ER/LA opioids is preferable, given potentially increased risk.

2244 When an ER/LA opioid is prescribed, using one with predictable pharmacokinetics and
2245 pharmacodynamics is preferred to minimize unintentional overdose risk. In particular, unique
2246 characteristics of methadone and of transdermal fentanyl make safe prescribing of these medications
2247 for pain especially challenging. Methadone should not be the first choice for an ER/LA opioid. **Only**
2248 ***clinicians who are familiar with methadone’s unique risk profile and who are prepared to educate and***
2249 ***closely monitor their patients, including risk assessment for QT prolongation and consideration of***
2250 ***electrocardiographic monitoring, should consider prescribing methadone for pain.*** A clinical practice
2251 guideline regarding methadone prescribing for pain has been published previously (Chou et al., 2014).
2252 ***Because dosing effects of transdermal fentanyl are often misunderstood by both clinicians and***
2253 ***patients, only clinicians who are familiar with the dosing and absorption properties of transdermal***
2254 ***fentanyl and are prepared to educate their patients about its use should consider prescribing it.***

2255

2256 4. **When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain,**
2257 **clinicians should prescribe the lowest dosage to achieve expected effects. If opioids are continued**
2258 **for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage,**

2259 should carefully evaluate individual benefits and risks when considering increasing dosage, and
2260 should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative
2261 to risks to patients (recommendation category: A, evidence type: 3).

2262 *Implementation considerations:*

- 2263 • *When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain,*
2264 *clinicians should prescribe the lowest dosage to achieve expected effects.*
- 2265 • *For patients not already taking opioids, the lowest dose to achieve expected effects can be*
2266 *determined using product labeling as a starting point with calibration as needed based on the*
2267 *severity of pain and on other clinical factors such as renal or hepatic insufficiency (see*
2268 *Recommendation 8).*
- 2269 • *The lowest starting dose for opioid-naïve patients is often equivalent to a single dose of*
2270 *approximately 5 to 10 MME or a daily dosage of 20-30 MME/day. A listing of common opioid*
2271 *medications and their dosage in MME equivalents is provided (Table).*
- 2272 • *Risks of opioid use, including risk for overdose and overdose death, increase continuously with*
2273 *dosage, and there is no single dosage threshold below which risks are eliminated.*
- 2274 • *If opioids are continued for subacute or chronic pain, clinicians should use caution when*
2275 *prescribing opioids at any dosage and should generally avoid dosage increases when possible.*
- 2276 • *Many patients do not experience benefit in pain or function from increasing opioid dosages to*
2277 *≥50 MME/day but are exposed to progressive increases in risk as dosage increases. Therefore,*
2278 *before increasing total opioid dosage to ≥50 MME/day, clinicians should pause and carefully*
2279 *reassess evidence of individual benefits and risks. If a decision is made to increase dosage,*
2280 *clinicians should use caution and increase dosage by the smallest practical amount.*
- 2281 • *Additional dosage increases beyond 50 MME/day are progressively more likely to yield*
2282 *diminishing returns in benefits relative to risks to patients as dosage increases further. Clinicians*
2283 *should carefully evaluate a decision to further increase dosage based on individualized*
2284 *assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for*
2285 *pain and function relative to risks with previous dosage increases, other treatments and*
2286 *effectiveness, and patient values and preferences.*
- 2287 • *The recommendations related to opioid dosages are not intended to be used as an inflexible,*
2288 *rigid standard of care; rather, they are intended to be guideposts to help inform clinician-patient*
2289 *decision making. Further, these recommendations apply specifically to starting opioids or to*
2290 *increasing opioid dosages, and a different set of benefits and risks applies to reducing opioid*
2291 *dosages (see Recommendation 5).*

2292
2293 *Supporting Rationale*

2294 Benefits of high-dose opioids for pain are not well established. Few trials evaluated opioid
2295 dosages of (≥ 90 MME/day) (Chou et al., April 2020). Opioid dosages of 50 to 90 MME/day were
2296 associated with a minimally greater (below the threshold for small) improvement in mean pain intensity
2297 compared with doses less than 50 MME/day (mean difference -0.26, 95% CI -0.57 to -0.02); there was
2298 no difference in mean improvement in function (Chou et al., April 2020). Analyses of placebo-controlled
2299 trials also found some evidence of a plateauing effect at 50 mg or greater MME/day (Chou et al., April
2300 2020). One trial of more liberal dose escalation compared with maintenance of current dosage found no
2301 difference in outcomes related to pain or function (Chou et al., April 2020).

2302 At the same time, risks for serious harms related to opioid therapy, including opioid misuse,
2303 overdose, and death, increase at higher opioid dosage, without a single point below which there is no
2304 risk (Coyle et al., 2018). One cohort study from the clinical evidence reviews found higher dosages of
2305 opioids were associated with increased risk of all-cause mortality; one cohort study found modest
2306 associations between higher dose of long-term opioid and increased risk of falls and major trauma; one
2307 case-control study found opioid doses higher than 20 MME/day were associated with increased odds of
2308 road trauma injury when the analysis was restricted to drivers, with no dose-dependent association at
2309 doses higher than 20 MME/day; and cohort studies found association between higher opioid dose and
2310 risk of various endocrinological adverse events (Chou et al., April 2020). Patients on higher doses
2311 reported reliance on opioids despite ambivalence about their benefits (Chou et al., April 2020).

2312 Four observational studies identified in the clinical evidence reviews consistently found an
2313 association between higher doses of long-term opioids and risk of overdose or overdose mortality (Chou
2314 et al., April 2020). Opioid dosages for chronic pain of 50–<100 MME/day in observational studies have
2315 been associated with increased risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages
2316 of 1–<20 MME/day, and dosages ≥ 100 MME/day with increased risks of overdose 2.0–8.9 times the risk
2317 at 1–<20 MME/day, after adjusting for confounders based on demographics, comorbidities, concomitant

2318 medications, and other factors (Bohnert et al., 2011; Dunn et al., 2010; Gomes, Mamdani, Dhalla,
2319 Paterson, & Juurlink, 2011). When prescribed for acute pain, similar associations have been found, with
2320 dosages of 50–<100 MME/day associated with 4.73 times and dosages ≥100 MME/day associated with
2321 6.64 times the risk for opioid overdose compared with dosages of 1–<20 MME/day (Bohnert et al.,
2322 2011). The MME cut points in these studies (e.g., 20 MME, 50 MME, 100 MME) were selected by the
2323 authors for research purposes, and while their findings are consistent with progressive increases in
2324 overdose risk being associated with increases in prescribed opioid dosages, they do not demonstrate a
2325 specific dosage threshold below which opioids are never associated with overdose. In a national sample
2326 of Veterans Health Administration patients with chronic pain who were prescribed opioids, mean
2327 prescribed opioid dosage among patients who died from opioid overdose was 98 MME (median 60
2328 MME) compared with mean prescribed opioid dosage of 48 MME (median 25 MME) among patients not
2329 experiencing fatal overdose (Bohnert, Logan, Ganoczy, & Dowell, 2016). A narrative review conducted
2330 by FDA staff concluded that although there is not a single dosage threshold below which overdose risk is
2331 eliminated (Coyle et al., 2018), the studies included in the review show an increasing risk of serious
2332 adverse health outcomes, including misuse, overdose, and death associated with increasing opioid dose.
2333 Note that these studies examined dose-response risk of overdose for full-agonist opioids and not for
2334 partial agonist opioids such as buprenorphine, which is unlikely to have the same continuous association
2335 between dosage and overdose risk because respiratory depressant effects of buprenorphine reach a
2336 plateau (Dahan et al., 2006).

2337 Several experts expressed concern that including specific dosage thresholds in a main
2338 recommendation statement would emphasize them as “authoritative” absolutes and would lead to non-
2339 collaborative tapers or other potentially harmful consequences. In addition, experts noted the lack of a
2340 single standard formula for calculating MMEs (Dasgupta et al., 2021). However, experts agreed there is a
2341 need for thresholds as benchmarks and suggested instead including them in the supporting text

2342 following the main recommendation statement. Experts also agreed with separating recommendations
2343 on dosage into a recommendation applying to patients starting opioids and patients already receiving
2344 opioids at higher dosages.

2345 When opioids are used for acute, subacute, or chronic pain, clinicians should start opioids at the
2346 lowest possible effective dosage. ***For patients not already taking opioids, the lowest dose to achieve***
2347 ***expected effects can be determined using product labeling as a starting point with calibration as***
2348 ***needed based on the severity of pain and on other clinical factors such as renal or hepatic insufficiency***
2349 ***(see Recommendation 8). The lowest starting dosage for opioid-naïve patients is often equivalent to a***
2350 ***single dose of approximately 5 to 10 MME or a daily dosage of 20-30 MME/day.*** A listing of common
2351 opioid medications and their dosage in MME equivalents is provided (Table). For example, a label for
2352 hydrocodone bitartrate (5mg) and acetaminophen (SpecGx LLC, 2021) (300mg) states that “the usual
2353 adult dosage is one or two tablets every four to six hours as needed for pain. The total daily dosage
2354 should not exceed 8 tablets.” Clinicians should use additional caution when initiating opioids for patients
2355 aged ≥65 years and for patients with renal or hepatic insufficiency because of a potentially smaller
2356 therapeutic window between safe dosages and dosages associated with respiratory depression and
2357 overdose (see Recommendation 8). Formulations with lower opioid doses (e.g., hydrocodone bitartrate
2358 2.5 mg with acetaminophen 325 mg) are available and can facilitate dosing when additional caution is
2359 needed. Product labeling regarding tolerance includes guidance for patients already taking opioids. In
2360 addition to opioids, clinicians should consider cumulative dosages of other medications, such as
2361 acetaminophen, that are combined with opioids in many formulations and for which decreased
2362 clearance of medications might result in accumulation of medications to toxic levels. Acetaminophen
2363 can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol
2364 use or liver disease (American Geriatrics Society Panel on the Pharmacological Management of
2365 Persistent Pain in Older Persons, 2009).

2366 Clinicians should generally avoid unnecessary dosage increases, use caution when increasing
2367 opioid dosages, and increase dosage by the smallest practical amount because overdose risk increases
2368 with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for
2369 dosage titration, rapid dosage increases put patients at greater risk for sedation, respiratory depression,
2370 and overdose. For opioid-naïve outpatients with acute pain treated with an opioid for a few days or less,
2371 dosage increases are usually unnecessary and should not be attempted without close monitoring, given
2372 the risks of respiratory depression. In the context of long-term opioid use, when dosage is increased,
2373 clinicians should re-evaluate patients after increasing dosage for changes in pain, function, and risk for
2374 harm (see Recommendation 7).

2375 *Before increasing total opioid dosage to ≥ 50 MME/day, clinicians should pause, given that*
2376 *dosage increases to more than 50 MME/day are unlikely to provide significantly improved pain control*
2377 *for most patients while overdose risk increases with dosage, and carefully reassess evidence of*
2378 *individual benefits and risks. If a patient's opioid dosage for all sources of opioids combined reaches or*
2379 *exceeds 50 MME/day, clinicians should implement additional precautions, including increased frequency*
2380 *of follow-up (see Recommendation 7) and offer naloxone and overdose prevention education to both*
2381 *patients and the patients' household members (see Recommendation 8).*

2382 ***Additional dosage increases beyond 50 MME/day are progressively more likely to yield***
2383 ***diminishing returns in benefits relative to risks to patients, and clinicians should carefully evaluate a***
2384 ***decision to increase dosage based on individualized assessment of benefits and risks and weighing***
2385 ***factors such as diagnosis, incremental benefits for pain and function relative to risks with previous***
2386 ***dosage increases, other treatments and effectiveness, and patient values and preferences.***

2387 Some states require clinicians to implement clinical protocols at specific dosage levels. For
2388 example, before increasing long-term opioid therapy dosage to >120 MME/day, clinicians in Washington
2389 state must obtain consultation from a pain specialist who agrees that this is indicated and appropriate

2390 (State of Washington Department of Health, 2019). Clinicians should be aware of rules related to MME
2391 thresholds and associated clinical protocols established by their states.

2392
2393 **5. For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and**
2394 **risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of**
2395 **continued opioid therapy, clinicians should optimize other therapies and work closely with**
2396 **patients to gradually taper to lower dosages or, if warranted based on the individual clinical**
2397 **circumstances of the patient, to appropriately taper and discontinue opioids. Unless there are**
2398 **indications of a life-threatening issue, such as warning signs of impending overdose, e.g.,**
2399 **confusion, sedation, or slurred speech, opioid therapy should not be discontinued abruptly, and**
2400 **clinicians should not abruptly or rapidly reduce opioid dosages from higher dosages**
2401 **(recommendation category: B, evidence type: 4).**

2402 Implementation considerations:

- 2403 • *Clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing*
2404 *opioid therapy, and discuss these approaches with patients prior to initiating changes, when*
2405 *risks outweigh benefits (potentially including avoiding risks of tapering) of continued opioid*
2406 *therapy.*
- 2407 • *Patient agreement and interest in tapering is likely to be a key component of successful tapers.*
- 2408 • *For patients agreeing to taper to lower opioid dosages as well as for those remaining on higher*
2409 *opioid dosages, clinicians should establish goals with the patient for continued opioid therapy*
2410 *(see Recommendations 2 and 7) and maximize pain treatment with nonpharmacologic and*
2411 *nonopioid pharmacologic treatments as appropriate (see Recommendation 2).*
- 2412 • *Clinicians should collaborate with the patient on the tapering plan, including patients in decisions*
2413 *such as how quickly tapering will occur and when pauses in the taper may be warranted.*
- 2414 • *Clinicians should follow up frequently (at least monthly) with patients engaging in opioid*
2415 *tapering.*
- 2416 • *When opioids are reduced or discontinued, a taper slow enough to minimize symptoms and signs*
2417 *of opioid withdrawal (e.g., anxiety, insomnia, abdominal pain, vomiting, diarrhea, diaphoresis,*
2418 *mydriasis, tremor, tachycardia, or piloerection) should be used.*

- 2419 • *Tapers can be completed over several months to years depending on the opioid dosage and*
 2420 *should be individualized based on patient goals and concerns. Longer durations of previous*
 2421 *opioid therapy might require longer tapers.*
- 2422 • *Tapers of 10% per month or slower are likely to be better tolerated than more rapid tapers,*
 2423 *particularly when patients have been taking opioids for longer durations (e.g., for a year or*
 2424 *longer).*
- 2425 • *Significant opioid withdrawal symptoms can signal the need to further slow the taper rate.*
- 2426 • *At times, tapers might have to be paused and restarted again when the patient is ready and*
 2427 *might have to be slowed once patients reach low dosages.*
- 2428 • *Tapers should not be reversed without careful assessment of benefits and risks of increasing*
 2429 *opioid dosage or without maximizing nonopioid treatments for pain and addressing behavioral*
 2430 *distress.*
- 2431 • *Once the smallest available dose is reached, the interval between doses can be extended.*
- 2432 • *Goals of the taper may vary—some patients might achieve discontinuation; others might attain*
 2433 *a reduced dosage. If the clinician has determined with the patient that the ultimate goal of*
 2434 *tapering is discontinuing opioids, opioids may be stopped when taken less frequently than once a*
 2435 *day.*
- 2436 • *Clinicians should access appropriate expertise if considering tapering opioids during pregnancy*
 2437 *because of possible risk to the pregnant patient and to the fetus if the patient goes into*
 2438 *withdrawal.*
- 2439 • *Clinicians should advise patients that there is an increased risk for overdose on abrupt return to a*
 2440 *previously prescribed higher dose, caution that it takes as little as a week to lose tolerance,*
 2441 *provide opioid overdose education, and offer naloxone.*
- 2442 • *Clinicians should remain alert to signs of anxiety, depression, and opioid misuse or opioid use*
 2443 *disorder (see Recommendations 8 and 12) that might be revealed by an opioid taper and provide*
 2444 *treatment or arrange for management of these co-morbidities.*
- 2445 • *Clinicians should closely monitor patients who are unable to taper and who continue on high-*
 2446 *dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with*
 2447 *benzodiazepines) and should work with patients to mitigate overdose risk (e.g., by providing*
 2448 *overdose education and naloxone—see Recommendation 8).*
- 2449 • *Clinicians can use periodic and strategic motivational questions and statements to encourage*
 2450 *movement toward appropriate therapeutic changes and functional goals.*
- 2451 • *Clinicians have a responsibility to provide or arrange for coordinated management of patients’*
 2452 *pain and opioid-related problems, including opioid use disorder. **Clinicians should not abandon***
 2453 *patients.*

2454 • *Payers, health systems, and state medical boards should not use this clinical practice guideline to*
2455 *set rigid standards related to dose or duration of opioid therapy, and should ensure that policies*
2456 *based on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of*
2457 *opioids, and that policies do not penalize clinicians for accepting new patients who are using*
2458 *prescribed opioids for chronic pain, including those receiving high doses of opioids.*

2459 • *While Recommendation 5 specifically refers to patients using long-term, high-dose opioid*
2460 *therapy for subacute or chronic pain, many of the principles in these implementation*
2461 *considerations and supporting rationale, including communication with patients, pain*
2462 *management and behavioral support, and slower taper rates, are also relevant when*
2463 *discontinuing opioids in patients receiving shorter durations and/or lower-dosages (see also*
2464 *Recommendations 6 and 7).*

2465 *Supporting Rationale*

2466 Patients receiving long-term, high dose opioid therapy for chronic pain are at increased risk for
2467 adverse events including overdose mortality (Bohnert et al., 2011; Dunn et al., 2010; Gomes et al., 2011;
2468 K. S. Gordon et al., 2020; Kaplovitch et al., 2015). However, discontinuation of long-term, high dose
2469 opioid therapy has been associated with adverse events including mental health crisis, overdose events,
2470 and overdose mortality (Agnoli et al., 2021; K. S. Gordon et al., 2020; James et al., 2019; Mark & Parish,
2471 2019). One study found that while sustained opioid therapy discontinuation (defined by the authors as
2472 opioid discontinuation for at least 3 months) was associated with an approximate 50% reduction in risk
2473 of overdose, dose variability was a risk factor for opioid overdose (Glanz, Binswanger, Shetterly,
2474 Narwaney, & Xu, 2019). Another study found that both starting and stopping opioids were associated
2475 with overdose or suicide risk; risk associated with stopping increased the longer patients had received
2476 opioids before stopping. Death rates for overdose or suicide increased immediately after starting or
2477 stopping treatment with opioids, with the incidence decreasing over about three to twelve months (E.
2478 M. Oliva et al., 2020). In particular, discontinuation of opioids over short time periods has been
2479 associated with greater risks. FDA has advised that risks of rapid tapering or sudden discontinuation of
2480 opioids in physically dependent patients include acute withdrawal symptoms, exacerbation of pain,
2481 serious psychological distress, and thoughts of suicide (U.S. Food and Drug Administration, 2019c). One

2482 observational study found that among adults prescribed stable higher opioid dosages (mean ≥ 50
2483 MME/day) long-term, increasing maximum monthly dose reduction velocity by 10% was associated with
2484 an adjusted incidence rate ratio of 1.09 for overdose (95% CI, 1.07-1.11) and of 1.18 for mental health
2485 crisis (95% CI, 1.14-1.21) (Agnoli et al., 2021). Another study of patients on long-term, high-dose (≥ 120
2486 MME/day) opioid therapy found that each additional week of tapering time before opioid
2487 discontinuation was associated with a 7% relative reduction in the risk of opioid-related emergency
2488 department visits or hospitalizations (Mark & Parish, 2019). The clinical evidence reviews did not find
2489 studies comparing different rates of opioid tapering, but a taper support intervention (psychiatric
2490 consultation, opioid dosage tapering, and 18 weekly meetings with a physician assistant to explore
2491 motivation for tapering and learn pain self-management skills) was associated with better functional
2492 outcomes (specifically improvement in pain interference) compared to usual care, with effects persisting
2493 at 34-week follow-up (Chou et al., April 2020). A systematic review (Frank et al., 2017) found that among
2494 studies rated as “good” or “fair” quality, when opioids were tapered following discussion with patients
2495 who agreed to taper, opioid dose reduction was associated with improved pain, function, and quality of
2496 life. These results suggest that involving patients in decisions regarding continuation or discontinuation
2497 of opioid analgesics, as well as practices including behavioral support, integration of nonpharmacologic
2498 pain management, and slower tapers, may improve outcomes.

