CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will prescribe opioids safely and rationally

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Prescribing opioids in primary care: Safely starting, monitoring, and stopping

ABSTRACT

Chronic noncancer pain is common and often managed in the outpatient setting with chronic opioid therapy, even though the efficacy of this approach is uncertain and adverse effects are common. Some patients report meaningful benefit from opioids, but prescription drug abuse has reached epidemic proportions, and many suffer harm from opioid misuse, abuse, and diversion. Primary care providers and their care teams often struggle to balance these risks and benefits with little outside support. The authors review common challenges when starting, monitoring, and discontinuing opioids, and offer strategies for risk-reduction and patient communication.

KEY POINTS

Predicting which patients will benefit and which ones will be harmed is difficult. We generally recommend a conservative approach to starting opioid treatment.

Providers must periodically reassess the safety and efficacy of opioid therapy to be sure it is still indicated.

Monitoring should be transparent and consistent. By framing monitoring in terms of safety and employing it universally, providers can minimize miscommunication and accidental stigmatization.

When opioids are no longer safe or effective, they should be stopped. The decision can be difficult for the patient and the provider.

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Chronic pain affects an estimated 100 million Americans, at a cost of $635 billion each year in medical expenses, lost wages, and reduced productivity.[1] It is often managed in primary care settings with opioids by clinicians who have little or no formal training in pain management.[2,3] Some primary care providers may seek assistance from board-certified pain specialists, but with only four such experts for every 100,000 patients with chronic pain, primary care providers are typically on their own.[4]

Although opioids may help in some chronic pain syndromes, they also carry the risk of serious harm, including unintentional overdose and death. In 2009, unintentional drug overdoses, most commonly with opioids, surpassed motor vehicle accidents as the leading cause of accidental death in the United States.[5] Additionally, nonmedical use of prescription drugs is the third most common category of drug abuse, after marijuana and alcohol.[6]

Unfortunately, clinicians cannot accurately predict future medication misuse.[7] And while the potential harms of opioids are many, the long-term benefits are questionable.[8,9]

For these reasons, providers need to understand the indications for and potential benefits of opioids, as well as the potential harms and how to monitor their safe use. Also important to know is how and when to discontinue opioids while preserving the therapeutic relationship.

This paper offers practical strategies to primary care providers and their care teams on how to safely initiate, monitor, and discontinue chronic opioid therapy.

STARTING OPIOID THERAPY FOR CHRONIC PAIN

Guidelines recommend considering starting patients on opioid therapy when the benefits are likely to outweigh the risks, when pain is moderate to severe, and when other multimodal treatment strategies have not achieved functional goals.[10] Unfortunately, few studies have examined or demonstrated long-term benefit, and those that did examine this outcome reported reduction of pain severity but did not assess functional improvement.[9] Meanwhile, data are increasingly clear that long-term use increases the risk of harm, both acute (eg, overdose) and chronic (eg, osteoporosis), especially with high doses.

Tools have been developed to predict the risk of misuse,[11–13] but few have been validated in primary care, where most opioids are prescribed. This limitation aside, consensus guidelines state that untreated substance use disorders, poorly controlled psychiatric disease, and erratic treatment adherence are contraindications to opioid therapy, at least until these other issues are treated.[10]

Faced with the benefit-harm conundrum, we recommend a generally conservative approach to opioid initiation. With long-term functional benefit questionable and toxicity relatively common, we are increasingly avoiding chronic opioid therapy in younger patients with chronic pain.

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Empathize and partner with your patient

Chronic pain care can be fraught with frustration and mutual distrust between patient and provider.[14] Empathy and a collaborative stance help signal to the patient that the provider has the patient's best interest in mind,[15] whether initiating or deciding not to initiate opioids.

Optimize nonopioid therapy

In light of the risks associated with chronic opioid therapy, the clinician is urged to review and optimize nonopioid therapy before starting a patient on opioid treatment, and to maintain this approach if opioid therapy is started. Whenever possible, nonopioid treatment should include disease-modifying therapy and nondrug modalities such as physical therapy.

