# Chapter 14
# Safe Opioid Prescribing and Controlled Substance Policies


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## Introduction

The management of chronic pain is a responsibility of primary care physicians and, by extension, the medical residency continuity clinic. Chronic pain is quite prevalent; more than 100 million Americans suffer from chronic pain at an estimated cost of over $600 billion each year in lost wages, reduced productivity, and medical expenses [1]. As a result, evaluating chronic pain is unavoidable, and its management is extremely important to the functionality and well-being of our patients. Unfortunately, the majority of medical residents graduate from medical school without any formal training in pain management [2], and there is a severe shortage of board-certified pain specialists to turn to for help [3]. Consequently, the Clinic Director plays an essential role to make sure that trainees and faculty have the appropriate education, tools, and support needed to treat chronic pain safely and rationally.

Sometimes chronic severe pain will require treatment with opioid therapy, although there are many associated risks, and their efficacy for the management of

Author's Note: Although we focus on opioid prescribing throughout this chapter, many of the identified practice management principles also apply to other controlled substances (such as benzodiazepines, other sedatives, and stimulants).

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L.B. Lu et al. (eds.), *Leading an Academic Medical Practice*,
https://doi.org/10.1007/978-3-319-68267-9_14

chronic non-cancer pain has been called into question [4]. Opioids should not be used as monotherapy and are best prescribed as part of a multimodal approach to managing pain that also includes physical activity (e.g., physical therapy), behavioral therapy (e.g., relaxation training, cognitive behavioral therapy), non-opioid analgesics (e.g., topical agents, acetaminophen, nonsteroidal anti-inflammatory drugs), and other adjunctive medications (e.g., serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptics) depending upon the underlying etiology of the pain syndrome [5]. Opioid prescribing is complex and requires proactive risk management to use safely. However, some patients do functionally benefit from their use, and we strongly urge against the generalized refusal to prescribe opioids as a matter of clinic policy. Instead, we challenge the Clinic Director to create an environment that enables faculty and trainees to prescribe as safely and effectively as possible.

## Learning Objectives

1. Review the role of opioid therapy in the management of chronic pain and the potential risks and benefits of their use in an academic medical practice.
2. Consider how practice variation impacts controlled substance prescribing safety as well as patient and provider satisfaction. Develop standard operational workflows to address this in a busy resident clinic.
3. Effectively utilize risk assessment and reduction tools such as controlled substance agreements, prescription monitoring programs, and urine toxicology testing in an evidence-based manner.
4. Explore best practices when discontinuing controlled substances, and implement communication strategies to minimize conflict while offering support to patients.

## Outline

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## The Role of Chronic Opioid Therapy

Opioid analgesics may be appropriate for the treatment of chronic pain syndromes when pain is severe and negatively affects function and quality of life, and non-opioid analgesics do not sufficiently control symptoms [6]. When prescribed, opioids should be used as part of a comprehensive multimodal pain management plan that also includes nonpharmacologic and non-opioid therapy. Opioids should not be prescribed when contraindications are present (explored later in this chapter) or the risks associated with opioid prescribing cannot be managed safely or outweigh expected benefit. There are no specific "opioid appropriate" pain diagnoses, but there is scant evidence that opioids are helpful for functional pain syndromes such as fibromyalgia, and they are best avoided in that setting [7]. Additionally, there is increasing evidence that opioids are of limited utility in the management of chronic low back pain, and the American College of Physicians recently released a guideline discouraging providers from using opioids for that indication except when other treatment options have failed [8]. Importantly, chronic opioid therapy is sometimes ineffective for the management of chronic pain from any source, and studies on efficacy are frequently of small sample size, short duration, and observational, and most failed to assess for functional improvement [4]. As a result, the introduction of chronic opioid therapy should be considered a "therapeutic trial" that will only be continued if there is evidence of benefit for the individual patient that exceeds any evidence of harm [9]. Realistic expectation and goal setting with an emphasis on functional improvement is critical; providers should explicitly discuss this at the start of the therapy and reassess it frequently. We explore these concepts in more depth elsewhere in this chapter.

## Risks of Opioid Prescribing

The use of chronic opioid therapy (COT) for non-cancer pain syndromes has become common, despite the lack of robust efficacy data. In 2014, over 240 million opioid prescriptions were written in the United States, which is enough supply for every adult American to have their own bottle of pills [10]. Given the prevalence of chronic pain and the widespread use of opioids in recent years, both hospital-based and community-situated resident clinic practices will undoubtedly need to manage patients seeking opioid therapy.