2499 Experts appreciated the complexity of managing patients already receiving higher dosages of
2500 opioids long-term. While some experts felt there should be more consideration of obtaining informed
2501 consent prior to tapering opioids, others believed that informed discussion is more appropriate than
2502 informed consent when considering tapering opioids given clinicians’ overriding responsibility to avoid
2503 providing treatment that harms patients. Some experts were concerned that over-emphasizing risks of
2504 tapering could increase harm from continued high-dosage opioid use.

2505

2506 **Determining whether, when, and how to taper opioids**

2507 The benefits and the risks of opioid therapy change over time and should be re-evaluated
2508 periodically (see Recommendations 6 and 7). Opioid therapy should be limited to circumstances where
2509 benefits of therapy outweigh risks. Because tapering opioids can be harmful in some circumstances,
2510 benefits of continuing opioids in patients who have already received them long term might include
2511 avoiding risks of tapering and discontinuing opioids. In situations where benefits and risks of continuing
2512 opioids are considered to be close, shared decision-making with patients is particularly important.
2513 ***Unless there is a life-threatening issue, such as imminent overdose, the benefits of rapidly tapering or***
2514 ***abruptly discontinuing opioids are unlikely to outweigh the significant risks of these practices*** (Mark &
2515 Parish, 2019; U.S. Department of Health and Human Services, 2019a). However, following slow,
2516 voluntary reduction of long-term opioid dosages, many patients report improvements in function,
2517 quality of life, anxiety, and mood without worsening pain or with decreased pain levels (Frank et al.,
2518 2017). Clinicians and patients should consider whether opioids continue to meet treatment goals,
2519 whether opioids are exposing the patient to an increased risk for serious adverse events or opioid use
2520 disorder, and whether benefits continue to outweigh risks of opioids. Clinicians should not insist on
2521 opioid tapering or discontinuation when opioid use may be warranted (i.e., when benefits of opioids
2522 outweigh risks) (Kroenke et al., 2019; U.S. Department of Health and Human Services, 2019a). Clinicians
2523 should access appropriate expertise if considering tapering opioids during pregnancy because of
2524 possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal. For pregnant
2525 people with opioid use disorder, medications for opioid use disorder are preferred over withdrawal
2526 management (i.e., discontinuation of opioids through either short- or medium-term tapering) (American
2527 Society of Addiction Medicine, 2015; Ecker et al., 2019; Substance Abuse and Mental Health Services
2528 Administration, 2018b).

2529 Some patients using more than one respiratory depressant (e.g., benzodiazepines and opioids)
2530 might require tapering one or more medications to reduce risk for respiratory depression. Tapering
2531 decisions and plans should be coordinated with prescribers of all respiratory depressant medications
2532 (see Recommendation 11). If benzodiazepines are tapered, they should be tapered gradually due to risks
2533 of benzodiazepine withdrawal (anxiety, hallucinations, seizures, delirium tremens, and, in rare cases,
2534 death (Haque, Watson, & Bryant, 1990; Lann & Molina, 2009)). Patients who are not actually taking
2535 opioids (such as patients who are diverting all opioids they obtain) do not require tapers.

2536 Consistent with the HHS Guide for Clinicians on the Appropriate Dosage Reduction or
2537 Discontinuation of Long-Term Opioid Analgesics (U.S. Department of Health and Human Services,
2538 2019a), clinicians should consider tapering to a reduced opioid dosage, or tapering and discontinuing
2539 opioid therapy, and discuss with these approaches with patients prior to initiating changes when

- 2540 • The patient requests dosage reduction or discontinuation
- 2541 • Pain improves and might indicate resolution of an underlying cause
- 2542 • When opioid therapy has not meaningfully reduced pain or improved function
- 2543 • The patient has been treated with opioids for a prolonged period (e.g., years), and current
2544 benefit-risk balance is unclear (e.g., decreased positive effects due to tolerance, symptoms such
2545 as reduced focus or memory that might be due to opioids)
- 2546 • The patient is receiving higher opioid doses without evidence of benefit from the higher dose
- 2547 • The patient experiences side effects that diminish quality of life or impair function
- 2548 • There is current evidence of opioid misuse
- 2549 • The patient experiences an overdose or other serious event (e.g., an event leading to
2550 hospitalization or injury) or has warning signs for an impending event such as confusion,
2551 sedation, or slurred speech

2552 • The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., lung
2553 disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for
2554 adverse outcomes

2555
2556 Clinicians should review benefits and risks of continued high-dose opioid therapy with patients.
2557 Established patients already taking high dosages of opioids, as well as patients transferring from other
2558 clinicians, might consider the possibility of opioid dosage reduction to be substantially anxiety-
2559 provoking, and tapering opioids can be especially challenging after years on high dosages because of
2560 physical and psychological dependence. However, patients should be offered the opportunity to re-
2561 evaluate their continued use of opioids at high dosages. Clinicians should empathically review benefits
2562 and risks of continued high-dosage opioid therapy and should offer to work collaboratively with the
2563 patient to taper opioids to safer dosages.

2564 Whenever possible, clinicians should collaborate with patients in making decisions about
2565 whether and how to taper opioids and share decision-making with patients. Whether the goal of the
2566 taper is stopping opioids or reducing opioids to a point where benefits outweigh risks depends on the
2567 individual patient's circumstances and individualized assessment of benefits and risks, informed by open
2568 discussion between the patient and clinician. Tapering is more likely to be successful when patients
2569 collaborate in the taper (Dowell & Haegerich, 2017). Clinicians should review risks and benefits of the
2570 current therapy with the patient and decide if tapering is appropriate based on individual circumstances.
2571 Clinicians can discuss with patients their perceptions of risks, benefits, and adverse effects of continued
2572 opioid therapy, include patient concerns in taper planning, and include patients in decisions such as
2573 which medication will be decreased first and how quickly tapering will occur. If the current opioid
2574 regimen does not put the patient at imminent risk, tapering does not need to occur immediately, and
2575 clinicians can take time to obtain patient buy-in (Dowell & Haegerich, 2017). For patients who agree to

2576 taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan,
2577 including patients in decisions, such as which medication will be decreased first (e.g., in patients
2578 prescribed more than one opioid) and how quickly tapering will occur.

2579 **Advice to patients prior to tapering**

2580 Patients should be advised that overall, following voluntary reduction of long-term opioid
2581 dosages, most patients report stable or improved function, anxiety, and mood without worsening pain
2582 or even with decreased pain levels (Berna, Kulich, & Rathmell, 2015; Darnall et al., 2018; Frank et al.,
2583 2017; Goesling et al., 2019; Kroenke et al., 2019; Sullivan et al., 2017). Other patients report insomnia,
2584 anxiety, depression, and increased pain, particularly in the short term (Berna et al., 2015; Goesling et al.,
2585 2019; Kroenke et al., 2019; Manhapra, Arias, & Ballantyne, 2018; Sturgeon, Sullivan, Parker-Shames,
2586 Tauben, & Coelho, 2020). Increased pain may be related to hyperalgesia or opioid withdrawal and can
2587 be prolonged in some patients (Manhapra et al., 2018). It can be helpful to counsel patients that
2588 worsening of pain is a frequent symptom of opioid withdrawal that tends to diminish over time (U.S.
2589 Department of Health and Human Services, 2019a). Clinicians should advise patients that there is an
2590 increased risk for overdose on abrupt return to a previously prescribed higher dose, caution that it takes
2591 as little as a week to lose tolerance, and warn that there is a risk of overdose if they return to their
2592 original dose (U.S. Department of Veterans Affairs and Department of Defense, 2017). Clinicians should
2593 provide opioid overdose education and offer naloxone.

2594 **Pain management during tapering**

2595 Clinicians should commit to working with patients to improve function and decrease pain,
2596 whether or not opioids are tapered. Nonopioid treatments should be integrated into patients' pain
2597 management plans based on an individualized assessment of benefits and risks considering the patient's
2598 diagnosis, circumstances, and unique needs (see Recommendation 2). Integrating behavioral and
2599 nonopioid pain therapies before and during a taper can help manage pain (Frank et al., 2017) and

2600 strengthen the therapeutic relationship. For patients agreeing to taper to lower opioid dosages as well
2601 as for those remaining on higher opioid dosages, clinicians should establish goals with the patient for
2602 continued opioid therapy (see Recommendations 2 and 7) and maximize pain treatment with
2603 nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 2).

2604 **Behavioral health support during tapering**

2605 Integrating behavioral and nonopioid pain therapies and treatment for comorbid mental health
2606 conditions before and during a taper can help manage pain (Frank et al., 2017), strengthen the
2607 therapeutic relationship, and improve the likelihood of positive tapering outcomes (Sullivan et al., 2017).
2608 Mental health co-morbidities including depression and anxiety are common in patients with painful
2609 conditions, especially in patients receiving long-term opioid therapy (Sullivan, 2018). Depressive
2610 symptoms predict taper dropout (Berna et al., 2015; Darnall et al., 2018). Primary care clinicians should
2611 collaborate with mental health specialists and with other specialty clinicians as needed to optimize
2612 nonopioid pain management (see Recommendation 2), as well as psychosocial support for anxiety
2613 related to the taper. Clinicians should consider arranging for consultation with a behavioral health
2614 specialist before initiating a taper in patients with serious mental illness, who are at high suicide risk, or
2615 with suicidal ideation (U.S. Department of Health and Human Services, 2019a). Clinicians should remain
2616 alert to signs of anxiety, depression, and opioid misuse or opioid use disorder (see Recommendations 8
2617 and 12) that might be revealed by an opioid taper and provide treatment or arrange for management of
2618 these co-morbidities. Successful tapering studies have used at least weekly follow-up (Frank et al.,
2619 2017), and clinicians should follow up frequently (at least monthly) with patients engaging in opioid
2620 tapering. Clinicians can acknowledge patient fears about tapering (Veterans Health Administration PBM
2621 Academic Detailing Service, 2016), ask how they can support the patient (Veterans Health
2622 Administration PBM Academic Detailing Service, 2016), and make sure patients receive appropriate and
2623 accessible psychosocial support (Sullivan et al., 2017; U.S. Department of Veterans Affairs and

2624 Department of Defense, 2017). Many patients fear stigma, withdrawal symptoms, pain, and/or
2625 abandonment (Henry et al., 2019), and it can be helpful to tell patients what to expect (e.g., the rate will
2626 be kept slow to minimize withdrawal symptoms; pain may worsen at first but usually improves over
2627 time) and that the clinician will support them through the process.

2628 **Tapering rate**

2629 Evidence to support specific tapering rates is limited. The rate of tapering should be
2630 individualized based on the clinical situation of the patient. When opioids are reduced or discontinued, a
2631 taper slow enough to minimize symptoms and signs of opioid withdrawal (e.g., anxiety, insomnia,
2632 abdominal pain, vomiting, diarrhea, diaphoresis, mydriasis, tremor, tachycardia, or piloerection) should
2633 be used. Tapers can be completed over several months to years depending on the opioid dosage and
2634 should be individualized based on patient goals and concerns. Longer durations of previous opioid
2635 therapy might require longer tapers. Evidence on optimal taper rate is emerging. ***Tapers of***
2636 ***approximately 10% per month or slower are likely to be better tolerated than more rapid tapers,***
2637 ***particularly when patients have been taking opioids for longer durations (e.g., for a year or longer).*** A
2638 decrease of 10% of the original dose per week or slower (until approximately 30% of the original dose is
2639 reached, followed by a weekly decrease of approximately 10% of the remaining dose) is unlikely to
2640 trigger withdrawal (Berna et al., 2015) and can be successful for some patients, particularly after opioid
2641 use for weeks to months rather than years. Significant opioid withdrawal symptoms can signal the need
2642 to further slow the taper rate. At times, tapers might have to be paused and restarted again when the
2643 patient is ready and might have to be slowed once patients reach low dosages to allow gradual
2644 accommodation to lower opioid dosages and development of new skills for management of pain and
2645 emotional distress. Tapers should not be reversed without careful assessment of benefits and risks of
2646 increasing opioid dosage or without maximizing nonopioid treatments for pain and addressing
2647 behavioral distress (Rich et al., 2020). Once the smallest available dose is reached, the interval between

2648 doses can be extended. If the clinician has determined with the patient that the goal is discontinuing
2649 opioids, opioids may be stopped when taken less frequently than once a day.

2650 More rapid tapers might be needed for patient safety under certain circumstances (e.g., for
2651 patients who have experienced overdose on their current dosage). However, ***unless there are***
2652 ***indications of a life-threatening issue, such as warning signs of impending overdose, opioid therapy***
2653 ***should not be discontinued abruptly, and clinicians should not abruptly reduce opioid dosages from***
2654 ***higher dosages***. When opioids have been prescribed continuously for longer than a few days, sudden
2655 discontinuation may precipitate significant opioid withdrawal (Mark & Parish, 2019). Rapid tapering or
2656 sudden discontinuation of opioids in physically dependent patients can also increase risks of
2657 psychological distress and opioid-related emergency department visits and hospitalizations (Mark &
2658 Parish, 2019; U.S. Food and Drug Administration, 2019c). Ultrarapid detoxification under anesthesia is
2659 associated with substantial risks, including death, and should not be used (Berlin et al., 2013).

2660 **Management of opioid withdrawal during tapering**

2661 The first approach to withdrawal symptoms and signs should generally be consideration of
2662 slowing or pausing the taper rate. If needed, short-term oral medications might also help manage
2663 withdrawal symptoms (Veterans Health Administration PBM Academic Detailing Service, 2016). These
2664 include alpha-2 agonists for the management of autonomic signs and symptoms (e.g., sweating,
2665 tachycardia). Alpha-2 agonists clonidine and lofexidine are more effective than placebo in reducing
2666 severity of withdrawal (Gowing, Farrell, Ali, & White, 2016) from heroin or methadone in the context of
2667 abrupt (not gradual) discontinuation. There is not similar research in patients tapering from long-term
2668 opioid treatment for pain (Berna et al., 2015), but the alpha-2 agonist tizanidine has been used to help
2669 taper patients from long-term, high-dose opioids for chronic pain (Sturgeon et al., 2020). Other
2670 medications addressing specific symptoms (NSAIDs, acetaminophen, or topical menthol/methyl
2671 salicylate for muscle aches; trazodone for sleep disturbance; prochlorperazine, promethazine, or

2672 ondansetron for nausea; dicyclomine for abdominal cramping; and loperamide or bismuth subsalicylate
2673 for diarrhea) have also been used (Veterans Health Administration PBM Academic Detailing Service,
2674 2016).

2675 **Tapering when patients have opioid use disorder**

2676 Some patients with unanticipated challenges to tapering, such as inability to make progress in
2677 tapering despite opioid-related harm, might have undiagnosed opioid use disorder. Therefore, patients
2678 experiencing such challenges should be assessed for opioid use disorder using *Diagnostic and Statistical*
2679 *Manual of Mental Disorders (Fifth Edition)* criteria and if criteria for opioid use disorder are met, offered
2680 medication treatment (see Recommendation 12) and naloxone for opioid overdose reversal (see
2681 Recommendation 8).

2682 **Other challenges to tapering**

2683 Emerging evidence suggests that patients for whom risks of continued high-dose opioid use
2684 outweigh benefits but who are unable to taper and who do not meet criteria for opioid use disorder
2685 might benefit from transition to buprenorphine (Chou, Ballantyne, & Lembke, 2019; Fishman & Kim,
2686 2018; U.S. Department of Health and Human Services, 2019a). Buprenorphine is an opioid partial
2687 agonist that can treat pain as well as opioid use disorder (Pade, Cardon, Hoffman, & Geppert, 2012), and
2688 has other properties that may be helpful (U.S. Department of Veterans Affairs and Department of
2689 Defense, 2017), including less respiratory depression (Dahan et al., 2006) and overdose risk than other
2690 opioids (Chou et al., 2019). While overdose is less likely with buprenorphine than with full agonist
2691 opioids, overdose is still possible, particularly if buprenorphine is taken concurrently with other
2692 respiratory depressants, such as full agonist opioids, benzodiazepines, or alcohol (Paone et al., 2015). A
2693 specialty clinic offering opioid tapering services for patients receiving high-dosage opioids (defined in
2694 this study as ≥ 90 MME/day) for chronic pain found that 44.6% of patients referred for opioid taper were

2695 able to successfully taper to <90 MME/day, and an additional 18.8% who were unable to taper were
2696 able to successfully transition to sublingual buprenorphine (Sturgeon et al., 2020). Different
2697 buprenorphine products, available at different doses, are approved for the treatment of pain (e.g.,
2698 Belbuca, Butrans) and for the treatment of opioid use disorder (e.g., Suboxone). While prescription of
2699 buprenorphine for treatment of opioid use disorder requires the clinician to have a waiver from the
2700 Substance Abuse and Mental Health Services Administration (SAMHSA) (see Recommendation 12),
2701 prescription of buprenorphine for treatment of chronic pain does not require a waiver (Chou et al.,
2702 2019).

2703 To avoid precipitating withdrawal, transitioning any patient taking full agonist opioids to
2704 buprenorphine requires careful timing of the initial buprenorphine dose (U.S. Department of Health and
2705 Human Services, 2019a) (see Recommendation 12 for application to patients with opioid use disorder).
2706 Patients should be in mild to moderate withdrawal from full agonist opioids before the first
2707 buprenorphine dose (U.S. Department of Health and Human Services, 2019a). To do this, it has been
2708 advised to wait at least 8 to 12 hours after the last dose of short-acting full agonist opioids and waiting
2709 longer following the last dose of long-acting full agonist opioids (e.g., at least 12-24 hours after the last
2710 dose of an ER/LA full-agonist opioid, longer for methadone) before the first dose of buprenorphine
2711 (Manhapa et al., 2018). As an alternative for patients not yet in opioid withdrawal, some authors have
2712 described low dose initiation of buprenorphine to allow for initiation of buprenorphine in patients
2713 currently receiving full agonist opioids for acute or chronic pain (Cohen et al., 2021). SAMHSA's
2714 Providers Clinical Support System (<https://pcssnow.org/>) offers training and technical assistance as well
2715 as mentors to assist clinicians who are unfamiliar with initiation of buprenorphine and have additional
2716 questions related to the diagnosis and treatment of opioid use disorder in particular. Because the
2717 duration of action for analgesia is shorter than the duration of action for suppression of opioid
2718 withdrawal and stabilization of opioid use disorder (Alford, Compton, & Samet, 2006), dosing

2719 buprenorphine for pain is typically multiple times daily (e.g., 8mg sublingual tablet three times a day)
2720 rather than once a day dosing as done for the treatment of OUD (Manhapra et al., 2018; U.S.
2721 Department of Veterans Affairs and Department of Defense, 2017).