Judicious use of adequately dosed analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs may be sufficient to achieve analgesic goals if not contraindicated, and in some patients the addition of a topical analgesic (eg, diclofenac gel, lidocaine patches), a tricyclic or serotonin-norepinephrine reuptake inhibitor antidepressant, an anticonvulsant (eg, gabapentin), or a combination of the above can effectively address underlying pain-generating mechanisms.[16] As with opioids, the risks and benefits of nonopioid pharmacotherapy should be reviewed both at initiation and periodically thereafter.

Frame the opioid treatment plan as a 'therapeutic trial'

Starting an opioid should be framed as a "therapeutic trial." These drugs should be continued only if safe and effective, at the lowest effective dose, and as one component of a multimodal pain treatment plan. Concurrent use of nonpharmacologic therapies (eg, physical therapy, structured exercise, yoga, relaxation training, biofeedback, cognitive behavioral therapy) and rational pharmacotherapy while promoting patient self-care is the standard of pain management called for by the Institute of Medicine.[1]

Set functional goals

We recommend clearly defining functional goals with each patient before starting therapy. These goals should be written into the treatment plan as a way for patient and provider to evaluate the effectiveness of chronic opioid therapy. A useful mnemonic to help identify such goals is SMART, an acronym for **s**pecific, **m**easurable, **a**ction-oriented, **r**ealistic, and **t**ime-bound. Specific goals will depend on pain severity, but examples could include being able to do grocery shopping without assistance, to play on the floor with grandchildren, or to engage in healthy exercise habits such as 20 minutes of moderately brisk walking 3 days per week.

Obtain informed consent, and document it thoroughly

Providers must communicate risks, potential benefits, and safe medication-taking practices, including how to safely store and dispose of unused opioids, and document this conversation clearly in the medical record. From a

TABLE 1

Initiating chronic opioid therapy: recommended steps

Step	Details
Express empathy, partner with your patient	Empathy signals that the provider has the patient's best interests in mind Expressing empathy does not commit the provider to prescribing opioid therapy
Optimize nonopioid therapy	Utilize nonpharmacologic treatments, adequately dose nonopioid analgesics, and use disease-modifying therapy when appropriate, typically in combination
Frame the treatment plan as a therapeutic trial	Opioids should only be continued: If safe and effective At the lowest effective dose, and As one component of a multimodal pain treatment plan
Target functional goals	Treatment goals should be based on functional improvement, not pain reduction A useful mnemonic to help identify such goals is SMART: **s**pecific, **m**easurable, **a**ction-oriented, **r**ealistic, and **t**ime-bound
Obtain informed consent, document thoroughly	Communicate risks, potential benefits, and safe medication-taking practices, including safe storage and disposal of unused opioids Document this conversation clearly in the medical record
Employ safe, rational pharmacotherapy	Consider opioid potency, onset of action, and half-life when choosing a medication Comorbid conditions and concurrent prescriptions should affect choice of formulation, dosage, and rapidity of titration Methadone accumulates in adipose tissue and needs to be up-titrated slowly

medicolegal perspective, if it wasn't documented, it did not happen.[17]

Informed consent can be further advanced with the use of a controlled substance agreement that outlines the treatment plan as well as potential risks, benefits, and practice policies in a structured way. Most states now either recommend or mandate the use of such agreements.[18]

Controlled substance agreements give providers a greater sense of mastery and comfort when prescribing opioids,[19] but they have important limitations. In particular, there is a lack of consensus on what the agreement should say and relatively weak evidence that these agreements are efficacious. Additionally, a poorly written agreement can be stigmatizing and can erode trust.[20] However, we believe that when the agreement is written in an appropriate framework of safety at an appropriate level of health literacy and with a focus on shared decision-making, it can be very helpful and should be used.