Unfortunately, physicians are notoriously poor at predicting which patients will experience problems with opioid use, including who will misuse or divert their opioid prescriptions [11]. As a result, some risk must be assumed in all patients, and so-called universal precautions to mitigate risk should be implemented; we explore strategies to reduce risk later in the chapter. Without appropriate resident education, clear policies for prescribing opioids, and appropriate utilization of risk-reduction tools (e.g., signed treatment agreements, urine drug tests, and prescription drug monitoring programs), your clinic may become a magnet for drug-seeking patients. Earning a reputation as a "loose" prescribing clinic, even if only due to the habits of a few providers, risks an onslaught of opioid-seeking patients. This will undoubtedly strain clinic resources and become fatiguing. It also risks changing the focus of the practice away from general internal medicine. For these reasons, as well as the urgent importance protecting patients from harm, it is critically important for the Clinic Director to develop and implement rational, controlled substance prescribing policies.

### *Side Effects, Drug Interactions, and Overdose Risk*

There are many known adverse effects from opioid therapy, including numerous side effects; drug interactions; a significant risk for diversion, misuse, and addiction (explored in the next section); as well as the frightening risk of potentially fatal overdoses.

Many of the potential side effects from opioids are common and predictable, and the prescriber should anticipate and manage them proactively whenever possible. For example, opioid-induced constipation is quite common and typically does not improve over time, so it may be prudent to utilize stool softeners at the start of therapy. Bulking agents should typically be avoided because opioid-induced intestinal dysmotility may increase risk for obstruction. When refractory and severe, peripherally acting mu-opioid receptor antagonists can also be used [12]. In contrast, nausea and vomiting is also common but may improve with continued opioid use, so reassurance is sometimes the only treatment required. However, these symptoms can be managed with antiemetics if necessary, and a trial of an alternate opioid may also improve symptoms.

Additional common side effects include itching (due to histamine release triggered by opioid agonism of mu receptors found on mast cells), urinary retention, sedation, and endocrinopathy. Antihistamines may improve mild itching and dose reduction, or trial of a different opioid may help with urinary retention. Sedation should be considered an early sign of overdose, and if present, the prescriber must reduce the dose immediately to lower the risk of respiratory depression. Endocrinopathy may result from reduced secretion of gonadotropin-releasing hormone from the hypothalamus and direct osteoblast inhibition, raising the risk for both hypogonadism and osteoporosis. Prescribers should consider screening for sexual dysfunction while on opioid therapy, and high-risk patients may need screening for osteoporosis [13]. A less well-understood potential side effect is opioid-induced hyperalgesia. When present, neuropathic pain symptoms such as diffuse hyperalgesia and allodynia develop or worsen with ongoing treatment [14]. This syndrome can be difficult to distinguish from inadequate management of the underlying pain syndrome. Unlike undertreatment, discontinuing opioid therapy should lead to resolution of these symptoms.

In addition to side effects, numerous drug-drug and drug-disease interactions also exist and should be considered before prescribing opioids. For example, if a patient has an underlying congenital long QT syndrome or is on medications that prolong the QT interval, opioids such as methadone should be used with extreme caution, if at all [15]. Similarly, tramadol and meperidine both lower the seizure threshold and should be avoided in patients with seizure disorder. Likewise, patients with advanced nephropathy should avoid using codeine and meperidine due to the risk of accumulating high levels of toxic metabolites. A full review of potential drug-drug and drug-disease interactions is beyond the scope of this chapter, but a wise prescriber will always consider these factors when initiating opioid therapy.

Overdose risk deserves special mention; as the prevalence of opioid use has increased over the past 20 years, so have deaths from unintentional overdoses. In fact, in 2009 unintentional overdose deaths exceeded motor vehicle accidents as the leading cause of accidental death in the United States [16]. The US Centers for Disease Control and Prevention (CDC) estimates that 78 people will die each day in America from an unintentional opioid overdose [17]. Furthermore, the risk for opioid overdose increases as the dose escalates; there is a greater than seven times increased risk of overdose death when using daily doses over 100 morphine milligram equivalents (MMEs) as compared with doses less than 20 mg [18]. The risk also increases when patients take benzodiazepines along with opioids, and the US Food and Drug Administration (FDA) recently included a “black box” warning on all opioid prescriptions cautioning against this combination [19]. Not surprisingly, the CDC recommends avoiding co-prescribing opioids and benzodiazepines whenever possible and suggests that the total daily combined opioid dose not exceed 90 MMEs in most circumstances [20].