2722 **Continuing high-dosage opioids**

2723 Clinicians should closely monitor patients who are unable to taper and who continue on high-
2724 dose or otherwise high-risk opioid regimens (e.g., opioids prescribed concurrently with benzodiazepines)
2725 and should work with patients to mitigate overdose risk (e.g., by providing overdose education and
2726 naloxone—see Recommendation 8). Clinicians can use periodic and strategic motivational questions and
2727 statements to encourage movement toward appropriate therapeutic changes (Dowell & Haegerich,
2728 2017). Increasing opioid dosage in patients already receiving high dosages is likely to be associated with
2729 diminishing returns for pain relief and increased risks for adverse effects and should be avoided.

2730 Management of chronic pain with opioids can be challenging, as can management of opioid
2731 discontinuation (Dowell, Haegerich, et al., 2019). However, ***clinicians have a responsibility to provide or***
2732 ***arrange for coordinated management of patients' pain and opioid-related challenges. Clinicians***
2733 ***should not abandon patients. Payers and health systems should not use this clinical practice guideline***
2734 ***to set rigid standards related to dose or duration of opioid therapy, should ensure that policies based***
2735 ***on cautionary dosage thresholds do not result in rapid tapers or abrupt discontinuation of opioids.***

2736 Care should be taken to ensure that policies do not penalize clinicians for accepting new patients who
2737 are receiving opioids for chronic pain. Patients prescribed opioids but unable to access ongoing care
2738 (Lagisetty et al., 2019) may be at risk for abrupt opioid discontinuation and may miss opportunities to
2739 receive life-saving interventions, including monitoring for and management of mental health and
2740 substance use co-morbidities.

2741 **Opioid duration and follow-up**

2742 6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than
2743 needed for the expected duration of pain severe enough to require opioids (recommendation
2744 category: A, evidence type: 4).

2745 Implementation considerations:

- 2746 • Nontraumatic, nonsurgical acute pain can often be managed without opioids (see
2747 Recommendation 1).
- 2748 • Opioids are sometimes needed for treatment of acute pain (see Recommendation 1). When the
2749 diagnosis and severity of acute pain warrant use of opioids, clinicians should prescribe no greater
2750 quantity than needed for the expected duration of pain severe enough to require opioids. For
2751 many common causes of nontraumatic, nonsurgical pain, when opioids are needed, a few days
2752 or less are often sufficient, and shorter courses can minimize the need to taper opioids to prevent
2753 withdrawal symptoms at the end of a course of opioids. However, durations should be
2754 individualized based on the clinical circumstances of the specific patient.
- 2755 • Clinicians should generally avoid prescribing additional opioids to patients “just in case” pain
2756 continues longer than expected.
- 2757 • For postoperative pain related to major surgery, procedure-specific opioid prescribing
2758 recommendations are available with ranges for amounts of opioids needed (based on actual use
2759 and refills and on consensus).
- 2760 • To minimize unintended impact on patients with an unexpectedly prolonged duration of severe
2761 acute pain, clinicians, practices, and health systems should have mechanisms in place to provide
2762 timely re-evaluation for the subset of patients who experience severe acute pain that continues
2763 longer than the expected duration to confirm or revise the initial diagnosis and to adjust
2764 management accordingly. In particular, clinicians, practices, and health systems should ensure
2765 all patients can access and afford additional evaluation and treatment, as needed, to minimize
2766 disparities across patients based on access to and affordability of care and refills.
- 2767 • Longer durations of opioid therapy are more likely to be needed when the mechanism of injury is
2768 expected to result in prolonged severe pain (e.g., severe traumatic injuries).
- 2769 • Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute
2770 pain.
- 2771 • If opioids are continued for a month or longer, clinicians should refer to recommendations on
2772 subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5).
- 2773 • If patients already receiving long-term opioids require additional opioids for superimposed
2774 severe acute pain (e.g., major surgery), opioids should be continued only for the duration of pain
2775 severe enough to require additional opioids, returning to the patient’s baseline opioid dosage as
2776 soon as possible, including a taper to baseline dosage if additional opioids were used around the
2777 clock for more than a few days.
- 2778 • If opioids are prescribed continuously (around the clock) for more than a few days for acute pain,
2779 clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of
2780 opioids.

- 2781
- 2782
- *Taper durations might need to be adjusted depending on the duration of the initial opioid prescription (see supporting rationale for this recommendation for additional details).*
- 2783
- *Tapering plans should be discussed with the patient prior to hospital discharge and with clinicians coordinating the patient’s care as an outpatient. For tapering considerations when patients have taken opioids continuously for longer than one month, see Recommendation 5.*
- 2784
- 2785

2786

2787 *Supporting Rationale*

2788 Data suggest that for many patients presenting with common types of acute pain in primary

2789 care or emergency department settings, pain improves within days. Analysis of nationwide U.S.

2790 commercial insurance claims in 2014 found median durations of initial opioid analgesic prescriptions for

2791 acute pain indications in primary care settings were 4–7 days (Mundkur et al., 2019), suggesting that in

2792 most cases, clinicians considered an initial opioid prescription of 4 to 7 days’ duration sufficient. Some

2793 patients (17.8%, ranging from 11.7% to 30.0% depending on the acute pain condition) obtained at least

2794 one refill within 30 days after their initial opioid prescription, suggesting that while for most patients,

2795 these durations might have been sufficient or more than necessary, there is likely to be variation across

2796 diagnoses and among patients in time to recovery. In an older study of the course of acute low back

2797 pain (not associated with malignancies, infections, spondyloarthropathies, fractures, or neurological

2798 signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment

2799 with paracetamol, with smaller decreases thereafter (Coste, Delecoeuillerie, de Lara, LeParc, & Paolaggi,

2800 1994). A more recent single-center survey of patients prescribed opioids for acute pain on emergency

2801 department discharge (McCarthy et al., 2021) found that patients taking opioids continued them for a

2802 median of 4 days (interquartile range [IQR] 2-7 days), including on the day of discharge, with variation

2803 across patients and diagnoses. Median numbers of days that patients continued taking prescribed

2804 opioids were 6 (IQR 4-8) for back pain and for fractures, 2 (IQR 1-5) for renal colic, 5.5 (IQR 4-7) for

2805 musculoskeletal injury, and 3 (IQR 2-6) for other diagnoses. Most patients (92.5%) reported having

2806 leftover pills, with 52.2% of pills unused overall. A Canadian study following patients for 14 days after

2807 discharge from the emergency department with opioid prescriptions for acute pain (Daoust et al., 2018)
2808 similarly found most (68%) total prescribed opioids were unused, and that the quantity of morphine
2809 5mg tablets to prescribe in order to adequately supply 80% of the patients with the amount of opioids
2810 they actually used was 20 tablets for musculoskeletal pain, 30 for fracture, 15 for renal colic or
2811 abdominal pain, and 20 for other pain conditions.

2812 Multiple studies since 2017 have found that many patients do not use all prescribed opioids
2813 after surgery and that prescribing a lower quantity of opioids postoperatively is associated with less
2814 opioid use without increases in pain score or in requests for refills of pain medication, and without
2815 significant reductions in satisfaction with pain management (Hill et al., 2017; Hill, Stucke, McMahon, et
2816 al., 2018; Howard et al., 2018). One study found that, following 5 common surgical procedures, median
2817 opioid consumption was three 5mg oxycodone pills or less, and that following consensus
2818 recommendations intended to reduce unnecessary postoperative opioid prescribing published in 2018
2819 and 2019 would still result in 47% to 56% of pills prescribed remaining unused (K. A. Robinson et al.,
2820 2020). There is also evidence of variation in opioid needs across patients undergoing the same
2821 procedures based on individual factors including pain at discharge and prior opioid use (Mallama et al.,
2822 2021). One study found that while a majority of patients used no or few (less than a total of 50 MME
2823 during their entire postoperative course) opioids, some patients required opioids for up to 15 days after
2824 surgery (Thiels et al., 2018).

2825 The clinical evidence reviews found observational evidence that opioid use for acute pain is
2826 associated with long-term opioid use, and that a greater amount of early opioid exposure is associated
2827 with greater likelihood of long-term use, noting recent evidence for a dose and duration-response
2828 relationship (Brat et al., 2018; Brummett et al., 2017; Mundkur et al., 2019; National Conference of State
2829 Legislatures, June 30, 2019.; Reznikoff, 2018; Shah et al., 2017). Opioids prescribed for surgery and other
2830 acute pain conditions that go unused (Bartels et al., 2016; Bicket, Long, Pronovost, Alexander, & Wu,

2831 2017; Mallama et al., 2021; Neuman, Bateman, & Wunsch, 2019) are a potential source for misuse and
2832 diversion. In addition, sudden discontinuation of opioids used continuously for longer than a few days
2833 may result in significant opioid withdrawal (Mark & Parish, 2019). Therefore, limiting duration of opioids
2834 prescribed can minimize the need for a taper to prevent distressing or unpleasant withdrawal
2835 symptoms.

2836 Many common causes of nonsurgical, nontraumatic acute pain can often be managed without
2837 opioids (see Recommendation 1). When the diagnosis and severity of acute pain warrant the use of
2838 opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain
2839 severe enough to require opioids. A few days or less are often sufficient when opioids are needed for
2840 many common causes of nonsurgical acute pain and limiting the duration of opioid therapy can
2841 minimize the need to taper to prevent withdrawal symptoms at the end of the course of opioids as well
2842 as limiting unused opioids. Certain circumstances (e.g., severe traumatic injuries) might require use of
2843 opioids for durations greater than 7 days. Durations should be individualized based on the clinical
2844 circumstances of the specific patient.

2845 When patients are discharged from the hospital following surgery, the course and dosage of any
2846 opioid medications given during hospitalization and prior to discharge can help predict ongoing pain
2847 management needs (Hill, Stucke, Billmeier, et al., 2018; Joo et al., 2020; Tamboli et al., 2020). For
2848 postoperative pain, procedure-specific opioid prescribing recommendations are available with ranges
2849 for amounts of opioids needed (based on actual use and refills and on consensus) (Michigan Opioid
2850 Prescribing Engagement Network, 2020; Overton et al., 2018) (Thiels et al., 2018).

2851 Clinicians should generally not prescribe additional opioids to patients “just in case” pain
2852 continues longer than expected. However, in the event that pain continues longer than expected, it
2853 might be challenging for some patients to successfully navigate the healthcare system (e.g., clinician and
2854 pharmacy contact, transportation, need for assistance) to obtain additional medication as needed,

2855 leading to potential disparities in treatment. Clinicians, practices, and health systems should have
2856 mechanisms in place to provide timely re-evaluation for the subset of patients who experience severe
2857 acute pain that continues longer than the expected duration to confirm or revise the initial diagnosis
2858 and to adjust pain management accordingly. In particular, clinicians, practices, and health systems
2859 should ensure all patients can access and afford additional evaluation and treatment as needed to
2860 minimize disparities across patients based on access to and affordability of care and refills.

2861 Patients should be evaluated at least every 2 weeks if they continue to receive opioids for acute
2862 pain, and if opioids are continued for a month or longer, clinicians should refer to recommendations on
2863 subacute and chronic pain for follow-up (Recommendation 7) and tapering (Recommendation 5). If
2864 patients already receiving long-term opioids require additional opioids for superimposed severe acute
2865 pain (e.g., major surgery), opioids should be continued only for the duration of pain severe enough to
2866 require additional opioids, returning to the patient's baseline opioid dosage as soon as possible,
2867 including a taper to baseline dosage if additional opioids were used around the clock for more than a
2868 few days.

2869 If opioids are prescribed continuously (around the clock) for more than a few days for acute
2870 pain, clinicians should prescribe a taper to minimize withdrawal symptoms on discontinuation of
2871 opioids. Taper durations might need to be adjusted depending on the duration of the initial opioid
2872 prescription. For example, if opioids are used continuously for more than 3 days but for less than one
2873 week, clinicians can consider reducing the daily dosage to 50% for 2 days to ameliorate withdrawal
2874 when discontinuing opioids. When patients have taken opioids continuously for at least one week but
2875 less than one month, clinicians might consider a slower taper (e.g., reducing the daily dosage by
2876 approximately 20% every 2 days), a range consistent with tapering rates successfully used in studies of
2877 postoperative opioid prescribing (Joo et al., 2020; Tamboli et al., 2020). When patients are discharged
2878 from the hospital following surgery, opioid dosages needed during hospitalization and prior to discharge

2879 can help predict tapering needs to prevent withdrawal (Hill, Stucke, Billmeier, et al., 2018; Joo et al.,
2880 2020; Tamboli et al., 2020). Tapering plans should be discussed with the patient prior to discharge and
2881 with clinicians coordinating the patient's care as an outpatient. For tapering considerations when
2882 patients have taken opioids continuously for longer than one month, see Recommendation 5.

2883
2884 **7. Clinicians should evaluate benefits and risks with patients within 1 to 4 weeks of starting opioid**
2885 **therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and**
2886 **risks of continued therapy with patients every 3 months or more frequently (recommendation**
2887 **category: A, evidence type: 4).**

2888 Implementation considerations:

- 2889 • *In addition to evaluating benefits and risks of opioids before starting opioid therapy (see*
2890 *Recommendation 2), clinicians should evaluate patients to assess benefits and risks of opioids*
2891 *within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation.*
- 2892 • *Clinicians should consider follow-up intervals within the lower end of this range when ER/LA*
2893 *opioids are started or increased, given increased risk for overdose within the first 2 weeks of*
2894 *treatment, or when total daily opioid dosage is ≥ 50 MME/day. (Note: Overdose risk is doubled*
2895 *across multiple studies for dosages of 50 to <100 MME/day relative to <20 MME/day - see*
2896 *Recommendation 4).*
- 2897 • *Shorter follow-up intervals (within 3 days) should be strongly considered when starting or*
2898 *increasing the dosage of methadone, given the variable half-life of this drug (see*
2899 *Recommendation 3) and the potential for drug accumulation during initiation and during*
2900 *upward titration of dosage.*
- 2901 • *An initial follow-up interval closer to 4 weeks can be considered when starting immediate-release*
2902 *opioids at a dosage <50 MME/day.*
- 2903 • *Clinicians should regularly reassess all patients receiving long-term opioid therapy, including*
2904 *patients who are new to the clinician but on long-term opioid therapy, at least every 3 months.*
- 2905 • *Clinicians seeing new patients already receiving opioids should establish treatment goals for*
2906 *continued opioid therapy (see Recommendation 2).*
- 2907 • *Clinicians should re-evaluate patients who are at higher risk for opioid use disorder or overdose*
2908 *(e.g., patients with depression or other mental health conditions, a history of substance use*
2909 *disorder, a history of overdose, taking ≥ 50 MME/day, or taking other central nervous system*
2910 *depressants with opioids) more frequently than every 3 months.*

- 2911 • *To minimize unintended impact on patients with challenges in accessing or affording follow-up*
2912 *visits, practices, and health systems should work to ensure all patients can access and afford*
2913 *follow-up evaluation.*
- 2914 • *In practice contexts where virtual visits are part of standard care (e.g., in remote areas where*
2915 *distance or other context makes follow-up visits challenging), follow-up assessments that allow*
2916 *the clinician to communicate with and observe the patient through telehealth modalities may be*
2917 *conducted.*
- 2918 • *At follow-up, clinicians should review patient perspectives and goals, determine whether opioids*
2919 *continue to meet treatment goals, including sustained improvement in pain and function;*
2920 *whether the patient has experienced common or serious adverse events or early warning signs of*
2921 *serious adverse events or has signs of opioid use disorder.*
- 2922 • *Clinicians should ensure that treatment for depression, anxiety, or other psychological co-*
2923 *morbidities is optimized.*
- 2924 • *Clinicians should ask patients about their preferences for continuing opioids, given their effects*
2925 *on pain and function relative to any adverse effects experienced. If risks outweigh benefits of*
2926 *continued opioid therapy (e.g., if patients do not experience meaningful, sustained*
2927 *improvements in pain and function compared with prior to initiation of opioid therapy; if*
2928 *patients are taking higher-risk regimens [e.g., dosages ≥ 50 MME/day or opioids combined with*
2929 *benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh*
2930 *risks; if patients request dosage reduction or discontinuation; or if patients experience overdose*
2931 *or other serious adverse events), clinicians should work with patients to reduce opioid dosage or*
2932 *to discontinue opioids when possible, using principles from Recommendation 5.*
- 2933 • *Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic*
2934 *treatments as appropriate (see Recommendation 2).*

2935 *Supporting Rationale*

2936 Although the clinical evidence reviews did not find studies evaluating the effectiveness of more
2937 frequent monitoring intervals (Chou et al., April 2020), they did identify an observational study (Edlund
2938 et al., 2014) finding risk for opioid use disorder was associated with continuing opioid therapy for 3
2939 months or longer. In addition, the reviews identified a study finding that risk for overdose associated
2940 with ER/LA opioids might be particularly high during the first 2 weeks of treatment (Miller et al., 2015).
2941 Another study found the first 3 months after opioid initiation to be a higher risk period for opioid
2942 overdose (E. M. Oliva et al., 2020). Patients who do not have pain relief with opioids at 1 month are
2943 unlikely to experience pain relief with opioids at 6 months (Kalso, Simpson, Slappendel, Dejonckheere, &

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2944 Richarz, 2007). Although evidence is insufficient to determine at what point within the first 3 months of
2945 opioid therapy the risks for opioid use disorder increase, reassessment of pain and function within 1
2946 month of initiating opioids provides an opportunity to modify the treatment plan to achieve pain
2947 treatment goals, minimize risks of long-term opioid use by tapering and discontinuing opioids among
2948 patients not receiving a clear benefit from these medications, and additional evaluation within the first
2949 three months might provide opportunities to identify and mitigate risks for opioid use disorder and
2950 overdose.

2951 Experts noted that although there is little evidence for specific follow-up time frames, the
2952 recommendation was reasonable and reflects common practice and therefore supported both the
2953 recommendation and the category A designation. Experts further noted that social determinants of
2954 health affecting ability to return frequently for care (e.g., role as unpaid caregiver, or work at a job with
2955 minimal paid time off) or payer issues (e.g., co-pays) could have consequences when recommending
2956 frequent visits and should be considered.

2957 Clinicians should evaluate patients to assess benefits and risks of opioids within 1 to 4 weeks of
2958 starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals
2959 within the lower end of this range when ER/LA opioids are started or increased, given increased risk for
2960 overdose within the first 2 weeks of treatment (Miller et al., 2015), or when total daily opioid dosage is
2961 ≥ 50 MME/day, given overdose risk is doubled across multiple studies for dosages of 50 to <100
2962 MME/day relative to <20 MME/day (see Recommendation 4). Shorter follow-up intervals (within 3 days)
2963 should be strongly considered when starting or increasing the dosage of methadone, given the variable
2964 half-life of this drug (see Recommendation 3) and the potential for drug accumulation during initiation
2965 and during upward titration of dosage. An initial follow-up interval closer to 4 weeks can be considered
2966 when starting immediate-release opioids at a dosage <50 MME/day.