Employ safe, rational pharmacotherapy

Considerations when choosing an opioid include its potency, onset of action, and half-life. Comorbid conditions (eg, advanced age,[21] sleep-disordered breathing[22]) and concurrent medications (eg, benzodiazepines, anticonvulsants, muscle relaxants) also affect decisions about the formulation, starting dose, rapidity of titration, and ceiling dose. Risk of harm increases in patients with such comorbid factors, and it is prudent to start with lower doses of

shorter-acting medications until patients can demonstrate safe use. Risk of unintentional overdose is higher with higher prescribed doses.[23] Pharmacologically there is no analgesic dose ceiling, but we urge caution, particularly in opioid-naive patients.

A patient's response to any particular opioid is idiosyncratic and variable. There are more than 100 known polymorphisms in the human opioid mu-receptor gene, and thus differences in receptor affinity and activation as well as in metabolism make it difficult to predict which opioid will work best for a particular patient.[24] However, a less potent opioid receptor agonist with less addictive potential, such as tramadol or codeine, should generally be tried first before escalating to a riskier, more potent opioid such as hydrocodone, oxycodone, or morphine. This "analgesic ladder," a concept introduced by the World Health Organization in 1986 to provide a framework for managing cancer pain, has been adapted to a variety of chronic pain syndromes.[25]

Methadone deserves special mention. A strongly lipophilic molecule with a long and variable half-life, it accumulates in fat,[26] and long after the analgesic effect has worn off, methadone will still be present. Repeated dosing or rapid dose escalation in an attempt to achieve adequate analgesia may result in inadvertent overdose. Additionally, methadone can prolong the QT interval, and periodic electrocardiographic monitoring is recommended.[27] For these reasons, we recommend avoiding the use of methadone in most cases unless the provider has significant experience, expertise, or support in the safe use of this medication.

From a medicolegal perspective, if it wasn't documented, it didn't happen

Table 1 summarizes these recommendations.

MONITORING AND SAFETY

Providers must periodically reassess the safety and efficacy of chronic opioid therapy to be sure that it is still indicated.[10] Since we cannot accurately predict which patients will suffer adverse reactions or demonstrate aberrant behaviors,[7] it is important to be transparent and consistent with monitoring practices for all patients on chronic opioid therapy.[17] By framing monitoring in terms of safety and employing it universally, providers can minimize miscommunication and accidental stigmatization.

Prescription monitoring programs

In 2002, Congress appropriated funding to the US Department of Justice to support prescription monitoring programs nationally.[28] At the time of this writing, Missouri is the only state without an approved monitoring program.[29]

Although the design and function of the programs vary from state to state, they require pharmacies to collect and report data on controlled substances for individual patients and prescribers. These data are sometimes shared across state lines, and the programs enhance the capacity of regulatory and law enforcement agencies to analyze controlled substance use.

Prescribers can (and are sometimes required to) register for access in their state and use this resource to assess the opioid refill history of their patients. This powerful tool improves detection of "doctor-shopping" and other common scams.[30]

Additionally, recognizing that the risk of death from overdose increases as the total daily dose of opioids increases,[23] some states provide data on their composite report expressing the morphine equivalent daily dose or daily morphine milligram equivalents of the opioids prescribed. This information is valuable to the busy clinician; at a glance the prescriber can quickly discern the total daily opioid dose and use that information to assess risk and manage change. Furthermore, some states restrict further dose escalation when the morphine equivalent daily dose exceeds a predetermined amount (typically 100 to 120 morphine milligram equivalents).