## *Diversion, Misuse, and Addiction*

The careful provider must understand, screen for, and recognize diversion, misuse, and opioid use disorders when they occur; risk modification strategies are described later in this chapter. Definitions are as follows:

*Diversion*: Patients acquire opioids with the intent to sell, barter, or simply share them.

*Misuse*: Use of opioids in a manner other than that intended by the prescriber. For example, patients may take opioids for pain but not as prescribed (e.g., intermittent use with variable or higher than prescribed dosing) or may use opioids for a different reason than intended (e.g., insomnia, other pain syndromes, or for intoxication).

*Opioid Use Disorder*: Compulsive use of opioids despite adverse consequences. Diagnosis requires 2 out of 11 criteria (see Table 1) within a 12-month period as defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [21].

The incidence of opioid misuse and addiction in patients receiving chronic opioid therapy has been estimated in the scientific literature. A recent systematic review of 38 studies, 26% from primary care settings and 53% from pain clinics, estimated the incidence rates for misuse at 21–29% ([95%CI] 13–38%) and for addiction at 8–12% ([95% CI] 3–17%) [22]. There are very limited data specifically from the resident clinic setting, but presumably the incidence is similar. Thus, misuse and addiction are unfortunately both prevalent and highly impactful. The prudent Clinic Director will carefully consider this risk when developing practice policies regarding controlled substance prescribing.

**Table 1** Opioid use disorder

| Problematic opioid use characterized by two or more of the following criteria within a 12-month period | |
|---|---|
| 1. | Using opioids in larger amounts or for a longer duration than was intended |
| 2. | Continuing desire or unsuccessful struggles to cut down or control opioid use |
| 3. | Spending a lot of time obtaining, using, or recovering from the effects of opioid drugs |
| 4. | Having a strong desire or craving to use opioids |
| 5. | Failing to fulfill important obligations at home, work, or school because of opioid use |
| 6. | Ongoing opioid use despite interpersonal problems worsened by opioid drugs |
| 7. | Giving up or reducing important social, work-related, or leisure activities because of opioid use |
| 8. | Recurrent opioid use in situations when it is physically dangerous |
| 9. | Ongoing opioid use despite knowing that it is causing or worsening a physical or psychological problem |
| 10. | Opioid tolerance |
| 11. | Withdrawal symptoms when opioids are not taken |

Mild, 2–3 criteria; moderate, 4–5 criteria; severe, 6 or more criteria
*Adapted from the American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [21]

### *Prescriber Risk Factors and Errors*

Physicians who overprescribe opioids commonly fall into one of the six "Ds": (1) the physician's knowledge base may be *dated*, (2) the physician may be *duped* by a patient and fall victim to a scam, (3) the prescriber may be *dishonest* and prescribe unsafely for personal gain, (4) the provider may be *disabled* and have developed "loose" prescribing habits because of their own experience as a patient, (5) the provider may be *distracted* by multiple demands on their limited time, and (6) the *defiant* provider may simply refuse to adhere to best practices [23]. The underlying drivers in each case may differ, and intervention should be personalized to the prescriber. Two specific factors frequently seen in an academic medical practice (but also encountered in other settings) deserve further mention:

*Inappropriate patient selection*: The resident may not consider appropriate indications and contraindications to chronic opioid therapy. For example, a resident may prescribe opioids to a patient with a functional pain syndrome not known to be opioid responsive, such as fibromyalgia [7]. Alternatively, the resident may prescribe to a high-risk patient without adequate risk screening or suitable multimodal therapy, functional goal setting, or clear diagnostic indications. Although risk assessment is imprecise and physicians have difficulty accurately making this assessment, there are validated tools available to help estimate risk and guide patient selection and monitoring. For example, the Screener and Opioid Assessment for Patients with Pain (SOAPP®-R) and the shorter and simpler Opioid Risk Tool (ORT) are screening devices often used for this purpose [24, 25]. The ORT assesses variables known to be associated with a higher risk of opioid misuse such as personal and family history of substance use disorders, younger age (16–45), comorbid psychiatric disease, and a history of sexual abuse to gauge individual risk. Depending on the assessed level of risk, the provider may choose to defer the use of opioids completely, increase safety-monitoring practices, or refer the patient to a specialist to assist with comanagement and risk mitigation. A high-risk patient may still achieve benefit from COT, but the prescriber needs to make sure that he/she has the resources and ability to ramp up monitoring as necessary or COT should not be prescribed. These calculators, and many other prescriber resources, are widely available on the internet. A resource for prescribers developed by Boston Medical Center called TOPCARE (Transforming Opioid Prescribing in Primary Care) is an excellent example; it can be accessed at http://mytopcare.org/.