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2967 In analyses of placebo-controlled trials, the clinical evidence reviews found that effects of
2968 opioids on mean improvement in pain and in function were greater at 1 to 3 months than at 3 to 6
2969 months (Chou et al., April 2020). A cohort study found an association between longer duration of
2970 therapy and increased risk of new-onset depression (Chou et al., April 2020). Because of potential
2971 changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly
2972 reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician
2973 but on long-term opioid therapy, at least every 3 months. Clinicians seeing new patients already
2974 receiving opioids should establish treatment goals for continued opioid therapy (see Recommendation
2975 2). Clinicians should re-evaluate patients who are at greater risk for opioid use disorder or overdose
2976 (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a
2977 history of overdose, taking ≥ 50 MME/day, or taking other central nervous system depressants with
2978 opioids) more frequently than every 3 months. To minimize unintended impact on patients with
2979 challenges in accessing or affording follow-up visits, practices, and health systems should work to ensure
2980 all patients can access and afford follow-up evaluation. In addition, policymakers should minimize
2981 barriers to care (e.g., through promotion of paid time off). In practice contexts where virtual visits are
2982 part of standard care (e.g., in remote areas where distance or other context makes follow-up visits
2983 challenging), follow-up assessments that allow the clinician to communicate with and observe the
2984 patient through telehealth modalities may be conducted.

2985 At follow-up, clinicians should review patient perspectives on progress and challenges in moving
2986 toward treatment goals, determine whether opioids continue to meet treatment goals, including
2987 sustained improvement in pain and function; whether the patient has experienced common or serious
2988 adverse events or early warning signs of serious adverse events or has signs of opioid misuse or opioid
2989 use disorder (e.g., difficulty controlling use, cravings, work, social or family problems related to opioid
2990 use); whether benefits of opioids continue to outweigh risks; and whether there is a need for opioid

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2991 dosage reduction or discontinuation. Clinicians should assess benefits in function, pain control, and
2992 quality of life by asking patients about progress toward person-centered functional goals that have
2993 meaning for them (see Recommendation 2) and/or by using tools such as the three-item “Pain average,
2994 interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale
2995 (Krebs et al., 2009); clinically meaningful improvement has been defined as a 30% improvement in
2996 scores for both pain and function (Ostelo et al., 2008). Clinicians should also ask patients about common
2997 adverse effects such as constipation and drowsiness (see Recommendation 2), as well as asking about
2998 and assessing for effects that might be early warning signs for more serious problems such as overdose
2999 (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater
3000 quantities or more frequently than prescribed, difficulty controlling use, work, social, or family problems
3001 related to opioid use). Because depression, anxiety, and other psychological co-morbidities often coexist
3002 with and can interfere with resolution of pain, clinicians should use validated instruments to assess for
3003 these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized.
3004 Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain
3005 and function relative to any adverse effects experienced.

3006 If risks outweigh benefits of continued opioid therapy (e.g., if patients do not experience
3007 meaningful, sustained improvements in pain and function compared with prior to initiation of opioid
3008 therapy; if patients are taking higher-risk regimens [e.g., dosages ≥ 50 MME/day or opioids combined
3009 with benzodiazepines] without evidence of benefit; if patients believe benefits no longer outweigh risks;
3010 if patients request dosage reduction or discontinuation; or if patients experience overdose or other
3011 serious adverse events), clinicians should work with patients to reduce opioid dosage or to discontinue
3012 opioids when possible, using principles from Recommendation 5. Clinicians should maximize pain
3013 treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see
3014 Recommendation 2).

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3016 **Assessing risk and addressing harms of opioid use**

3017 **8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate**
3018 **risk for opioid-related harms and discuss with patients. Clinicians should work with patients to**
3019 **incorporate into the management plan strategies to mitigate risk, including offering naloxone**
3020 **when factors that increase risk for opioid overdose are present (recommendation category: A,**
3021 **evidence type: 4).**

3022 Implementation considerations:

- 3023 • *Clinicians should offer naloxone when prescribing opioids to patients at increased risk for*
3024 *overdose, including patients with a history of overdose, patients with a history of substance use*
3025 *disorder, patients with sleep-disordered breathing, patients taking higher dosages of opioids*
3026 *(e.g., ≥50 MME/day), patients taking benzodiazepines with opioids (see Recommendation 11),*
3027 *and patients at risk for returning to a high dose to which they have lost tolerance (e.g., patients*
3028 *undergoing tapering or recently released from prison).*
- 3029 • *Practices should provide education on overdose prevention and naloxone use to patients and*
3030 *offer to provide education to members of their households.*
- 3031 • *Naloxone co-prescribing can be facilitated by clinics or practices with resources to provide*
3032 *naloxone training and by collaborative practice models with pharmacists or through standing*
3033 *orders for naloxone at pharmacies.*
- 3034 • *Resources for prescribing naloxone in primary care and emergency department settings can be*
3035 *found through Prescribe to Prevent at <http://prescribetoprevent.org>; additional resources are at*
3036 *<https://samhsa.gov>.*
- 3037 • *In part because of concerns about cost of naloxone and access for some patients, this*
3038 *recommendation specifies that naloxone should be “offered” to patients. Clinicians, health*
3039 *systems, and payers should work to ensure patients can access naloxone, a potentially lifesaving*
3040 *treatment.*
- 3041 • *Clinicians should avoid prescribing opioids to patients with moderate or severe sleep-disordered*
3042 *breathing when possible to minimize risks for opioid overdose.*
- 3043 • *When making decisions about whether to initiate opioid therapy for pain during pregnancy,*
3044 *clinicians and patients together should carefully weigh benefits and risks. For pregnant people*
3045 *already receiving opioids, clinicians should access appropriate expertise if considering tapering*
3046 *opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into*
3047 *withdrawal (see Recommendation 5).*
- 3048 • *For pregnant people with opioid use disorder, medications for opioid use disorder*
3049 *(buprenorphine or methadone) have been associated with improved maternal outcomes and*
3050 *should be offered (see Recommendation 12).*

- 3051 • *Clinicians should use additional caution and increased monitoring (see Recommendation 7) to*
3052 *minimize risks of opioids prescribed for patients with renal or hepatic insufficiency and for*
3053 *patients aged ≥65 years and should implement interventions to mitigate common risks of opioid*
3054 *therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk*
3055 *assessment for falls, and patient monitoring for cognitive impairment.*
- 3056 • *Clinicians should ensure that treatment for depression and other mental health conditions is*
3057 *optimized, consulting with behavioral health specialists when needed.*
- 3058 • *Clinicians should ask patients about their drug and alcohol use.*
- 3059 • *Clinicians should use PDMP data (see Recommendation 9) and toxicology screening (see*
3060 *Recommendation 10) as appropriate to assess for concurrent substance use that might place*
3061 *patients at higher risk for opioid use disorder and overdose.*
- 3062 • *Clinicians should provide specific counseling on increased risks for overdose when opioids are*
3063 *combined with other drugs or alcohol (see Recommendation 2) and ensure that patients are*
3064 *provided or receive effective treatment for substance use disorders when needed (see*
3065 *Recommendation 12).*
- 3066 • *Although substance use disorder can alter the expected benefits and risks of opioid therapy for*
3067 *pain, patients with co-occurring pain and substance use disorder require ongoing pain*
3068 *management that maximizes benefits relative to risks. See “Pain management for patients with*
3069 *opioid use disorder” section of Recommendation 12 for additional considerations specific to*
3070 *patients with pain and opioid use disorder.*
- 3071 • *If clinicians consider opioid therapy for chronic pain for patients with substance use disorder,*
3072 *they should discuss increased risks for opioid use disorder and overdose with patients, carefully*
3073 *consider whether benefits of opioids outweigh increased risks, and incorporate strategies to*
3074 *mitigate risk into the management plan, such as offering naloxone (see Offering Naloxone to*
3075 *Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing*
3076 *frequency of monitoring (see Recommendation 7).*
- 3077 • *If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use disorder*
3078 *and treat or arrange treatment if needed. Clinicians should work with patients to reduce opioid*
3079 *dosage and to discontinue opioids when indicated (see Recommendation 5) and should ensure*
3080 *continued close monitoring and support for patients prescribed or not prescribed opioids.*
- 3081 *If clinicians continue opioid therapy in patients with prior opioid overdose, they should discuss*
3082 *increased risks for overdose with patients, carefully consider whether benefits of opioids*
3083 *outweigh substantial risks, and incorporate strategies to mitigate risk into the management*
3084 *plan, such as considering offering naloxone and increasing frequency of monitoring (see*
3085 *Recommendation 7).*

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3087 *Supporting Rationale*
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3089 The clinical evidence reviews found evidence too limited to determine effects of patient
3090 demographics and comorbidities on risk of opioid-related harms (Chou et al., April 2020). However,
3091 based on observational studies and expert opinion, certain risk factors are likely to increase

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3092 susceptibility to opioid-related harms and warrant incorporation of additional strategies into the
3093 management plan to mitigate risk. Clinicians should assess these risk factors periodically, with frequency
3094 individualized to patient comorbidities and other risk factors. For example, factors that vary more
3095 frequently over time, such as alcohol use, require more frequent assessment. In addition, clinicians
3096 should offer naloxone and re-evaluate patients more frequently (see Recommendation 7) when factors
3097 that increase risk for harm, such as sleep-disordered breathing, history of overdose, history of substance
3098 use disorder, higher dosages of opioids (e.g., ≥ 50 MME/day), and concurrent use of benzodiazepines
3099 with opioids, are present. Experts noted concerns with potential downstream effects of offering
3100 naloxone for patients of limited means to afford the cost of purchasing naloxone. In part because of this
3101 concern, and also because in some settings, naloxone is directly provided by a practice or health system
3102 to patients, “offering” naloxone is recommended. Clinicians, health systems, and payers should work to
3103 ensure patients can access naloxone, a potentially lifesaving treatment.

3104 **Patients with sleep-disordered breathing, including sleep apnea**

3105 A case-control analysis among Veterans prescribed opioids found that sleep apnea and chronic
3106 pulmonary disease were associated with increased risk for life-threatening respiratory central nervous
3107 system depression or overdose (Zedler et al., 2014). Careful monitoring and cautious dose titration
3108 should be used if opioids are prescribed for patients with mild sleep-disordered breathing. Clinicians
3109 should avoid prescribing opioids to patients with moderate or severe sleep-disordered breathing,
3110 whenever possible, to minimize risks for opioid overdose.

3111 **Pregnant people**

3112 Opioids used during pregnancy might be associated with risks to both parent and fetus. Some
3113 studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term
3114 delivery, and birth defects (Broussard et al., 2011; Lind et al., 2017; Whiteman et al., 2014; Yazdy, Desai,

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3115 & Brogly, 2015; Yazdy, Mitchell, Tinker, Parker, & Werler, 2013). In some cases, opioid use during
3116 pregnancy leads to neonatal opioid withdrawal syndrome (Hadi, da Silva, Natale, Boyd, & Morley-
3117 Forster, 2006). At the same time, as noted by the American College of Obstetricians and Gynecologists,
3118 “a cautious approach to prescribing opioids should be balanced with the need to address pain...
3119 Pregnancy should not be a reason to avoid treating acute pain” (“Committee Opinion No. 711: Opioid
3120 Use and Opioid Use Disorder in Pregnancy,” 2017). Clinicians and patients together should carefully
3121 weigh benefits and risks when making decisions about whether to initiate opioid therapy for pain during
3122 pregnancy. In addition, before initiating opioid therapy for individuals who can become pregnant,
3123 clinicians should discuss family planning and how long-term opioid use might affect any future
3124 pregnancy. When opioids are needed for treatment of acute pain in pregnant people, the lowest dose to
3125 achieve expected effects (see Recommendation 4) should be used for no longer than the expected
3126 duration of pain severe enough to require opioids (see Recommendation 6). For pregnant people with
3127 chronic pain, the American College of Obstetricians and Gynecologists recommends that “practice goals
3128 include strategies to avoid or minimize the use of opioids for pain management, highlighting alternative
3129 pain therapies such as nonpharmacologic (e.g., exercise, physical therapy, behavioral approaches), and
3130 nonopioid pharmacologic treatments” (“Committee Opinion No. 711: Opioid Use and Opioid Use
3131 Disorder in Pregnancy,” 2017). For pregnant people already receiving opioids, clinicians should access
3132 appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient
3133 and to the fetus if the patient goes into withdrawal (see Recommendation 5).

3134 The American College of Obstetricians and Gynecologists notes that early universal screening,
3135 brief intervention (e.g., engaging in a short conversation, providing feedback and advice), and referral
3136 for treatment of pregnant people with opioid use disorder improve both maternal and infant outcomes
3137 (The American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American
3138 Society of Addiction Medicine, 2017). For pregnant people with opioid use disorder, medications for

3139 opioid use disorder (buprenorphine or methadone) have been associated with improved maternal
3140 outcomes and should be offered (The American College of Obstetricians and Gynecologists Committee
3141 on Obstetric Practice & American Society of Addiction Medicine, 2017) (see Recommendation 12).

3142 The American Academy of Pediatrics has published recommendations for the care of infants
3143 with neonatal opioid withdrawal syndrome, including that pregnant people with opioid use disorder
3144 should receive antenatal counseling to provide education on the clinical signs of withdrawal and
3145 enhance maternal understanding of postnatal treatment for neonatal opioid withdrawal syndrome (e.g.,
3146 nonpharmacologic treatment including breastfeeding, and pharmacotherapy) and that all infants with
3147 long-term opioid exposure should be observed for at least 72 hours (4 to 7 days if exposed to
3148 buprenorphine or sustained released opioids and 5 to 7 days if exposed to methadone) to monitor for
3149 the development of withdrawal (Patrick, Barfield, & Poindexter, 2020). Clinicians caring for pregnant
3150 people receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder
3151 should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid
3152 withdrawal syndrome. In instances when travel to such a facility would present an undue burden on the
3153 pregnant person, it is appropriate to deliver locally, monitor and evaluate the newborn for neonatal
3154 opioid withdrawal syndrome, and transfer the newborn for additional treatment if needed. Previous
3155 guidelines have recommended that codeine be avoided whenever possible among mothers who are
3156 breastfeeding and, if used, should be limited to the lowest possible dose and to a 4-day supply with re-
3157 evaluation thereafter (National Opioid Use Guideline Group, 2010).

3158 **Patients with renal or hepatic insufficiency**

3159 A case-control study of risk of life-threatening respiratory central nervous system depression or
3160 overdose among veterans prescribed opioids found that renal disease and moderate or severe liver
3161 disease were associated with increased risk for life-threatening respiratory central nervous system
3162 depression or overdose (Zedler et al., 2014). Clinicians should use additional caution and increased

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3163 monitoring (see Recommendation 7) to minimize risks of opioids prescribed for patients with renal or
3164 hepatic insufficiency, given their decreased ability to process and excrete medications, susceptibility to
3165 accumulation of opioids, and reduced therapeutic window between safe dosages and dosages
3166 associated with respiratory depression and overdose (*Goodman and Gilman's The Pharmacologic Basis*
3167 *of Therapeutics, 9th ed, 1996*) (see Recommendations 3, 4, and 7).

3168 **Patients aged ≥65 years**

3169 Persons aged ≥65 years can be at risk for inadequate pain treatment (Becker et al., 2017;
3170 Bernabei et al., 1998; Institute of Medicine Committee on Advancing Pain Research Care and Education,
3171 2011; U.S. Department of Health and Human Services, 2019b). Older adults can also be at risk for
3172 changes in function that might be exacerbated by pain and contribute to deterioration in overall health
3173 and independence. Pain management for older patients can be challenging given increased risks of both
3174 nonopioid pharmacologic therapies (see Recommendation 2) and opioid therapy in this population. A
3175 case-control analysis among Veterans prescribed opioids found that age >55 years was associated with
3176 increased risk for life-threatening respiratory central nervous system depression or overdose (Zedler et
3177 al., 2014). Given reduced renal function and medication clearance even in the absence of renal disease,
3178 patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller
3179 therapeutic window between safe dosages and dosages associated with respiratory depression and
3180 overdose (*Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 9th ed, 1996*). Some older
3181 adults might have a cognitive impairment, such as dementia, which can increase risk for medication
3182 errors and make opioid-related confusion riskier. In addition, older adults are more likely than younger
3183 adults to experience co-morbid medical conditions and more likely to receive multiple medications,
3184 some of which might interact with opioids. Functional assessment is especially important in patients
3185 aged ≥65 years to better assess impact of pain on function and independence. Clinicians should use
3186 additional caution and increased monitoring (see Recommendation 7) for patients aged ≥65 years to

3187 ensure pain is addressed and to minimize risks of opioids prescribed and should educate older adults
3188 receiving opioids to avoid medication-related behaviors that increase risk such as saving unused
3189 medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy
3190 among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for
3191 falls, and patient monitoring for cognitive impairment.

3192 **Patients with mental health conditions**

3193 Because psychological distress frequently interferes with improvement of pain and function in
3194 patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-
3195 7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to support assessment for anxiety, post-
3196 traumatic stress disorder, and/or depression (Kroenke, Spitzer, Williams, & Löwe, 2010) might help
3197 clinicians improve overall pain treatment outcomes. Additional caution and increased monitoring (see
3198 Recommendation 7) might lessen the increased risk for overdose among patients with depression
3199 (Turner & Liang, 2015; Zedler et al., 2014). Previous guidelines have noted that acute psychiatric
3200 instability (severe depression, unstable bipolar disorder, or unstable psychotic disorder) or intermediate
3201 to high acute suicide risk precludes the safe use of self-administered long-term opioid therapy and that
3202 treatment for chronic pain with movement, exercise and cognitive behavioral therapy for pain may have
3203 benefit in treating depression, PTSD, and in reducing suicide risk (U.S. Department of Veterans Affairs
3204 and Department of Defense, 2017). In addition, patients with anxiety disorders and other mental health
3205 conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory
3206 depression and increase risk for overdose (see Recommendation 11). Clinicians should ensure that
3207 treatment for depression and other mental health conditions as well as treatment for pain is optimized,
3208 consulting with behavioral health specialists when needed. Treatment for depression can improve pain
3209 symptoms as well as depression and might decrease overdose risk (Turner & Liang, 2015). For treatment
3210 of chronic pain in patients with depression, clinicians should consider using tricyclic or SNRI

3211 antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise
3212 contraindicated (see Recommendation 2).

3213 **Patients with substance use disorders**

3214 Patients with substance use disorders including alcohol use disorder are likely to experience
3215 greater risks for opioid use disorder and overdose (Bohnert et al., 2011; Dunn et al., 2010; Zedler et al.,
3216 2014) than persons without these conditions. Despite increased risk for opioid misuse and opioid use
3217 disorder when prescribed opioid analgesics (Edlund, Steffick, Hudson, Harris, & Sullivan, 2007; Reid et
3218 al., 2002), patients with histories of substance use disorders are more likely than other patients to
3219 receive long-term opioid treatment for chronic pain (Edlund et al., 2010). Previous guidelines have
3220 recommended screening or risk assessment tools to identify patients at higher risk for opioid misuse or
3221 opioid use disorder. However, the clinical evidence reviews found that currently available risk
3222 stratification tools (e.g., Opioid Risk Tool, Screener and Opioid Assessment for Patients with Pain Version
3223 1, SOAPP-R, and Brief Risk Interview) show limited and variable accuracy for classification of patients as
3224 at low or high risk for opioid use disorder or misuse (Chou et al., April 2020). If these tools are used, they
3225 should be supplemented with other assessments, such as discussions with patients, family, and
3226 caregivers, clinical records, PDMP data (see Recommendation 9), and toxicology screening data (see
3227 Recommendation 10). Clinicians should always exercise caution when considering or prescribing opioids
3228 and should not overestimate the ability of currently available risk stratification tools to rule out risks
3229 from long-term opioid therapy.