Tamper-resistant prescribing

To minimize the risk of prescription tampering, simple techniques such as writing out the number of tablets dispensed can help, and use of tamper-resistant prescription paper has been required for Medicaid recipients since 2008.[31]

When possible, we recommend products with abuse-deterrent properties. Although the science of abuse deterrence is relatively new and few products are labeled as such, a number of opioids are formulated to resist deformation, vaporization, dissolving, or other physical tampering. Additionally, some abuse-deterrent opioid formulations contain nalox-

TABLE 2

Characteristics of substances on screening immunoassays

Substance	How it appears on standard urine toxicology screening	How long it remains detectable after use[a]	Sources of false positivity[b]
Amphetamine	Amphetamine	2–3 days (occasional use) 1 week (very heavy use)	Bupropion Ephedrine Vicks Vapor Inhaler[c]
Barbiturate	Barbiturate	Short-acting: 1–3 days Long acting: 2–3 weeks	Ibuprofen Naproxen
Benzodiazepine	Benzodiazepine	2–3 days	Efavirenz Sertraline
Buprenorphine	Usually requires separate assay	1–3 days	Amisulpride (rare) Tramadol
Cannabis	Cannabinoid	3–4 days (occasional use) 7–10 days (regular use) 4+ weeks (heavy use)	Efavirenz
Cocaine	Cocaine	2–3 days (occasional use) 3 weeks (heavy use)	Topical anesthetics containing cocaine
Methadone	Methadone	2–3 days	Quetiapine
Codeine **Hydrocodone** **Hydromorphone** **Morphine**	Opiate	2–3 days	Heroin Levofloxacin Other opiates Ofloxacin Oxycodone
Oxycodone	Oxycodone	2–3 days	Naloxone
Phencyclidine (PCP)	Phencyclidine (PCP)	2–3 days (occasional use) 1 week (very heavy use)	Tramadol Venlafaxine

[a] Duration of detection varies with dose taken, frequency of use, and individual metabolism.
[b] Gas chromatography-mass spectrometry is needed to distinguish; false-positives vary by specific assay used.
[c] Vicks Vapor inhaler contains levomethamphetamine, which is the L-entaniomer of methamphetamine. Although the L isomer has no addictive potential or central nervous system effects, repeated use may result in a positive urine drug screen.

Compiled from information in references 1–3, 37–49.

one, which is released only when the drug is deformed in some way, thereby decreasing the user's response to an abused substance or resulting in opioid withdrawal.[32]

Urine drug testing

Although complex and nuanced, guidelines recommend urine drug testing to confirm the presence or absence of prescribed and illicit substances in the body.[10] There is no consensus on when or how often to test, but it should be done randomly and without forewarning to foil efforts to defeat testing such as provision of synthetic, adulterated, or substituted urine.

Providers underuse urine drug testing.[33] We recommend that it be done at the start of opioid therapy, sporadically thereafter, when

therapy is changed, and whenever the provider is concerned about possible aberrant drug use.

Understanding opioid metabolism, cross-reactivity, and the types of tests available will help avoid misinterpretation of results.[34] For example, a positive "opiate" result in most screening immunoassay tests does not reflect oxycodone use, since tests for synthetic opioids often need to be ordered separately; the commonly used Cedia opiate assay cross-reacts with oxycodone at a concentration of 10,000 ng/mL only 3.1% of the time.[35] Immunoassay screening tests are widely available, sensitive, inexpensive, and fast, but they are qualitative, have limited specificity, and are subject to false-positive and false-negative results.[36] **Table 2** outlines some common characteristics of substances on screening immunoassays, including reported causes of false-positive results.[37–39]

Confirmatory testing using gas chromatography or mass spectroscopy is more expensive and slower to process, but is highly sensitive and specific, quantitative, and useful when screening results are difficult to interpret.

Knowing how and when to order the right urine drug test and knowing how to interpret the results are skills prescribers should master.

Try a less addictive agent such as tramadol or codeine before escalating to hydrocodone, oxycodone, or morphine

DISCONTINUING OPIOIDS

When opioids are no longer safe or effective, they should be stopped. The decision can be difficult for both the patient and provider, and a certain degree of equanimity is needed to approach it rationally.