3230 Non-prescribed drugs (e.g., heroin, illicitly manufactured fentanyl, cocaine, methamphetamine)
3231 (Gladden, O'Donnell, Mattson, & Seth, 2019) and alcohol (Jones, Paulozzi, & Mack, 2014) are listed as
3232 contributory factors on a substantial proportion of death certificates for prescription opioid-involved
3233 overdose deaths. Clinicians should ask patients about their drug (U.S. Preventive Services Task Force,
3234 2020) and alcohol use. Single screening questions can be used (Saitz, Cheng, Allensworth-Davies, Winter,

3235 & Smith, 2014). For example, the question “How many times in the past year have you used an illegal
3236 drug or used a prescription medication for nonmedical reasons?” (with an answer of one or more
3237 considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the
3238 detection of a drug use disorder compared with a standardized diagnostic interview (P. C. Smith,
3239 Schmidt, Allensworth-Davies, & Saitz, 2010). Validated screening tools such as the Drug Abuse Screening
3240 Test (DAST) (Yudko, Lozhkina, & Fouts, 2007), the Tobacco, Alcohol, Prescription medication, and other
3241 Substance use Tool (TAPS) (McNeely et al., 2016), and the Alcohol Use Disorders Identification Test
3242 (AUDIT) (Reinert & Allen, 2007) can also be used. Clinicians should use PDMP data (see
3243 Recommendation 9) and toxicology screening (see Recommendation 10) as appropriate to assess for
3244 concurrent substance use that might place patients at higher risk for opioid use disorder and overdose.
3245 Clinicians should also provide specific counseling on increased risks for overdose when opioids are
3246 combined with other drugs or alcohol (see Recommendation 2) and ensure that patients receive
3247 effective treatment for substance use disorders when needed (see Recommendation 12).

3248 If clinicians consider opioid therapy for chronic pain, they should discuss increased risks for
3249 opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh
3250 increased risks, and incorporate strategies to mitigate risk into the management plan, such as offering
3251 naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms
3252 Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are
3253 prescribed. Clinicians should communicate with patients’ substance use disorder treatment providers if
3254 opioids are prescribed. Although substance use disorder can alter the expected benefits and risks of
3255 opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain
3256 management that maximizes benefits relative to risks. See “Pain management for patients with opioid
3257 use disorder” section of Recommendation 12 for additional considerations specific to patients with
3258 opioid use disorder.

3259 **Patients with prior nonfatal overdose**

3260 Prior nonfatal overdose is associated with substantially increased risk for future nonfatal or fatal
3261 opioid overdose (M. R. Larochelle, Liebschutz, Zhang, Ross-Degnan, & Wharam, 2016). Yet, a cohort
3262 study of commercially insured patients found that opioids were dispensed to 91% of patients after an
3263 overdose, and a substantial percentage experienced a repeated opioid overdose, with a cumulative
3264 incidence at 2 years of 17% among patients receiving 100 or more MME/day, 15% among those
3265 prescribed 50 to 100 MME/day, 9% among those prescribed <50 MME/day, and 8% among those
3266 prescribed no opioids (M. R. Larochelle et al., 2016).

3267 If patients experience nonfatal opioid overdose, clinicians should evaluate for opioid use
3268 disorder and treat or arrange treatment if needed. Buprenorphine or methadone for opioid use disorder
3269 following nonfatal overdose are associated with reduced all-cause and opioid-related mortality (Marc R
3270 Larochelle et al., 2018). Clinicians should work with patients to reduce opioid dosage and to discontinue
3271 opioids when indicated (see Recommendation 5) and should ensure continued close monitoring and
3272 support for patients prescribed or not prescribed opioids. If clinicians continue opioid therapy in
3273 patients with prior opioid overdose, they should discuss increased risks for overdose with patients,
3274 carefully consider whether benefits of opioids outweigh substantial risks, and incorporate strategies to
3275 mitigate risk into the management plan, such as considering offering naloxone (see Offering Naloxone to
3276 Patients When Factors That Increase Risk for Opioid-Related Harms Are Present), involving patient-
3277 identified trusted family members, and increasing frequency of monitoring (see Recommendation 7).

3278 **Offering naloxone to patients when factors that increase risk for opioid-related harms are present**

3279 Naloxone is an opioid antagonist that can reverse severe respiratory depression; its
3280 administration by laypersons, such as friends, family, and caregivers of persons who experience opioid
3281 overdose, can save lives (Walley et al., 2013). Naloxone precipitates acute withdrawal among patients
3282 physically dependent on opioids. Serious adverse effects, such as pulmonary edema, cardiovascular

3283 instability, and seizures, have been reported but are rare at doses consistent with labeled use for opioid
3284 overdose (Enteen et al., 2010). The clinical evidence reviews identified one observational study (Coffin
3285 et al., 2016) finding that provision of naloxone to patients prescribed opioids in primary care clinics was
3286 associated with decreased likelihood of emergency department visits (but no difference in risk of
3287 overdose) (Chou et al., April 2020).

3288 ***Clinicians should offer naloxone when prescribing opioids to patients at increased risk for***
3289 ***overdose, including patients with a history of overdose, patients with a history of substance use***
3290 ***disorder, patients taking benzodiazepines with opioids*** (see Recommendation 11), ***patients at risk for***
3291 ***returning to a high dose to which they have lost tolerance (e.g., patients undergoing tapering or***
3292 ***recently released from prison), and patients taking higher dosages of opioids (≥50 MME/day).***

3293 Practices should provide education on overdose prevention and naloxone use to patients receiving
3294 naloxone prescriptions and to members of their households. Naloxone co-prescribing can be facilitated
3295 by clinics or practices with resources to provide naloxone training and by collaborative practice models
3296 with pharmacists. Resources for prescribing naloxone in primary care settings can be found through
3297 Prescribe to Prevent at <http://prescribetoprevent.org>.

3298
3299 **9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically**
3300 **during opioid therapy for chronic pain, clinicians should review the patient’s history of controlled**
3301 **substance prescriptions using state prescription drug monitoring program (PDMP) data to**
3302 **determine whether the patient is receiving opioid dosages or combinations that put the patient at**
3303 **high risk for overdose (recommendation category: B, evidence type: 4).**

3304 ***Implementation considerations:***

- 3305 • *Ideally, PDMP data should be reviewed before every opioid prescription for acute, subacute, or*
3306 *chronic pain. This is recommended in all jurisdictions where PDMP availability and access*
3307 *policies, as well as clinical practice settings, make this practicable (e.g., clinician and delegate*
3308 *access permitted).*

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- *At a minimum, during long-term opioid therapy, PDMP data should be reviewed before an initial opioid prescription and then every 3 months or more frequently. The recommendation category B acknowledges variation in PDMP availability and circumstances. However, because PDMP information can be most helpful when results are unexpected, and to minimize bias in application, clinicians should apply this recommendation when feasible to all patients rather than differentially based on assumptions about what they will learn about different patients.*
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- *Clinicians should use specific PDMP information about medications prescribed to their patient in the context of other clinical information, including their patient’s history, physical findings, and other relevant testing, in order to help them communicate with and protect their patient.*
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- *Clinicians should review PDMP data specifically for prescription opioids and other controlled medications patients have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the patient at high risk for overdose.*
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- *PDMP-generated risk scores have not been validated against clinical outcomes such as overdose and should not take the place of clinical judgment. Clinicians should not dismiss patients from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of prescription opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendations 1 and 2], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendations 8 and 12]).*
- 3330
- *Clinicians should take actions to improve patient safety:*
 - *Discuss information from the PDMP with their patient and confirm that the patient is aware of any additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient’s identity to obtain prescriptions).*
 - *Discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving prescription opioids from more than one clinician or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines; see Recommendation 11) and offer naloxone (see Recommendation 8).*
 - *Use extreme caution when prescribing opioids and benzodiazepines concurrently, appreciating that some patient circumstances warrant prescribing of these medications concomitantly. Clinicians should communicate with others managing the patient to discuss the patient’s needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11).*
 - *Consider the total MME/day for concurrent opioid prescriptions to help assess the patient’s overdose risk (see Recommendation 4). Buprenorphine should not be counted in the total MME/day in calculations given its opioid partial agonist properties that confer a ceiling effect on respiratory depression. If patients are found to be receiving high total daily dosages of opioids, discuss safety concerns with the patient, consider in collaboration with the*
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3349 *patient if tapering to a safer dosage is warranted (see Recommendation 5), and offer*
3350 *naloxone (see Recommendation 8).*

3351 ○ *Discuss safety concerns with other clinicians who are prescribing controlled substances for*
3352 *their patient. Ideally, clinicians should first discuss concerns with their patient and inform*
3353 *him or her that they plan to coordinate care with the patient's other clinicians to improve the*
3354 *patient's safety.*

3355 ○ *Screen for substance use and discuss concerns with their patient (see Recommendations 8*
3356 *and 12).*

3357 *If clinicians believe their patient might be diverting (sharing or selling prescription opioids*
3358 *and not taking them), consider toxicology testing to assist in determining whether*
3359 *prescription opioids can be discontinued without causing withdrawal (see Recommendations*
3360 *5 and 10). A negative toxicology test for prescribed opioids might indicate the patient is not*
3361 *taking prescribed opioids, although clinicians should consider other possible reasons for this*
3362 *test result, such as false negative results or misinterpretation of results (see*
3363 *Recommendation 10).*

3364

3365 *Supporting Rationale*

3366 PDMPs are databases overseen by states, territories, counties, and the District of Columbia that
3367 collect information on controlled prescription drugs dispensed by pharmacies in most jurisdictions and,
3368 in select jurisdictions, by dispensing clinicians as well. The clinical evidence reviews did not find studies
3369 evaluating the effectiveness of PDMPs for risk mitigation. However, among patients receiving
3370 concurrent treatment with opioids and benzodiazepines, overdose risk is further increased among
3371 patients receiving these treatments from multiple prescribers rather than one prescriber, highlighting
3372 potential room for improvement in care coordination (K. P. Chua, Brummett, Ng, & Bohnert, 2021).
3373 PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for
3374 patients from other locales) and when patients transition care to a new clinician. A contextual evidence
3375 review (Chou et al., April 2020) identified a survey of physicians in Maryland (D. H. Lin et al., 2017)
3376 finding that while barriers towards PDMP review were noted, including not knowing about the program,
3377 registration difficulties, and difficulty accessing data, most participants felt that PDMPs improved opioid
3378 prescribing by decreasing opioid prescription amounts and increasing comfort with prescribing opioids

3379 (Chou et al., April 2020). Integration of PDMPs with electronic health records (EHRs) can reduce burden
3380 on clinicians compared to having to access a separate system (Centers for Disease Control and
3381 Prevention, 2017; U.S. Government Accountability Office, 2020). Special attention should be paid to
3382 ensure that PDMP information is not used in a way that is harmful to patients. For example, PDMP
3383 information has been used to dismiss patients from clinician practices (Irvine et al., 2014), which might
3384 adversely affect patient safety and result in untreated or undertreated pain. Many state laws require
3385 PDMP use under specific circumstances (B. Lee, Zhao, Yang, Ahn, & Perry, 2021). Experts noted concern
3386 about PDMP risk scores or other algorithmic interpretations from software platforms that can lead to
3387 distrust between clinicians and patients and stigmatization, particularly for patients with conditions such
3388 as opioid use disorder. Risk scores are reportedly generated by applying trade secret-protected
3389 algorithms to information from patient EHRs and other sources such as court records and criminal and
3390 sexual trauma histories; these algorithms may disparately impact women, people of color, and people
3391 who live in poverty (J. Oliva, 2021). Importantly, while one PDMP-generated risk measure has shown fair
3392 concurrence with the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), these
3393 scores have not been externally validated against clinical outcomes (Cochran et al., 2021) (J. Oliva,
3394 2021). Such risk scores should not take the place of clinical judgment. Rather, clinicians should use
3395 specific PDMP information about medications prescribed to their patient in the context of other clinical
3396 information, including their patient's history, physical findings, and other relevant testing, in order to
3397 help them communicate with and protect their patient. Experts raised varying points regarding
3398 frequency of PDMP use, with many agreeing PDMPs should be consulted prior to every opioid
3399 prescription, several agreeing that universal application would mitigate bias in application to different
3400 patients, and others believing it might not be warranted or feasible to check the PDMP in all cases,
3401 particularly prior to prescribing opioids for acute pain for a small number of days. Ideally, PDMP data
3402 should be reviewed before every opioid prescription for acute, subacute, or chronic pain. This is

3403 recommended in all jurisdictions where PDMP availability and access policies make this practicable (e.g.,
3404 clinician and delegate access permitted). At a minimum, PDMP data should be reviewed before initial
3405 opioid prescriptions for subacute or chronic pain and then every 3 months or more frequently during
3406 long-term opioid therapy. The recommendation category B acknowledges variation in PDMP availability
3407 (PDMPs now exist in most but not all U.S. jurisdictions) and circumstances (e.g., a clinician might
3408 reasonably determine that a patient with severe acute pain presenting in the emergency department
3409 during a PDMP system access failure would be adversely impacted by waiting hours for a prescription).
3410 However, because PDMP information can be most helpful when results are unexpected, and to minimize
3411 bias in application, clinicians should apply this recommendation when feasible to all patients rather than
3412 differentially based on assumptions about what they will learn about specific patients.

3413 Clinicians should review PDMP data for prescription opioids and other controlled medications
3414 patients might have received from additional prescribers to determine whether a patient is receiving
3415 high total opioid dosages or combinations (e.g., opioids combined with benzodiazepines) that put the
3416 patient at high risk for overdose. If patients are found to have high opioid dosages or combinations of
3417 medications that might put them at risk for overdose, or multiple controlled substance prescriptions
3418 written by different clinicians, clinicians should take actions to improve patient safety (see above
3419 Implementation Considerations).

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3421 **10. When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology**
3422 **testing to assess for prescribed medications as well as other prescribed and non-prescribed**
3423 **controlled substances (recommendation category: B, evidence type: 4).**

3424 Implementation considerations:

- 3425 • Clinicians should not dismiss patients from care based on a toxicology test result because this
3426 could constitute patient abandonment and could have adverse consequences for patient safety,
3427 potentially including the patient obtaining opioids or other drugs from alternative sources and
3428 the clinician missing opportunities to facilitate treatment for substance use disorder.

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- *Prior to starting opioids and periodically during opioid therapy, clinicians should consider toxicology testing to assess for prescribed opioids as well as other prescription and nonprescription controlled substances that increase risk for overdose when combined with opioids, including nonprescribed and illicit opioids and benzodiazepines.*
 - *Clinicians, practices, and health systems should aim to minimize bias testing and should not apply this recommendation differentially based on assumptions about what they will learn about different patients.*
 - *Predicting risk is challenging, and currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorder. Rather, clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients, and consider toxicology screening whenever its potential problems can be mitigated.*
 - *Clinicians should explain to patients that toxicology testing will not be used to dismiss patients from care and is intended to improve their safety.*
 - *Clinicians should explain expected results (e.g., presence of prescribed medication and absence of drugs, including non-prescribed controlled substances, not reported by the patient) and ask patients about use of prescribed and other drugs and whether there might be unexpected results.*
 - *Toxicology screening can be performed with a relatively inexpensive presumptive immunoassay panel that tests for opiates as a class, benzodiazepines as a class, and several non-prescribed substances.*
 - *The use of confirmatory testing can add substantial costs and should be based on the need to detect specific opioids, such as those that are being prescribed, and those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology test results.*
 - *Clinicians should be familiar with the drugs included in toxicology screening panels used in their practice and should understand how to interpret results for these drugs. For example, a positive “opiates” immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but does not detect synthetic opioids and might not detect semisynthetic opioids. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive.*
 - *Restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of toxicology testing.*
 - *Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and should discuss unexpected results with the patient.*
 - *Discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted.*

- |
- 3471 • *Clinicians should use unexpected results to improve patient safety (e.g., change pain*
3472 *management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or*
3473 *continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see*
3474 *Recommendation 7], offer naloxone [see Recommendation 8], offer or refer for substance use*
3475 *disorder treatment [see Recommendation 12], all as appropriate).*

3476

3477 *Supporting Rationale*

3478 The clinical evidence reviews did not find studies evaluating the effectiveness of toxicology
3479 screening for risk mitigation during opioid prescribing for pain. However, concurrent use of opioid pain
3480 medications with other opioid pain medications, benzodiazepines, or heroin or other non-
3481 pharmaceutical opioids can increase patients' risk for overdose. Toxicology tests can provide
3482 information about drug use that is not reported by the patient. In addition, toxicology tests can assist
3483 clinicians in identifying when patients are not taking opioids prescribed for them, which might in some
3484 cases indicate diversion or other clinically important issues such as difficulties with adverse effects. The
3485 most commonly drug-tested bodily specimen is urine; oral fluid (saliva) testing is also available (Cone &
3486 Huestis, 2007), but testing protocols using oral fluid are not as well-established. On October 25, 2019,
3487 SAMHSA published guidelines for the inclusion of oral fluid specimens in federal executive branch
3488 agencies' toxicology testing programs (Substance Abuse and Mental Health Services Administration,
3489 2019), effective January 1, 2020. Toxicology testing results can be associated with outcomes and
3490 practices that harm patients (e.g., stigmatization, inappropriate termination from care). False positive
3491 and false negative presumptive results are not uncommon, a problem which can be compounded
3492 because clinicians commonly misinterpret results (I. Chua et al., 2020; Starrels, Fox, Kunins, &
3493 Cunningham, 2012), leading to inappropriate consequences for patients. Urine toxicology tests do not
3494 provide accurate information about how much or what dose of opioids or other drugs a patient took.
3495 Testing for fentanyl is not currently available in widely-used toxicology assays, potentially leading to
3496 false assurance. Ideally, clinicians would only test for substances for which results could affect patient
3497 management. However, it can be challenging or impossible for clinicians to tailor widely used toxicology

3498 panels to include the specific substances most relevant to clinical decisions for their patient. Toxicology
3499 testing costs are not always covered fully by insurance and can be a burden for patients, and clinician
3500 time is needed to interpret, confirm, and communicate results.

3501 Experts noted concerns that biases and disparities affecting which patients have toxicology tests
3502 could have disproportionately negative consequences among Black and Latinx patients. In addition,
3503 testing costs would have the greatest consequences for patients with the least ability to pay. Because of
3504 these concerns, some experts felt grading the recommendation as category A could potentially reduce
3505 bias and disparities. However, others thought that while universal application could mitigate bias in who
3506 is tested, it would not mitigate stigma associated with testing. In addition, experts noted concerns about
3507 accuracy, clinician interpretation, testing costs, and potential for a wait for test results to delay care.