Strong indications for discontinuation

Respiratory depression, cognitive impairment, falls, and motor vehicle accidents mean harm is already apparent. At a minimum, dose reduction is warranted and discontinuation should be strongly considered. Similarly, overdose (intentional or accidental) and active suicidal ideation contraindicate ongoing opioid prescribing unless the ongoing risk can be decisively mitigated.

Certain aberrant behaviors such as prescription forgery or theft, threats of violence to obtain analgesics, and diversion (transfer of the drug to another person for nonmedical use) also warrant immediate discontinuation. Continuing to prescribe an opioid while knowing diversion is taking place may be a violation of federal or state law or both.[40]

Another reason to stop is failure to achieve the expected benefit from chronic opioid therapy (ie, agreed-upon functional goals) despite appropriate dose adjustment. In these cases, ongoing risk by definition outweighs observed benefit.

Relative indications for discontinuation

Opioid therapy has many potential adverse effects. Depending on the severity and duration of the symptom and its response to either dose reduction or adjunctive management, opioids may need to be discontinued.

For example, pruritus, constipation, urinary retention, nausea, sedation, and sexual dysfunction may all be reasons to stop chronic opioid therapy. Similarly, chronic opioid therapy may paradoxically worsen pain in some susceptible patients, a complication known as opioid-induced hyperalgesia; in these cases, tapering off opioids should be considered as well.[41] Aberrant behaviors should prompt reconsideration of chronic opioid therapy; these include hazardous alcohol consumption, use of illicit drugs, pill hoarding, and use of opioids in a manner different than intended by the prescriber.

Another relative indication for discontinuation is receipt of controlled substances from other providers. A well-written controlled substance agreement and adequate counseling may help mitigate this risk; poor communication between providers, lack of integration of electronic medical record systems, urgent or emergency room care, and poor health literacy may all lead to redundant prescribing in some circumstances. While unintentional use of controlled substances from different providers is no less dangerous than intentional misuse, the specifics of each case need to be considered before opioids are reflexively discontinued.

How to discontinue opioids

In most cases, opioids should be tapered to reduce the risk and severity of withdrawal symptoms. Decreasing the dose by 10% of the original dose per week is usually well tolerated with minimal adverse effects.[42] Tapering can be done much faster, and numerous rapid detoxification protocols are available. In general, a patient needs 20% of the previous day's dose to prevent withdrawal symptoms.[43]

TABLE 3

Discontinuing opioids: Do's and don'ts

Do	Don't
Frame the discussion in terms of safety and efficacy, consistent with the treatment agreement	Debate your decision with the patient
Present your reasoning in a considered manner	Use accusatory or blaming language
Focus on the treatment and the patient's response to it	Focus on the patient's character or use labels (eg, "drug addict")
Emphasize your commitment to the patient's well-being and details of the new treatment plan (ie, nonabandonment)	Abandon the patient
Respond to emotional distress with empathy	Allow empathy to change your decision on discontinuation

Withdrawal symptoms are rarely life-threatening but can be very uncomfortable. Some providers add clonidine to attenuate associated autonomic symptoms such as hypertension, nausea, cramps, diaphoresis, and tachycardia if they occur. Other adjunctive medications include nonsteroidal anti-inflammatory drugs for body aches, antiemetics for nausea and vomiting, bismuth subsalicylate for diarrhea, and trazodone for insomnia.

It is unlawful for primary care physicians to use another opioid to treat symptoms of withdrawal in the outpatient setting unless it is issued through a federally certified narcotic treatment program or prescribed by a qualified clinician registered with the US Drug Enforcement Administration to prescribe buprenorphine-naloxone.[44]

In some circumstances, it may be appropriate to abruptly discontinue opioids without a taper, such as when diversion is evident. However, a decision to discontinue opioids due to misuse should not equate to an automatic decision to terminate a patient from the practice. Instead, providers should use this opportunity to offer empathy and referral to drug treatment counseling and rehabilitation. A decision to discontinue opioids because they are no longer safe or effective does not mean that the patient's pain is not real—it is "real" for them, even if caused by the pain of addiction—or that shared decision-making is no longer possible or appropriate.

Handling difficult conversations when discontinuing opioids

The conversation between patient and provider when discontinuing opioids can be difficult. Misaligned expectations of both parties, patient fear of uncontrolled pain, and provider concern about causing suffering are frequent contributing factors. Patients abusing prescription drugs may also have a stronger relationship with their medication than with their provider and may use manipulative strategies including overt hostility and threats to obtain a prescription. Providers need to maintain their composure to de-escalate these potentially upsetting confrontations.

Providers underuse urine drug testing

Table 3 outlines some specific suggestions that may be helpful, including the following:

- Frame the discussion in terms of safety—opioids are being discontinued because the benefit no longer outweighs the risk
- Don't debate your decision with the patient, but present your reasoning in a considered manner
- Focus on the appropriateness of the treatment and not on the patient's character
- Avoid the use of labels (eg, "drug addict")
- Emphasize your commitment to the patient's well-being and an alternative treatment plan (ie, nonabandonment)
- Respond to emotional distress with empathy, but do not let that change your decision to discontinue opioids.

Finally, we strongly encourage providers to insist on being treated respectfully. When safety cannot be ensured, providers should remove themselves from the room until the patient can calm down or the provider can ask for assistance from colleagues.

Maintaining empathy by understanding grief

Discontinuing opioids may trigger in a patient an emotional response similar to grief. When considered in this framework, it may empower an otherwise frustrated provider to remain empathetic even in the midst of a difficult confrontation. Paralleling Kübler-Ross's five stages of grief,[45] we propose a similar model we call the "five stages of opioid loss"; this model has been successfully used in the residency continuity clinic at the University of Connecticut as a training aid.

Hopelessness and helplessness. During the first stage of the discussion the patient struggles with how to move forward. This conversation is frequently characterized by tearfulness and explanations to account for aberrant behavior or willingness to continue to suffer side effects. Active listening, empathy, and a focus on the factors that led to discontinuation of opioids while still validating pain are important.

Demanding and indignant. During the second stage, patients frequently push the limits of "no." Accusations of abandonment and lack of empathy may accompany this stage and can be quite upsetting for the unprepared provider. A novice clinician can use role-play as a tool to better prepare for this type of encounter. Patients should be allowed to express their frustration but ultimatums and threats of violence should not be tolerated. Reassuring patients that their pain will be addressed using nonopioid therapy can be helpful, and a simple offer of continued care can help to preserve the therapeutic relationship.

Some patients go through five stages of opioid loss when stopping these drugs

Bargaining, the third stage of this model, is characterized by attempts to negotiate continued prescribing. While it can be frustrating, this push and pull is the beginning of real conversation and identification of a treatment plan for the future.

Resignation. The fourth stage begins when the patient has resigned himself or herself to your decision, but may not have accepted the available treatment options. At this point the patient may return for care or seek out a new provider. Empathy is again the element most crucial to success; this stage carries an opportunity to develop mutual respect.

Acceptance. The patients who choose to continue care with you have progressed to the final phase. They begin to look toward the future, having chosen the better of the two paths: partnering with a caring provider to develop a shared therapeutic plan.

A CONSISTENT AND TRANSPARENT APPROACH

Opioids can be useful for selected patients when they are carefully prescribed, but the prescriber must fully consider the risks and benefits specific to each patient and mitigate risk whenever possible.

Collaborating with patients to use opioids rationally is easier when it is part of a multimodal pain management plan and is initiated with clear functional goals and parameters for discontinuation. Presenting risks and benefits in a framework of safety and educating patients will help to reduce the stigma that may otherwise accompany safety monitoring using tools such as controlled substance agreements and urine toxicology testing.