3508 Because of concerns about imperfect accuracy, problems in interpretation, potential stigma, and
3509 cost, the recommendation is rated category B. However, clinicians, practices, and health systems should
3510 aim to minimize bias in its application and should not apply this recommendation differentially based on
3511 assumptions about what they will learn about different patients. Predicting risk is challenging, and
3512 currently available tools do not allow clinicians to reliably identify patients who are at low risk for
3513 substance use disorder (Chou et al., April 2020). Rather, clinicians should consider toxicology test results
3514 as potentially useful data, in the context of other clinical information, for all patients, and consider
3515 toxicology testing whenever its potential problems can be mitigated. For example, clinicians can become
3516 familiar with the drugs included in toxicology testing panels used in their practice and understand how
3517 to interpret results, and practices and health systems can ensure a laboratorian or toxicologist is
3518 available to discuss unexpected results, that costs to patients are not burdensome, and that practice
3519 policies regarding testing and frequency can minimize bias. For example, routine use of testing with
3520 standardized policies at the practice or clinic level might help destigmatize their use. Because truly

3521 random testing might not be feasible in clinical practice, some clinics obtain a specimen at every visit,
3522 but only send it for testing on a random schedule.

3523 Prior to starting opioids and periodically during opioid therapy, clinicians should consider
3524 toxicology testing to assess for prescribed opioids as well as other prescription and non-prescribed
3525 substances that increase risk for overdose when combined with opioids, including non-prescribed and
3526 illicit opioids and benzodiazepines. Before ordering toxicology testing, clinicians should have a plan for
3527 responding to unexpected results. Clinicians should explain to patients that toxicology testing will not be
3528 used punitively (e.g., will not be used to dismiss patients from care) and is intended to improve their
3529 safety. Clinicians should also explain expected results (e.g., presence of prescribed medication and
3530 absence of substances, including non-prescribed substances, not reported by the patient). Clinicians
3531 should ask patients about use of prescribed medications and other substances and ask whether there
3532 might be unexpected results. This will provide an opportunity for patients to provide information about
3533 changes in their use of prescribed opioids or other drugs.

3534 In most situations, initial toxicology testing can be performed with a relatively inexpensive
3535 immunoassay panel that tests for opiates and benzodiazepines as classes, and several non-prescribed
3536 substances. Patients prescribed oxycodone or non-morphine-based opioids (e.g., buprenorphine,
3537 methadone) require specific testing for those agents. The use of confirmatory testing can add
3538 substantial costs and should be based on the need to detect the specific opioid that is prescribed and
3539 those that cannot be identified on standard immunoassays or on the presence of unexpected toxicology
3540 test results. Clinicians and health systems should work to minimize inequitable cost burdens for patients
3541 and limit specific testing to situations when it is necessary. Clinicians should be familiar with the
3542 compounds included in toxicology testing panels used in their practice and should understand how to
3543 interpret results. For example, a positive opiate immunoassay test result detects morphine, which might
3544 reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic

3545 opioids (e.g., fentanyl or methadone) and might not detect semisynthetic opioids (e.g., oxycodone or
3546 buprenorphine). Many laboratories use an oxycodone immunoassay that detects oxycodone and
3547 oxymorphone, but these may need to be ordered or identified separately in a toxicology testing panel.
3548 In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is
3549 taking and might not mean the patient is taking the specific opioid for which the test was positive. For
3550 example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of
3551 oxycodone. Detailed considerations for interpretation of urine toxicology test results, including which
3552 tests to order and expected results, drug detection time in urine, and drug metabolism have been
3553 published previously (Washington State Agency Medical Directors' Group, 2015). A review including
3554 interpretation of oral fluid sample toxicology test results is also available (Cone & Huestis, 2007).
3555 Restricting confirmatory testing to situations and substances for which results can reasonably be
3556 expected to affect patient management can reduce costs of toxicology testing, given the substantial
3557 costs associated with confirmatory testing methods.

3558 Clinicians may wish to discuss unexpected results with the local laboratory or toxicologist and
3559 should discuss unexpected results with the patient. Discussion with patients prior to specific
3560 confirmatory testing can sometimes yield a candid explanation of why a particular substance is present
3561 or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient
3562 might explain that the test is negative for prescribed opioids because she felt opioids were no longer
3563 helping and discontinued them. If unexpected results are not explained, a confirmatory test using a
3564 method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid
3565 chromatography/mass spectrometry) might be warranted to clarify the situation.

3566 Clinicians should use unexpected results to improve patient safety (e.g., change pain
3567 management strategy [see Recommendation 2], carefully weigh benefits and risks of reducing or
3568 continuing opioid dosage [see Recommendation 5], re-evaluate more frequently [see Recommendation

3569 7], offer naloxone [see Recommendation 8], offer or refer for substance use disorder treatment [see
3570 Recommendation 12], all as appropriate). If tests for prescribed opioids are repeatedly negative,
3571 including confirmatory tests, and the clinician has verified that the patient is not taking the prescribed
3572 opioid, clinicians can discontinue the prescription without a taper and discuss options for safe disposal
3573 of unused opioids (U.S. Food and Drug Administration, 2020a).

3574 ***Clinicians should not dismiss patients from care based on a toxicology test result because this***
3575 ***could constitute patient abandonment and could have adverse consequences for patient safety,***
3576 ***potentially including the patient obtaining opioids from alternative sources and the clinician missing***
3577 ***opportunities to facilitate treatment for substance use disorder.***

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3579 **11. Clinicians should use extreme caution when prescribing opioid pain medication and**
3580 **benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent**
3581 **prescribing of opioids and other central nervous system depressants (recommendation category:**
3582 **B, evidence type: 3).**

3583 ***Implementation considerations:***

- 3584 • *Although there are circumstances when it might be appropriate to prescribe opioids to a patient*
3585 *who is also prescribed benzodiazepines (e.g., severe acute pain in a patient taking long-term,*
3586 *stable low-dose benzodiazepine therapy), clinicians should use extreme caution when prescribing*
3587 *opioids and benzodiazepines concurrently. In addition, clinicians should consider whether*
3588 *benefits outweigh risks of concurrent use of opioids with other central nervous system*
3589 *depressants (e.g., muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating*
3590 *anticonvulsant medications such as gabapentin and pregabalin).*
- 3591 • *Clinicians should check the PDMP for concurrent controlled medications prescribed by other*
3592 *clinicians (see Recommendation 9) and should consider involving pharmacists as part of the*
3593 *management team when opioids are co-prescribed with other central nervous system*
3594 *depressants.*
- 3595 • *In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh the*
3596 *benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with*
3597 *patients and other members of the patient's care team.*

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- *Risks of concurrent opioid and benzodiazepine use are likely to be greater with unpredictable use of either medication, with use of high-dose opioids and high-dose benzodiazepines in combination, or with use with other substances including alcohol (as compared to long-term stable use of low-dose opioids and low-dose benzodiazepines without other substances).*
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- *In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing.*
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- *Buprenorphine or methadone for opioid use disorder should not be withheld from patients taking benzodiazepines or other medications that depress the central nervous system.*
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- *If risks are determined to outweigh benefits of continuing opioid and benzodiazepine therapy at current dosages and a decision is made to taper, it might be safer and more practical to taper opioids first. There can be greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with anxiety (see Recommendation 5).*
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- *Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death. The rate of tapering should be individualized.*
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- *If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific antidepressants or other nonbenzodiazepine medications approved for anxiety should be offered.*
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- *Clinicians should communicate with clinicians managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.*

3620
3621 *Supporting Rationale*

3622 Benzodiazepines and opioids both cause central nervous system depression, and
3623 benzodiazepines can potentiate opioid-induced decreases in respiratory drive. Epidemiologic studies
3624 find concurrent benzodiazepine use in large proportions of opioid-related overdose deaths (Dasgupta et
3625 al., 2016; Gomes et al., 2011; Jones & McAninch, 2015). The clinical evidence reviews identified 3 cohort
3626 studies finding an association between concurrent use of benzodiazepines and opioids versus opioids
3627 alone and increased risk of overdose (Chou et al., April 2020). A case-cohort study found concurrent
3628 benzodiazepine prescription with opioid prescription to be associated with a near-quadrupling of risk for
3629 overdose death compared with opioid prescription alone (Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015).

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3630 The clinical evidence reviews did not find studies evaluating the effectiveness of avoiding co-prescribing
3631 of benzodiazepines and opioids on risk of overdose (Chou et al., April 2020). The clinical evidence
3632 reviews additionally identified 3 observational studies finding an association between concurrent use of
3633 gabapentinoids and opioids versus opioids alone and increased risk of overdose, with higher risks at
3634 increased gabapentinoid doses (Chou et al., April 2020).

3635 Experts noted that rather than necessarily being a direct cause of overdose, benzodiazepines
3636 might serve as a marker for risk of overdose due to underlying conditions, that—in specific situations—
3637 benzodiazepines can be beneficial, and that stopping benzodiazepines can be destabilizing. In addition,
3638 experts noted that long-term, stable use might be safer than erratic, unpredictable use. Due to these
3639 considerations, several experts felt recommending extreme caution with concurrent prescription of
3640 opioids and benzodiazepines was more appropriate than a recommendation to avoid prescribing opioid
3641 pain medication and benzodiazepines concurrently and that category B would be more appropriate than
3642 category A for this recommendation.

3643 Although there are circumstances when it might be appropriate to prescribe opioids to a patient
3644 receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low-dose
3645 benzodiazepine therapy), clinicians should use extreme caution when prescribing opioids and
3646 benzodiazepines concurrently. In addition, given that other central nervous system depressants (e.g.,
3647 muscle relaxants, non-benzodiazepine sedative hypnotics, potentially sedating anticonvulsant
3648 medications such as gabapentin and pregabalin) (U.S. Food and Drug Administration, 2019b) can
3649 potentiate respiratory depression associated with opioids, clinicians should consider whether benefits
3650 outweigh risks of concurrent use of these medications. Clinicians should check the PDMP for concurrent
3651 controlled medications prescribed by other clinicians (see Recommendation 9) and should consider
3652 involving pharmacists as part of the management team when opioids are co-prescribed with other
3653 central nervous system depressants.

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3654 In patients receiving opioids and benzodiazepines long-term, clinicians should carefully weigh
3655 the benefits and risks of continuing therapy with opioids and benzodiazepines and discuss with patients
3656 and other members of the patient’s care team. In specific situations, benzodiazepines can be beneficial,
3657 and stopping benzodiazepines can be destabilizing. Importantly, as emphasized in an FDA advisory (U.S.
3658 Food and Drug Administration, 2017), buprenorphine or methadone for opioid use disorder should not
3659 be withheld from patients taking benzodiazepines or other medications that depress the central nervous
3660 system. While the combined use of these medications increases risks, the harm caused by untreated
3661 opioid use disorder can outweigh these risks.

3662 If risks are determined to outweigh benefits of continuing opioids for pain and benzodiazepine
3663 therapy at current dosages and a decision is made to taper one or more medications, it might be safer
3664 and more practical to taper opioids first (see Recommendation 5). There can be greater risks of
3665 benzodiazepine withdrawal relative to opioid withdrawal, and tapering opioids can be associated with
3666 anxiety. Clinicians should taper benzodiazepines gradually prior to discontinuation because abrupt
3667 withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and, in
3668 rare cases, death (Haque et al., 1990; Lann & Molina, 2009). Tapering rates should be individualized.
3669 Examples of benzodiazepine tapers and tips for managing benzodiazepine withdrawal are available (U.S.
3670 Department of Veterans Affairs and Department of Defense, 2015; Veterans Health Administration PBM
3671 Academic Detailing Service). CBT increases tapering success rates and might be particularly helpful for
3672 patients struggling with a benzodiazepine taper (Paquin, Zimmerman, & Rudolph, 2014). If
3673 benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids
3674 require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-
3675 depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Clinicians
3676 should communicate with mental health professionals managing the patient to discuss the patient’s

3677 needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and
3678 coordinate care.

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3680 **12. Clinicians should offer or arrange treatment with medication for patients with opioid use disorder**
3681 **(recommendation category: A, evidence type: 1).**

3682 Implementation considerations:

- 3683 • *Although stigma can reduce the willingness of individuals with opioid use disorder to seek*
3684 *treatment, opioid use disorder is a chronic, treatable disease from which people can recover and*
3685 *continue to lead healthy lives.*
- 3686 • *If clinicians suspect opioid use disorder, they should discuss their concern with their patient and*
3687 *provide an opportunity for the patient to disclose related concerns or problems.*
- 3688 • *Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria.*
- 3689 • *For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians*
3690 *should offer or arrange for patients to receive treatment with medication for opioid use disorder.*
- 3691 • *Clinicians should not dismiss patients from their practice because of opioid use disorder because*
3692 *this can adversely affect patient safety and could represent patient abandonment.*
- 3693 • *Medication treatment of opioid use disorder has been associated with reduced overdose and*
3694 *overall mortality. Identification of opioid use disorder represents an opportunity for a clinician to*
3695 *initiate potentially life-saving interventions, and it is important for the clinician to collaborate*
3696 *with the patient regarding their safety to increase the likelihood of successful treatment.*
- 3697 • *For pregnant people with opioid use disorder, medication therapy with buprenorphine or*
3698 *methadone has been associated with improved maternal outcomes and should be offered.*
- 3699 • *Clinicians unable to provide treatment themselves should arrange for patients with opioid use*
3700 *disorder to receive care from a substance use disorder treatment specialist, such as an office-*
3701 *based buprenorphine or naltrexone treatment provider, or from an opioid treatment program*
3702 *certified by SAMHSA to provide methadone or buprenorphine for patients with opioid use*
3703 *disorder.*
- 3704 • *All clinicians, and particularly clinicians prescribing opioids in communities without sufficient*
3705 *treatment capacity for opioid use disorder, should obtain a waiver to prescribe buprenorphine.*
- 3706 • *Clinicians prescribing opioids should identify treatment resources for opioid use disorder in the*
3707 *community and should work together to ensure sufficient treatment capacity for opioid use*
3708 *disorder at the practice level.*

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- *Although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and opioid use disorder require ongoing pain management that maximizes benefits relative to risks.*

3712 *Supporting Rationale*

3713 Opioid use disorder (previously classified as opioid abuse or opioid dependence in the

3714 *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV] [American Psychiatric

3715 Association, 2000]) is defined in the DSM-5 as a “problematic pattern of opioid use leading to clinically

3716 significant impairment or distress.” (American Psychiatric Association, 2013). Treatment with opioids for

3717 pain is associated with increased risk for opioid use disorder, particularly if opioids are prescribed for

3718 more than 90 days (Edlund et al., 2014). A systematic review found the rate of opioid “addiction” among

3719 chronic pain patients averaged between 8% and 12% in studies published between 2000 and 2013

3720 (Vowles et al., 2015). More recently, studies have found prevalence estimates of 23.9% and 26.5% for

3721 any prescription opioid use disorder and 5.2% and 9.0% for moderate to severe opioid use disorder

3722 (using DSM-5 diagnostic criteria) among adults receiving long-term opioid therapy for pain, with slightly

3723 lower prevalence (21.5% for any and 4.2% for moderate to severe opioid use disorder) in clinics with

3724 more consistent use of risk reduction practices (Boscarino et al., 2020) (Von Korff et al., 2017).

3725 Opioid use disorder is manifested by at least 2 out of 11 defined criteria occurring within a year

3726 (American Psychiatric Association, 2013):

- 3727 (1) Taking opioids in larger amounts or over a longer period of time than intended
- 3728 (2) Having a persistent desire or unsuccessful attempts to reduce or control opioid use
- 3729 (3) Spending excess time obtaining, using or recovering from opioids
- 3730 (4) Craving for opioids
- 3731 (5) Continuing opioid use causing inability to fulfill work, home, or school responsibilities
- 3732 (6) Continuing opioid use despite having persistent social or interpersonal problems
- 3733 (7) Lack of involvement in social, occupational or recreational activities

- 3734 (8) Using opioids in physically hazardous situations
- 3735 (9) Continuing opioid use in spite of awareness of persistent physical or psychological problems
- 3736 (10) Tolerance, as defined by either of the following:
- 3737 a. A need for markedly increased amounts of opioids to achieve intoxication or desired
- 3738 effect, or
- 3739 b. Markedly diminished effect with continued use of the same amount of an opioid.
- 3740 (11) Withdrawal, as manifested by either of the following:
- 3741 a. The characteristic opioid withdrawal syndrome, or
- 3742 b. Opioids (or a closely related) substance is taken to relieve or avoid withdrawal
- 3743 symptoms.

3744 Note: Criteria 10 and 11 are not considered to be met for those taking opioids solely under

3745 appropriate medical supervision (American Psychiatric Association, 2013).

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3747 Severity is specified as mild (2-3 criteria), moderate (4-5 criteria) or severe (≥ 6 criteria)

3748 (American Psychiatric Association, 2013).

3749 FDA-approved medications indicated for the treatment of opioid use disorder and/or the

3750 prevention of relapse include buprenorphine, methadone, and naltrexone. The clinical evidence reviews

3751 found evidence on the effectiveness of interventions (e.g., medications, behavioral treatments) for

3752 opioid use disorder related to prescription opioids to be limited (Chou et al., April 2020). However,

3753 moderate quality evidence shows buprenorphine (a partial agonist opioid) and methadone (a full

3754 agonist opioid) to be effective in preventing relapse among patients with opioid use disorder involving

3755 heroin (Fullerton et al., 2014; Mattick, Breen, Kimber, & Davoli, 2009, 2014), though the presence of

3756 pain among patients in these studies is generally not described. In addition, a small number of studies

3757 have evaluated buprenorphine for patients with prescription opioid dependence (based on DSM-IV

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3758 (American Psychiatric Association, 2000) criteria) and found it effective in preventing relapse (Fiellin et
3759 al., 2014; Weiss et al., 2011). One study found that among people with opioid use disorder, prior
3760 prescription opioid use predicts stabilization on buprenorphine (Varisco, Shen, & Thornton, 2020).
3761 Another trial that performed buprenorphine induction and then randomized patients to buprenorphine
3762 taper versus maintenance was terminated early without reporting of planned outcomes because all
3763 patients randomized to the taper arm switched to maintenance or experienced a relapse; five of six
3764 patients in the maintenance arm completed the trial (Blondell et al., 2010). In another trial identified by
3765 the clinical evidence reviews, there was no difference between buprenorphine/naloxone and
3766 methadone in likelihood of retention in the study, pain, function, or self-reported side effects (Neumann
3767 et al., 2013). Buprenorphine and methadone treatment of opioid use disorder have been associated
3768 with reduced overdose mortality (Krawczyk et al., 2020) and reduced overall mortality (Pearce et al.,
3769 2020). Naltrexone (an opioid antagonist) can also be used for opioid use disorder, particularly for highly
3770 motivated persons (Krupitsky et al., 2011; Minozzi et al., 2011). Naltrexone blocks the effects of opioids
3771 if they are used. Naltrexone has not been evaluated in people with concomitant pain and opioid use
3772 disorder, and opioid medications for pain cannot be used in patients receiving naltrexone. Naltrexone
3773 requires adherence to daily oral therapy or monthly, long-acting injections. The effectiveness of oral
3774 naltrexone can be limited by poor medication adherence (Minozzi et al., 2011); oral naltrexone should
3775 not be used except under very limited circumstances (American Society of Addiction Medicine, 2020),
3776 e.g., for patients who would be able to comply with observed dosing to enhance adherence (American
3777 Psychiatric Association, 2013; American Society of Addiction Medicine, 2020). Naltrexone must also be
3778 started following full withdrawal from opioids, which is a challenge for some patients, but for patients
3779 who have already completed or are able to complete withdrawal, naltrexone has been found to have
3780 comparable effectiveness as buprenorphine in prevention of relapse (J. D. Lee et al., 2018).