Despite these efforts, patients may become psychologically dependent on opioids and discontinuation may prove difficult. However, a consistent and transparent approach to prescribing with special efforts to empathize with suffering patients may empower providers to navigate this process effectively.

REFERENCES

1. **Institute of Medicine of the National Academies**. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. http://iom.nationalacademies.org/reports/2011/relieving-pain-in-america-a-blueprint-for-transforming-prevention-care-education-research.aspx. Accessed February 8, 2016.
2. **McCarberg BH, Nicholson BD, Todd KH, Palmer T, Penles L**. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. Am J Ther 2008; 15:312–320.
3. **Roehr B**. US needs new strategy to help 116 million patients in chronic pain. BMJ 2011; 343:d4206.
4. **Breuer B, Pappagallo M, Tai JY, Portenoy RK**. US board-certified pain physician practices: uniformity and census data of their locations. J Pain 2007; 8:244–250.
5. **Paulozzi L, Dellinger A, Degutis L**. Lessons from the past. Inj Prev 2012; 18:70.
6. **US Department of Health and Human Services; Substance Abuse and Mental Health Services Administration**. Results from the 2013 national survey on drug use and health: Summary of national findings, NSDUH series H-48, HHS publication no. (SMA) 14-4863. www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHTML2013/Web/NSDUHresults2013.htm. Accessed February 8, 2016.