3781 Some studies suggest that using behavioral therapies in combination with medications for
3782 opioid use disorder can reduce opioid misuse and increase retention during treatment (Amato, Minozzi,
3783 Davoli, & Vecchi, 2011; Connock et al., 2007). At the same time, a study of treatment for prescription
3784 opioid dependence (based on DSM-IV (American Psychiatric Association, 2000) criteria) found opioid
3785 agonist treatment with buprenorphine and standard medical management (including basic counseling
3786 recommending abstinence and self-help group participation) as effective as buprenorphine combined
3787 with more intensive opioid dependence counseling (ODC: addiction, recovery, and relapse prevention
3788 education with self-help and lifestyle change recommendations, interactive exercises, and take-home
3789 assignments delivered by trained substance use treatment or mental health professionals in 45-60
3790 minute sessions based on drug counseling manuals with demonstrated efficacy); neither standard
3791 medical management nor ODC alone, without buprenorphine, was effective in preventing relapse
3792 (Weiss et al., 2011). Current recommendations for treatment of opioid use disorder include that
3793 patients' psychosocial needs be assessed, and patients offered or referred to psychosocial treatment in
3794 collaboration with qualified behavioral healthcare providers based on individual patient needs, but that
3795 a patient's decision to decline psychosocial treatment or the absence of available psychosocial
3796 treatment should not preclude or delay medications for opioid use disorder (American Society of
3797 Addiction Medicine, 2020). Additional recommendations have been published on goals, components of,
3798 and types of effective psychosocial treatment to use in conjunction with pharmacological treatment of
3799 opioid use disorder (American Society of Addiction Medicine, 2020).

3800 Experts agreed with the strength of the language in the recommendation statement, specifically
3801 with the word "should" and with recommendation category A, and some noted they thought the
3802 evidence type should be 1. Several experts thought opioid agonist/opioid partial agonist and opioid
3803 antagonist treatment should not be framed as equal options for opioid use disorder, noting that opioid

3804 agonist and opioid partial agonist treatment have stronger evidence for better outcomes, does not
3805 require abstinence, have less challenges with inductions, and are much more widely utilized.

3806 If clinicians suspect opioid use disorder based on patient concerns or behaviors or on findings in
3807 prescription drug monitoring program data (see Recommendation 9) or from toxicology testing (see
3808 Recommendation 10), they should discuss their concern with their patient and provide an opportunity
3809 for the patient to disclose related concerns or problems. Clinicians should assess for the presence of
3810 opioid use disorder using DSM-5 criteria (American Psychiatric Association, 2013). Opioid use disorder
3811 can co-exist with other substance use disorders, and patients who are actively using substances
3812 during opioid use disorder treatment might require greater support, potentially including involvement
3813 of an addiction specialist (American Society of Addiction Medicine, 2020). Clinicians should ask about
3814 use of alcohol and other substances (see Recommendation 8). Alternatively, clinicians can arrange for a
3815 substance use disorder treatment specialist to assess for the presence of opioid and other substance use
3816 disorders.

3817 For patients meeting criteria for opioid use disorder, particularly if moderate or severe,
3818 clinicians should offer or arrange for patients to receive treatment with medication for opioid use
3819 disorder. Patients with opioid use disorder may benefit from counseling and referrals to mutual help
3820 groups such as Narcotics Anonymous (Substance Abuse and Mental Health Services Administration,
3821 2021c). Clinicians should also offer naloxone and training on proper use for overdose reversal to
3822 patients with opioid use disorder and to their household members/significant others (American Society
3823 of Addiction Medicine, 2020) (see Recommendation 8). Clinicians should not dismiss patients from their
3824 practice because of opioid use disorder because this can adversely affect patient safety and could
3825 represent patient abandonment. Identification of opioid use disorder represents an opportunity for a
3826 clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate
3827 with the patient regarding their safety to increase the likelihood of successful treatment. Detoxification

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3828 on its own, without medications for opioid use disorder, is not recommended for opioid use
3829 disorder due to increased risks of relapse, overdose, and overdose death (American Society of Addiction
3830 Medicine, 2020).

3831 For pregnant people with opioid use disorder, medication therapy with buprenorphine or
3832 methadone has been associated with improved maternal outcomes and should be offered (see
3833 Recommendation 8 (Substance Abuse and Mental Health Services Administration, 2018a)).
3834 Transmucosal buprenorphine (without naloxone) has been recommended during pregnancy to avoid
3835 potential prenatal exposure to naloxone, especially if injected, and evidence on the safety of naloxone in
3836 pregnant people remains limited (American Society of Addiction Medicine, 2020; The American College
3837 of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction
3838 Medicine, 2017). However, combination buprenorphine/naloxone products are frequently used, and
3839 experts have noted that combination products are likely to be safe and effective for pregnant individuals
3840 when taken as prescribed (American Society of Addiction Medicine, 2020; The American College of
3841 Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addiction
3842 Medicine, 2017). The American College of Obstetricians and Gynecologists also recommends that if a
3843 woman is stable on naltrexone prior to pregnancy, the decision regarding whether to continue
3844 naltrexone treatment during pregnancy should involve a careful discussion between the provider and
3845 the patient, weighing the limited safety data on naltrexone with the potential risk of relapse with
3846 discontinuation of treatment (The American College of Obstetricians and Gynecologists Committee on
3847 Obstetric Practice & American Society of Addiction Medicine, 2017). The American Academy of
3848 Pediatrics recommends that for infants of mothers receiving buprenorphine or methadone for opioid
3849 use disorder who have not had relapse for ≥ 90 days, breastfeeding should be supported if there are no
3850 other contraindications (e.g., HIV infection) while for infants of women with active substance use or with
3851 relapses within the last 30 days, breastfeeding should be discouraged (Patrick et al., 2020).

3852 To expand access to buprenorphine, in April 2021, the *Practice Guidelines for the Administration*
3853 *of Buprenorphine for Treating Opioid Use Disorder* (U.S. Department of Health and Human Services,
3854 2021) exempted eligible physicians, physician assistants, nurse practitioners, clinical nurse specialists,
3855 certified registered nurse anesthetists, and certified nurse midwives from previous Controlled
3856 Substances Act certification requirements related to training, counseling and other ancillary services
3857 (i.e., psychosocial services). To prescribe buprenorphine for opioid use disorder for up to 30 patients in
3858 an office-based setting, clinicians can now forgo or choose to undertake training but must still receive a
3859 waiver from SAMHSA. Information about qualifications and the process to obtain a waiver are available
3860 from SAMHSA (Substance Abuse and Mental Health Services Administration, 2021b).

3861 Additional recommendations have been published previously on induction, use, and monitoring
3862 of buprenorphine treatment for opioid use disorder (American Society of Addiction Medicine, 2020;
3863 Substance Abuse and Mental Health Services Administration, 2021c). Buprenorphine for treatment of
3864 opioid use disorder is usually combined with naloxone in a sublingual or buccal film or tablet (e.g.,
3865 Suboxone), to reduce the potential for misuse of buprenorphine when injected. Naloxone is not
3866 absorbed orally, but if buprenorphine/naloxone is manipulated and injected, naloxone can trigger opioid
3867 withdrawal (Indivior, 2017). Long-acting injectable formulations of [buprenorphine](#) became available in
3868 2018 (U.S. Food and Drug Administration, 2020b). As a partial agonist, buprenorphine should generally
3869 not be initiated until there are objective signs of withdrawal, in order to avoid precipitating withdrawal.
3870 As an alternative for patients not yet in opioid withdrawal, some authors have described a low-dose
3871 induction approach (sometimes referred to as “microdosing”) (Randhawa, Brar, & Nolan, 2020; Robbins,
3872 Englander, & Gregg, 2021) to avoid precipitated withdrawal when initiating buprenorphine, although
3873 there is limited evidence to date regarding this approach. For standard (not low-dose) buprenorphine
3874 induction, once objective signs of withdrawal are observed, buprenorphine should be initiated, usually
3875 at a dose of 2 to 4 mg (American Society of Addiction Medicine, 2020) and titrated upwards under

3876 supervision at approximately 2-hour intervals as needed to control withdrawal symptoms in 2 or 4 mg
3877 increments, up to 8 mg buprenorphine total over the first 24 hours (Indivior, 2017). On the second day,
3878 the patient can be given a single dose consisting of the total of the doses received the first day. If there
3879 are residual withdrawal symptoms, the dose may be increased in 4 mg increments, up to a maximum of
3880 16 mg total in the 2nd 24 hours (Indivior, 2017). Protocols for initiating buprenorphine by patients at
3881 home following an initial encounter with a healthcare provider to establish the diagnosis of OUD and
3882 discuss medication therapy options are in use by more experienced clinicians (Joshua D. Lee, Vocci, &
3883 Fiellin, 2014). Most patients are maintained on 8 mg to 16 mg per day (Soeffing, Martin, Fingerhood,
3884 Jasinski, & Rastegar, 2009), with a range of 4 to 24 mg per day (Indivior, 2017); (American Society of
3885 Addiction Medicine, 2020) there is some evidence that suggests that 16 mg per day or more might be
3886 more effective than lower dosages (American Society of Addiction Medicine, 2020).

3887 Importantly, opioid dosage thresholds for caution in the treatment of pain are not applicable to
3888 opioid agonist treatment of opioid use disorder (Houry, 2018) as recommended dosages of methadone
3889 and buprenorphine for opioid use disorder (American Society of Addiction Medicine, 2020) differ from
3890 those for pain management. There is no recommended duration limit for treatment of opioid use
3891 disorder with buprenorphine or methadone, and discontinuation is associated with risks for relapse and
3892 opioid overdose (American Society of Addiction Medicine, 2020). If discontinued, buprenorphine should
3893 be tapered very gradually (over several months) (American Society of Addiction Medicine, 2020).

3894 Compared to buprenorphine, which can be prescribed by waived clinicians in any setting or
3895 dispensed from a SAMHSA-certified opioid treatment program (OTP), ongoing methadone treatment for
3896 opioid use disorder can only be provided through an OTP. As short-term exceptions, any clinician can
3897 administer (but not prescribe) up to one day's supply of methadone or buprenorphine to treat acute
3898 opioid withdrawal per day for up to 3 days, while working to refer the patient to opioid use disorder
3899 treatment, and patients already receiving opioid use disorder treatment may continue to directly

3900 receive methadone or buprenorphine treatment in an emergency department or in a hospital during
3901 inpatient hospitalization (U.S. Department of Justice Drug Enforcement Administration).

3902 Naltrexone does not require a waiver and can be prescribed in any setting. Additional
3903 recommendations have been published previously on naltrexone treatment for opioid use disorder
3904 (American Society of Addiction Medicine, 2020). A minimum of 7 to 10 days free of opioids is
3905 recommended prior to the first naltrexone dose to avoid precipitation of severe opioid withdrawal
3906 (Alkermes, 2020). Extended-release injectable naltrexone is generally administered every 4 weeks by
3907 deep intramuscular (IM) injection in the gluteal muscle at 380 mg per injection (American Society of
3908 Addiction Medicine, 2020), alternating buttocks for each subsequent injection (Alkermes, 2020). Some
3909 patients, including those who metabolize naltrexone more rapidly, might benefit from dosing as
3910 frequently as every 3 weeks (American Society of Addiction Medicine, 2020). There is no recommended
3911 duration limit for treatment of opioid use disorder with naltrexone. If discontinued, naltrexone can be
3912 stopped abruptly without withdrawal symptoms (American Society of Addiction Medicine, 2020).
3913 Clinicians should warn patients who discontinue naltrexone of the risk of potentially fatal opioid
3914 overdose if opioid use is resumed (American Society of Addiction Medicine, 2020), due to the loss of
3915 tolerance to previous opioid dosage.

3916 Clinicians are strongly encouraged to provide medication treatment for their patients with
3917 opioid use disorder. Clinicians unable to provide treatment themselves should arrange for patients with
3918 opioid use disorder to receive care from a substance use disorder treatment specialist, such as an office-
3919 based buprenorphine or naltrexone treatment clinician, or from an opioid treatment program certified
3920 by SAMHSA to provide methadone or buprenorphine for patients with opioid use disorder. Resources to
3921 help with arranging for treatment include SAMHSA's buprenorphine physician locator
3922 ([https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-](https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator)
3923 [practitioner-locator](https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator)) and SAMHSA's Opioid Treatment Program Directory

3924 (<https://dpt2.samhsa.gov/treatment/directory.aspx>). Clinicians should assist patients in finding qualified
3925 treatment specialists and should arrange for patients to follow up with these specialists, as well as
3926 arranging for ongoing coordination of care. Treatment need in a community is often not met by capacity
3927 to provide buprenorphine or methadone therapy (Jones, Campopiano, Baldwin, & McCance-Katz, 2015).
3928 Clinicians prescribing opioids in communities without sufficient treatment capacity for opioid use
3929 disorder should obtain a waiver to prescribe buprenorphine. SAMHSA's Providers Clinical Support
3930 System (<https://pcssnow.org/>) offers training and technical assistance as well as mentors to assist
3931 clinicians in assessment for and the treatment of substance use disorders and specifically of opioid use
3932 disorder, and on the interface of pain and opioid misuse. Clinicians prescribing opioids should identify
3933 treatment resources for substance use disorders including opioid use disorders in the community and
3934 should work together to ensure sufficient treatment capacity at the practice level.

3935

3936 **Management of opioid misuse that does not meet criteria for opioid use disorder**

3937 For patients with opioid misuse that does not meet criteria for opioid use disorder (e.g., taking
3938 opioids in larger amounts than intended without meeting other criteria for opioid use disorder),
3939 clinicians should reassess the patient's pain, ensure that therapies for pain management have been
3940 optimized (see Recommendation 2), discuss with patients, and carefully weigh benefits and risks of
3941 continuing opioids at the current dosage (see Recommendation 5). For patients who choose to but are
3942 unable to taper, clinicians may reassess for opioid use disorder and offer buprenorphine treatment or
3943 refer for buprenorphine or methadone treatment if criteria for opioid use disorder are met. Even
3944 without a diagnosis of opioid use disorder, transitioning to buprenorphine for pain can also be
3945 considered given reduced overdose risk with buprenorphine compared with risk associated with full
3946 agonist opioids (see Recommendation 5).

3947

3948 **Pain management for patients with opioid use disorder**

3949 Although identification of an opioid use disorder can alter the expected benefits and risks of
3950 opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain
3951 management that maximizes benefits relative to risks. Clinicians should use nonpharmacologic and
3952 nonopioid pharmacologic pain treatments as appropriate (American Society of Addiction Medicine,
3953 2020) (see Recommendations 1 and 2) to provide optimal pain management. For patients with pain who
3954 have an active opioid use disorder but are not in treatment, clinicians should consider buprenorphine or
3955 methadone treatment for opioid use disorder, which can also help with concurrent management of pain
3956 (American Society of Addiction Medicine, 2020). For patients who are treated with buprenorphine for
3957 opioid use disorder and experience acute pain, clinicians can consider temporarily increasing the
3958 buprenorphine dosing frequency (e.g., to twice a day (American Society of Addiction Medicine, 2020)) to
3959 help manage pain, given the duration of effects of buprenorphine is shorter for pain than for
3960 suppression of withdrawal (Alford et al., 2006). For severe acute pain (e.g., trauma and/or unplanned
3961 major surgery), clinicians can consider additional as-needed doses of buprenorphine for patients
3962 receiving buprenorphine for opioid use disorder and short-term use of higher-potency nonopioid
3963 analgesics (e.g., NSAIDs) for patients receiving naltrexone for opioid use disorder; patients receiving
3964 methadone for opioid use disorder who require additional opioids as treatment for pain management
3965 should be carefully monitored, and when feasible should optimally be treated by a clinician experienced
3966 in the treatment of pain in consultation with their opioid treatment program. (American Society of
3967 Addiction Medicine, 2020). The ASAM National Practice Guideline for the Treatment of Opioid Use
3968 Disorder (2020 Focused Update) provides additional recommendations (see Part 9) (American Society of
3969 Addiction Medicine, 2020) for the management of patients receiving medications for opioid use disorder
3970 who have planned surgeries for which nonopioid therapies are not anticipated to provide sufficient pain
3971 relief.

3972

Conclusions and future directions

3973 CDC indicated the intent to evaluate and reassess the 2016 CDC guideline as new evidence
3974 became available and to determine when the closure of research gaps would prompt an update. To
3975 achieve these aims, CDC funded the AHRQ to conduct systematic reviews of the scientific evidence in
3976 the following five areas: noninvasive nonpharmacological treatments for chronic pain; nonopioid
3977 pharmacologic treatments for chronic pain; opioid treatments for chronic pain; treatments for acute
3978 pain; and acute treatments for episodic migraine (Chou et al., April 2020; Chou et al., December 2020;
3979 Halker Singh et al., December 2020; McDonagh et al., April 2020; Skelly et al., April 2020). Based upon
3980 these reviews, an update to the CDC 2016 Guideline was warranted.

3981 The evidence reviews that informed this clinical practice guideline affirmed the appropriateness
3982 of the recommendations included in the 2016 CDC guideline for using opioids to treat chronic pain. The
3983 reviews also allowed CDC to expand the focus to include acute and subacute pain more explicitly. This
3984 clinical practice guideline also includes a new topline recommendation for patients with chronic pain
3985 who are already on higher opioid dosages. Specifically, the clinical practice guideline outlines how
3986 clinicians and patients should work together in assessing the benefits and risks of continued opioid use
3987 and if or when to taper opioids to a lower dosage or discontinue opioids all together in accordance with
3988 the HHS Tapering Guide (Dowell, Compton, & Giroir, 2019; U.S. Department of Health and Human
3989 Services, 2019a).

3990 There are 4 key domains covered by the updated clinical practice guideline for prescribing of
3991 opioid pain medication for patients 18 and older for pain outside of sickle cell disease-related pain
3992 management, cancer pain treatment, palliative care, and end-of-life care. These include whether to
3993 initiate opioids for pain treatment; opioid selection and dosage; opioid duration and follow-up; and
3994 assessing the risks and addressing harms of opioid use. In addition, five guiding principles were

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3995 identified to inform implementation across recommendations that focus on the appropriate treatment
3996 of pain, flexibility to meet the care needs and clinical circumstances of each patient through a
3997 multimodal and multidisciplinary approach to pain management, avoiding misapplying the clinical
3998 practice guideline beyond its intended use, and vigilantly attending to health inequities and ensuring
3999 access to an appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and
4000 pharmacologic pain treatment for all persons.

4001 A central tenet of this clinical practice guideline is that acute, subacute, and chronic pain needs
4002 to be appropriately and effectively treated independent of whether opioids are part of a treatment
4003 regimen. This is done by selecting one or more nonpharmacologic or pharmacologic treatment
4004 modalities that maximize patient safety and optimize outcomes in pain, function, and quality of life. A
4005 multimodal and multidisciplinary approach to pain management attending to the biological,
4006 psychological, and social characteristics of each person is critical (U.S. Department of Health and Human
4007 Services, 2019b). The care provided needs to be individualized and person-centered (U.S. Department of
4008 Health and Human Services, 2019b). Clinicians and patients should work together to identify treatment
4009 goals and tailor an approach that considers both the benefits and risks of available options (U.S.
4010 Department of Health and Human Services, 2019b). Progress should be monitored over time and
4011 treatment protocols adjusted accordingly. Health systems and payers should work to ensure multimodal
4012 treatment options are available, accessible, and reimbursed for patients. Public and private payers
4013 should support a broader array of nonpharmacologic interventions such as exercise, multidisciplinary
4014 rehabilitation, mind-body interventions, cognitive behavioral therapy, and some complementary and
4015 integrative medicine therapies like acupuncture and spinal manipulation, given their increasingly known
4016 effectiveness (Skelly et al., April 2020). Reimbursement is often cited as a principle barrier to why these
4017 nonpharmacologic treatments are not more widely used (Skelly et al., April 2020).

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4018 An integral part of providing access to and delivery of high-quality healthcare, including pain
4019 treatment, is understanding how the social determinants of health influence the healthcare provided
4020 and the differential outcomes observed (Agency for Healthcare Research and Quality, 2020). Social,
4021 economic, educational, and neighborhood-level factors may create and exacerbate health inequities
4022 experienced across the life course (Agency for Healthcare Research and Quality, 2020). These social
4023 determinants of health are borne out of historical and contemporary injustices that advantage some and
4024 disadvantage others in society leading to the systemic marginalization or oppression of some groups
4025 such as people from some racial and ethnic groups, people living in rural areas, persons experiencing
4026 homelessness, people with disabilities, people with substance use disorders, justice-involved
4027 populations, and non-US born persons among others (Centers for Disease Control and Prevention,
4028 2020a).

4029 Outcomes are also influenced by the healthcare context (Agency for Healthcare Research and
4030 Quality, 2020). Differential access to and coverage for high-quality, culturally and linguistically
4031 appropriate, health-literate care may influence attitudes towards healthcare and use of available
4032 services (Agency for Healthcare Research and Quality, 2020). Prejudice, bias, discrimination, and
4033 stereotyping by individual clinicians, practices, health systems, and payers serve to reinforce these
4034 health disparities (Institute of Medicine, 2003). Clinicians, practices, health systems, and payers should
4035 attend to health inequities to ensure access to appropriate, diversified, effective nonpharmacologic and
4036 pharmacologic pain management options that are person-centered, affordable, accessible, and well-
4037 coordinated as well as protect patient safety and guard against unnecessary risks. This begins with
4038 raising awareness and acknowledging the presence of these inequities, strengthening patient-clinician
4039 communication, leveraging community health workers, implementing multidisciplinary care teams,
4040 tracking and monitoring performance measures, and integrating quality improvement initiatives that
4041 support and invest in guideline concordant care for all persons (Institute of Medicine, 2003).

4042 Special attention should be given to avoid misapplying this updated clinical practice guideline
4043 beyond its intended use or implementing policies purportedly derived from it that result in unintended
4044 consequences for patients (Dowell, Haegerich, et al., 2019). This includes being inflexible on opioid dose
4045 and duration, discontinuing or dismissing patients from a practice, rapidly and non-collaboratively
4046 tapering patients who may be stable on a higher dose, and applying recommendations to populations
4047 that are not a focus of the clinical practice guideline such as patients with cancer, sickle cell disease, or
4048 during end-of-life care (Dowell, Haegerich, et al., 2019).

4049 The uptake and widespread utilization of the 2016 CDC guideline hinged on its successful
4050 dissemination. CDC invested in activities to support its translation and integration into clinical practice.
4051 Most notably, CDC produced a checklist and mobile app for clinicians to more readily follow guideline
4052 recommendations; fact sheets, posters, and public service announcements (PSAs) making key
4053 components of the guideline more accessible and understandable to clinicians and patients; and a 14-
4054 module interactive, web-based training featuring self-paced learning, case-based content, knowledge
4055 checks, and integrated resources for clinicians (Centers for Disease Control and Prevention, 2021b). CDC
4056 also developed and implemented a quality improvement (QI) and care coordination initiative to improve
4057 and encourage careful and selective use of long-term opioid therapy in the context of managing chronic
4058 pain (Centers for Disease Control and Prevention, 2018b). This included 16 clinical quality improvement
4059 measures (Shoemaker-Hunt et al., 2021) as well as practice-level strategies to help health systems
4060 organize and improve the management and coordination of opioid therapy using an interdisciplinary
4061 team approach, establishing practice policies and standards, and leveraging EHR data to develop
4062 registries and track QI measures (Centers for Disease Control and Prevention, 2018b). CDC invested in
4063 health IT and other clinical decision support tools by collaborating with the Office of the National
4064 Coordinator for Health Information Technology (ONC) to create and integrate guideline-concordant care
4065 into clinical workflow (Centers for Disease Control and Prevention, 2021b). In addition, CDC compiled

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4066 complementary clinical recommendations from professional organizations for clinicians to reference for
4067 several common conditions associated with acute pain – including acute migraines, ankle sprains, dental
4068 pain, acute low back pain, and post-surgical pain (Centers for Disease Control and Prevention, 2020b).
4069 All information in the web-based resource is based on external research (Mikosz et al., 2020) and
4070 existing published guidelines from professional organizations. The compilation can further assist
4071 clinicians and patients, working together, in making safer and more effective pain management
4072 decisions.

4073 This updated clinical practice guideline provides overarching voluntary recommendations on the
4074 use of opioids to treat pain. To assist in the uptake and understanding of this clinical practice guideline,
4075 CDC will update existing resources to align with the new clinical practice guideline and develop new
4076 tools and resources for clinicians, health systems, patients, and others on the use of opioid and non-
4077 opioid pain treatments — including resources supporting health equity. Finally, CDC will work with
4078 public and private payers with the aim of improving coverage for nonpharmacologic treatments,
4079 increasing access to non-opioid pain medication, supporting patient counseling and coordination of
4080 care, increasing access to evidence-based treatments of opioid use disorder, and enhancing availability
4081 of multidisciplinary and multimodal care. Robust coverage and access (e.g., limited utilization
4082 management and cost sharing for evidence-based treatments) and decision support (e.g., adjustment of
4083 EHR prescribing defaults) can be used to nudge clinicians and patients toward evidence-based
4084 treatments as default treatments for pain (Ancker et al., 2021; Montoy, Coralic, Herring, Clattenburg, &
4085 Raven, 2020).

4086 This clinical practice guideline updates and expands upon the recommendations in the 2016 CDC
4087 Guideline and is based on the best available evidence as interpreted and informed by expert opinion and
4088 attending to the values and preferences of patients, caregivers, and clinicians. While clinical scientific
4089 evidence continues to advance and supports the recommendations in the clinical practice guideline, the

4090 strength of the evidence is sometimes weak and research gaps remain (Chou et al., April 2020; Chou et
4091 al., December 2020; Halker Singh et al., December 2020; McDonagh et al., April 2020; National
4092 Academies of Sciences Engineering and Medicine, Health and Medicine Division, Board on Health
4093 Sciences Policy, & Committee on Pain Management and Regulatory Strategies to Address Prescription
4094 Opioid Abuse, 2017; Skelly et al., April 2020; U.S. Department of Health and Human Services, 2019b).
4095

The areas in need of additional research include but are not limited to

- Efficacy of screening tools to assess risk for opioid misuse and developing an opioid use disorder.
- Effective management of patients on high dose opioids; the application of multidisciplinary and multimodal models of pain treatment, and service delivery modalities including telehealth.
- Long-term comparative effectiveness of pharmacologic and nonpharmacologic therapies.
- Effects of therapies on non-pain outcomes.
- Treatment outcomes for specific pain conditions and how benefits and risks of therapies vary among sub-populations.
- Adapting evidence-based opioid prescribing and pain management strategies to meet the needs of special populations including people from some racial and ethnic groups, older adults, and rural communities.
- Improved diagnostics in measuring pain.

- Enhanced clinician and patient education about pain and the use of opioids; the assessment of practice-level strategies in health systems to improve management and care coordination for patients on opioid therapy.
- Transition from acute to chronic pain and how to apply effective diagnostic, preventive, and therapeutic approaches.
- Effect of stigma as a barrier for treating pain and getting treatment for an opioid use disorder.

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4098 In closing, the principle aim of this clinical practice guideline is to ensure people have access to
4099 safe, accessible, and effective pain management that improves their function and quality of life while
4100 illuminating and reducing risks associated with prescription opioids, and ultimately reducing the
4101 consequences of prescription opioid misuse and overdose. Lessons learned from the development of
4102 the 2016 CDC guideline informed the process used to generate this update. CDC will evaluate the clinical
4103 practice guideline to identify the impact of the recommendations on clinician and patient outcomes as
4104 well as the intended and unintended consequences. Communication between clinicians and patients
4105 about the risks and benefits of opioids should be central to treatment decisions for patients in pain. This
4106 clinical practice guideline can help inform those decisions and assist clinicians in meeting the unique
4107 needs of each person. CDC will revisit this clinical practice guideline when remaining evidence gaps have
4108 sufficiently been addressed and another update is warranted.

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4159 **References**

4160 **Note: Formatting is currently based on automatic EndNote settings and will be adjusted (e.g.,**
4161 **changing to numbered in-text citations).**

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5664

5665

TABLE. Morphine milligram equivalent (MME) doses for commonly prescribed opioids for pain management

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	5
Methadone	4.7
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol [†]	0.4
Tramadol [‡]	0.2

5666 **Source:** Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7; Nielsen S, Degenhardt L,
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5668

5669 *Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. For example, tablets
5670 containing hydrocodone 5 mg and acetaminophen 325 mg taken four times a day would contain a total of 20 mg of
5671 hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10mg and taken
5672 twice a day would contain a total of 20mg of oxycodone daily, equivalent to 30 MME daily.
5673 The following cautions should be noted: 1) All doses are in mg/day except for fentanyl, which is mcg/hr. 2)
5674 Equianalgesic dose conversions are only estimates and cannot account for individual variability in genetics and
5675 pharmacokinetics. 3) Do not use the calculated dose in MMEs to determine the doses to use when converting one
5676 opioid to another; when converting opioids, the new opioid is typically dosed at a substantially lower dose than
5677 the calculated MME dose to avoid overdose due to incomplete cross-tolerance and individual variability in opioid
5678 pharmacokinetics. 4) Use particular caution with methadone dose conversions because methadone has a long and
5679 variable half-life, and peak respiratory depressant effect occurs later and lasts longer than peak analgesic effect. 5)
5680 Use particular caution with transdermal fentanyl since it is dosed in mcg/hr instead of mg/day, and its absorption
5681 is affected by heat and other factors. 6) Buprenorphine products approved for the treatment of pain are not
5682 included in the table due to their partial mu receptor agonist activity and resultant ceiling effects compared to full
5683 mu receptor agonists. 7) These conversion factors should not be applied to dosage decisions related to the
5684 management of opioid use disorder.
5685

5686 [†]Tapentadol is a mu receptor agonist and norepinephrine reuptake inhibitor. MMEs are based on degree of mu-
5687 receptor agonist activity, but it is unknown if tapentadol is associated with overdose in the same dose-dependent
5688 manner as observed with medications that are solely mu receptor agonists.
5689

5690 [‡]Tramadol is a mu receptor agonist and norepinephrine and serotonin reuptake inhibitor. MMEs are based on
5691 degree of mu-receptor agonist activity, but it is unknown if tramadol is associated with overdose in the same dose-
5692 dependent manner as observed with medications that are solely mu receptor agonists.
5693

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5704 *At the time of drafting the updated guideline, peer reviewers had not yet been identified.*

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5729 **Disclosure of relationship**

5730 The Opioid Workgroup members disclose that they have no financial conflicts of interest.

5731 Members disclose the following activities related to the content of this clinical practice guideline: Anne

5732 L. Burns discloses that she is employed by the American Pharmacists Association, a nonprofit 501c6

5733 organization, where she is involved in advancing pharmacists' patient care services, including pain

5734 management services, and she serves on the Board of Directors for the Pharmacy Quality Alliance, a

5735 nonprofit organization that develops quality measures, including opioid-related measures. Beth Darnall

5736 discloses that she consulted with AppliedVR, a virtual reality for chronic and acute pain company. Neeraj

5737 Gandotra discloses that he provided expert testimony before the Senate Judiciary Committee on

5738 12/17/2019 on behalf of SAMHSA regarding the opioid epidemic. Christine Goertz discloses that she

5739 served as a consultant to the American Chiropractic Association until September 30, 2019, and that she

5740 has NIH foundation funding to conduct research on non-pharmacologic approaches to pain

5741 management. Jennifer Waljee discloses that she received research support funding from the Centers for

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5744 effect of opioid use prior to and after surgery on postoperative outcomes.

5745 The Board of Scientific Counselors of the National Center for Injury Prevention and Control

5746 (BSC/NCIPC) members disclose that they have no financial conflicts of interest. Three BSC/NCIPC

5747 members, Chinazo O. Cunningham, Frank Floyd, and Elizabeth Habermann, served on the Opioid

5748 Workgroup. Roger Chou is a co-author of the clinical practice guideline and AHRQ- sponsored systematic

5749 clinical evidence reviews. Dr. Chou disclosed that he receives funding to conduct reviews on opioids and

5750 recused himself from the July 16, 2021, BSC/NCIPC meeting and discussion of the OWG report on the

5751 draft clinical practice guideline. Wilson Compton discloses that he has long-term stock holdings in

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5752 General Electric, Pfizer, and 3M Companies; however, his investments in these companies did not
5753 exceed the U.S. Department of Health and Human Services threshold for significant financial interest.

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5754 **BOX 1. CDC recommendations for prescribing opioids for outpatients with pain outside of sickle cell**
5755 **disease-related pain management, cancer pain treatment, palliative care, and end-of-life care**

5756 **Determining whether or not to initiate opioids for pain**
5757

- 5758 1. Nonopioid therapies are effective for many common types of acute pain. Clinicians should only
5759 consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient.
5760 (recommendation category: B, evidence type: 3).
5761
- 5762 2. Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider
5763 initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks
5764 to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss
5765 with patients the known risks and realistic benefits of opioid therapy, should work with patients to
5766 establish treatment goals for pain and function, and should consider how opioid therapy will be
5767 discontinued if benefits do not outweigh risks (recommendation category: A, evidence type: 2).
5768

5769 **Opioid selection and dosage**
5770

- 5771 3. When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe
5772 immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids
5773 (recommendation category: A, evidence type: 4).
5774
- 5775 4. When opioids are started for opioid-naïve patients with acute, subacute, or chronic pain, clinicians
5776 should prescribe the lowest dosage to achieve expected effects. If opioids are continued for
5777 subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage,
5778 should carefully evaluate individual benefits and risks when considering increasing dosage, and
5779 should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to
5780 risks to patients (recommendation category: A, evidence type: 3).
5781
- 5782 5. For patients already receiving higher opioid dosages, clinicians should carefully weigh benefits and
5783 risks and exercise care when reducing or continuing opioid dosage. If risks outweigh benefits of
5784 continued opioid therapy, clinicians should optimize other therapies and work closely with patients
5785 to gradually taper to lower dosages or, if warranted based on the individual clinical circumstances of
5786 the patient, to appropriately taper and discontinue opioids. Unless there are indications of a life-
5787 threatening issue, such as warning signs of impending overdose, e.g., confusion, sedation, or slurred
5788 speech, opioid therapy should not be discontinued abruptly, and clinicians should not abruptly or
5789 rapidly reduce opioid dosages from higher dosages (recommendation category: B, evidence type: 4).
5790

5791 **Opioid duration and follow-up**
5792

- 5793 6. When opioids are needed for acute pain, clinicians should prescribe no greater quantity than
5794 needed for the expected duration of pain severe enough to require opioids (recommendation
5795 category: A, evidence type: 4).
5796
- 5797 7. Clinicians should evaluate benefits and risks with patients within 1 to 4 weeks of starting opioid
5798 therapy for subacute or chronic pain or of dose escalation. Clinicians should evaluate benefits and

5799 risks of continued therapy with patients every 3 months or more frequently (recommendation
5800 category: B, evidence type: 4).

5801

5802 **Assessing risk and addressing harms of opioid use**

5803

5804 8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk
5805 for opioid-related harms and discuss with patients. Clinicians should work with patients to
5806 incorporate into the management plan strategies to mitigate risk, including offering naloxone when
5807 factors that increase risk for opioid overdose are present (recommendation category: A, evidence
5808 type: 4).

5809

5810 9. When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during
5811 opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance
5812 prescriptions using state prescription drug monitoring program (PDMP) data to determine whether
5813 the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose
5814 (recommendation category: B, evidence type: 4).

5815

5816 10. When prescribing opioids for subacute or chronic pain, clinicians should consider toxicology
5817 testing to assess for prescribed medications as well as other prescribed and non-prescribed
5818 controlled substances (recommendation category: B, evidence type: 4).

5819

5820 11. Clinicians should use extreme caution when prescribing opioid pain medication and
5821 benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent
5822 prescribing of opioids and other central nervous system depressants (recommendation
5823 category: B, evidence type: 3).

5824

5825 12. Clinicians should offer or arrange treatment with medication for patients with opioid use disorder
5826 (recommendation category: A, evidence type: 1).

5827

5828

5829 * See full clinical practice guideline for recommendation categories and evidence ratings.

5830 These five guiding principles should broadly inform implementation across recommendations:

5831 1. Acute, subacute, and chronic pain need to be appropriately and effectively treated independent
5832 of whether opioids are part of a treatment regimen.

5833 2. Recommendations are voluntary and are intended to support, not supplant, individualized,
5834 person-centered care. Flexibility to meet the care needs and the clinical circumstances of a
5835 specific patient are paramount.

5836 3. A multimodal and multidisciplinary approach to pain management attending to the physical
5837 health, behavioral health, long-term services and supports, and expected health outcomes and
5838 well-being needs of each person is critical.

5839 4. Special attention should be given to avoid misapplying this updated clinical practice guideline
5840 beyond its intended use or implementing policies purportedly derived from it that might lead to
5841 unintended consequences for patients.

5842 5. Clinicians, practices, health systems, and payers should vigilantly attend to health inequities,
5843 provide culturally and linguistically appropriate communication, and ensure access to an

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5844 appropriate, affordable, diversified, coordinated, and effective nonpharmacologic and
5845 pharmacologic pain management regimen for all persons.

5846

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5849 **BOX 2. Interpretation of recommendation categories and evidence type**

5850

5851 **Recommendation categories**

5852 Based on evidence type, balance between desirable and undesirable effects, values and preferences,
5853 and resource allocation (cost).

5854 **Category A recommendation:** Applies to all persons; most patients should receive the recommended
5855 course of action.

5856 **Category B recommendation:** Individual decision making needed; different choices will be appropriate
5857 for different patients. Clinicians help patients arrive at a decision consistent with patient values and
5858 preferences and specific clinical situations.

5859

5860 **Evidence type**

5861 Based on study design as well as a function of limitations in study design or implementation,
5862 imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of
5863 treatment effects, dose-response gradient, and constellation of plausible biases that could change
5864 effects.

5865 **Type 1 evidence:** Randomized clinical trials or overwhelming evidence from observational studies.

5866 **Type 2 evidence:** Randomized clinical trials with important limitations, or exceptionally strong
5867 evidence from observational studies.

5868 **Type 3 evidence:** Observational studies or randomized clinical trials with notable limitations.

5869 **Type 4 evidence:** Clinical experience and observations, observational studies with important
5870 limitations, or randomized clinical trials with several major limitations.

5871