7. **Bronstein K, Passik S, Munitz L, Leider H**. Can clinicians accurately predict which patients are misusing their medications? J Pain 2011; 12(suppl):P3.
8. **Von Korff M, Kolodny A, Deyo RA, Chou R**. Long-term opioid therapy reconsidered. Ann Intern Med 2011; 155:325–328.
9. **Chou R, Turner JA, Devine EB, et al**. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015; 162:276–286.
10. **Chou R, Fanciullo GJ, Fine PG, et al; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel**. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009; 10:113–130.
11. **Butler SF, Budman SH, Fernandez K, Jamison RN**. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain 2004; 112:65–75.
12. **Compton PA, Wu SM, Schieffer B, Pham Q, Naliboff BD**. Introduction of a self-report version of the prescription drug use questionnaire and relationship to medication agreement noncompliance. J Pain Symptom Manage 2008; 36:383–395.
13. **Webster LR, Webster RM**. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the opioid risk tool. Pain Med 2005; 6:432–442.
14. **Chen JT, Fagan MJ, Diaz JA, Reinert SE**. Is treating chronic pain torture? Internal medicine residents' experience with patients with chronic nonmalignant pain. Teach Learn Med 2007; 19:101–105.
15. **Gallagher RM**. Empathy: a timeless skill for the pain medicine toolbox. Pain Med 2006; 7:213–214.
16. **Woolf CJ; American College of Physicians; American Physiological Society**. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 2004; 140:441–451.
17. **Gourlay DL, Heit HA, Almahrezi A**. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005; 6:107–112.
18. **Medscape**. A guide to state opioid prescribing policies resource center news. www.medscape.com/index/list_5657_1. Accessed February 8, 2016.
19. **Penko J, Mattson J, Miaskowski C, Kushel M**. Do patients know they are on pain medication agreements? Results from a sample of high-risk patients on chronic opioid therapy. Pain Med 2012; 13:1174–1180.
20. **McGee S, Silverman RD**. Treatment agreements, informed consent, and the role of state medical boards in opioid prescribing. Pain Med 2015; 16:25–29.
21. **Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S**. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 2010; 170:1968–1976.
22. **Wang D, Teichtahl H**. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007; 11:35–46.
23. **Bohnert AS, Valenstein M, Bair MJ, et al**. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA 2011; 305:1315–1321.
24. **Smith HS**. Variations in opioid responsiveness. Pain Physician 2008; 11:237–248.
25. **Vargas-Schaffer G**. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician 2010; 56:514-517.
26. **Inturrisi CE**. Clinical pharmacology of opioids for pain. Clin J Pain 2002; 18(suppl 4):S3–S13.
27. **Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC**. QTc interval screening in methadone treatment. Ann Intern Med 2009; 150:387–395.
28. 107th Congress Public Law 77. US Government Printing Office. Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies Appropriations Act, 2002. https://www.gpo.gov/fdsys/pkg/PLAW-107publ77/html/PLAW-107publ77.htm. Accessed February 8, 2016.
29. Missouri Prescription Drug Monitoring Program NOW Coalition. http://mopdmpnow.org/. Accessed February 8, 2016.
30. Prescription Drug Monitoring Program Center of Excellence at Brandeis. www.pdmpexcellence.org/sites/all/pdfs/Briefing%20on%20PDMP%20Effectiveness%203rd%20revision.pdf. Accessed February 8, 2016.
31. Centers for Medicare and Medicaid Services. Tamper Resistant Prescriptions. www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/FraudAbuseforProfs/TRP.html. Accessed February 8, 2016.
32. **Moorman-Li R, Motycka CA, Inge LD, Congdon JM, Hobson S, Pokropski B**. A review of abuse-deterrent opioids for chronic nonmalignant pain. P T 2012; 37:412–418.
33. **Starrels JL, Becker WC, Weiner MG, Li X, Heo M, Turner BJ**. Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. J Gen Intern Med 2011; 26:958–964.
34. **Herring C, Muzyk AJ, Johnston C**. Interferences with urine drug screens. J Pharm Pract 2011; 24:102–108.
35. Thermo Fisher Scientific. Cedia opiate 2K drugs of abuse assays. http://www.thermoscientific.com/en/product/cedia-opiate-2k-drugs-abuse-assays.html. Accessed February 8, 2016.
36. **Markway EC, Baker SN**. A review of the methods, interpretation, and limitations of the urine drug screen. Orthopedics 2011; 34:877–881.
37. **Saitman A, Park HD, Fitzgerald RL**. False-positive interferences of common urine drug screen immunoassays: a review. J Anal Toxicol 2014; 38:387–396.
38. **Standridge JB, Adams SM, Zotos AP**. Urine drug screening: a valuable office procedure. Am Fam Physician 2010; 81:635–640.
39. National Highway Traffic Safety Administration. Drugs and human performance fact sheet. www.nhtsa.gov/staticfiles/nti/pdf/809725-DrugsHumanPerformFS.pdf. Accessed February 8, 2016.
40. US Department of Health and Human Services; Centers for Medicare and Medicaid Services. Partners in Integrity: What is the Prescriber's Role in Preventing the Diversion of Prescription Drugs. www.cms.gov/Medicare-Medicaid-Coordination/Fraud-Prevention/Medicaid-Integrity-Education/Provider-Education-Toolkits/Downloads/prescriber-role-drugdiversion.pdf. Accessed February 8, 2016.
41. **Silverman SM**. Opioid induced hyperalgesia: clinical implications for the pain practitioner. Pain Physician 2009; 12:679–684.
42. US Department of Health and Human Services; Agency for Healthcare Research and Quality (AHRQ); National Guideline Clearinghouse. Interagency guideline on opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid therapy. www.guideline.gov/content.aspx?id=23792. Accessed February 8, 2016.
43. Department of Veterans Affairs/Department of Defense. Tapering and discontinuing opioids factsheet. www.healthquality.va.gov/guidelines/Pain/cot/OpioidTapering-FactSheet23May2013v1.pdf. Accessed February 8, 2016.
44. US Department of Justice Drug Enforcement Administration: Office of Diversion Control. Title 21 Code of Federal Regulations, Part 1306, Section 1306.04. Purpose of issue of prescription. www.deadiversion.usdoj.gov/21cfr/cfr/1306/1306_04.htm. Accessed February 8, 2016.
45. **Kübler-Ross E, Wessler S, Avioli LV**. On death and dying. JAMA 1972; 221:174–179.

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