*Inappropriate prescribing*: Due to inexperience and/or inadequate supervision, the resident may select too high a dose or too potent a drug as initial therapy or inappropriately prescribe an extended-release/long-acting opioid to a patient with an acute pain syndrome or insufficient opioid tolerance. The resident may also fail to account for drug-drug or drug-disease interactions, incorrectly convert one opioid to another, fail to use tamper-resistant prescription paper, issue unclear directions, or fail to follow state-specific legislation that limits how opioids may be prescribed (e.g., prescription quantity limits). Clinic preceptors need to be on the lookout for these common errors, and Clinic Directors are advised to anticipate and proactively manage these challenges. Another common prescribing error is failure to treat to a

realistic and functional analgesic goal. Due to issues of tolerance, overdose risk, and adverse effects, treating to a pain-free state is neither safe nor sustainable. Instead, pain treatment goals should be "S.M.A.R.T.," defined as specific, measurable, action-oriented, realistic, and time-sensitive [26]. Additionally, escalation of opioid therapy should be based on a multidimensional assessment of progress toward an identified functional goal and not solely on a unidimensional pain score. For example, a three-item tool called the PEG (pain, enjoyment of life, and general activity) score has been validated for use in primary care settings and can be an excellent way to assess pain and monitor its response to treatment over time [27]. This tool assesses pain severity and functional impact during the prior week on a scale of 0–10 with the total PEG score being the average of those three variables. A successful pain management plan should lead to improving PEG scores, while an unchanged or worsened score suggests that opioid use is ineffective and requires adjustment. In some cases, a pain syndrome does not respond to COT, and in these circumstances, opioids should be tapered and discontinued.

## Uniform Practice Patterns

Even in a modest-size clinic, opioid prescribing practices should be standardized, or marked variation will occur among both the residents and their attendings. Without consistent expectations, patients with pain and/or opioid use disorder may gravitate toward "loose" opioid prescribing physicians, and a few providers may quickly acquire a pain- and addiction-focused patient panel. In contrast, some trainees and their preceptors may uniformly refuse to prescribe opioids even to low-risk patients, leading to a challenging and irrational dichotomy of opioid use. This will only be exacerbated as patients are annually reassigned from a graduating resident to an incoming intern. Cross-coverage becomes confusing, and as patients talk to each other in the waiting room, the practice may be accused of having a double standard.

This type of practice variation is very disruptive. Some fortunate resource-rich practices may have access to pain specialists, but they are generally rare. Nationally, it has been estimated that there are only four board-certified pain specialists for every 100,000 people with chronic pain, and many of those providers limit access to privately insured patients [3]. Additionally, we believe that learning to appropriately assess pain and manage opioid analgesia should be a part of every internal medicine resident's postgraduate medical education.

With increased education, use of risk stratification tools, and consistent policy-setting that applies to all clinic providers and staff (including the residents, attendings, and nursing staff), everyone's comfort with safe opioid prescribing will increase, and patients will benefit from a more rational use of chronic opioid therapy.

### *Suggested Workflows to Decrease Practice Variation*

1. Educate interns early in their training. This should include education regarding commonly encountered clinical challenges such as (a) the established patient with poor pain control who has run out of non-opioid options, (b) the new patient already on high-dose opioids from another provider, (c) the established patient on opioids with poor pain control, and (d) the established patient on opioids with evidence of aberrant drug-taking behavior. Of course, it is equally important that faculty are similarly adept at handling these scenarios, and faculty development may be needed as well. Excellent curricula addressing these circumstances already exist and are frequently available free of charge. For example, the Safe and Competent Opioid Prescribing Education (SCOPE) course developed at Boston University to meet the FDA-mandated and grant-funded Risk Evaluation and Mitigation Strategy program required for extended-release/long-acting opioids has case videos freely accessible on their website at https://www.scopeofpain.com/tools-resources/.
2. Identify an internal expert (often the Clinic Director) who reviews selected cases when (a) discontinuing chronic opioid therapy, (b) restarting previously discontinued COT, (c) difficult cases are referred for administrative evaluation, and (d) patients on COT present to the emergency department with documented overdose. The Clinic Director should also periodically review cases for quality improvement purposes. Of note, this task can be beyond the skill set and resources of some Clinic Directors, so it is important to identify a group of local experts that can assist at your institution. In some cases, this may include an interprofessional team of physicians, nurses, behavioral health specialists, social workers, and administrators, among others.
3. Develop practice policies regarding when and how opioids will be prescribed. For example, some practices adopt a policy that chronic opioid therapy should not be started on the first office visit before a review of outside records, appropriate diagnostic testing, and pretreatment risk stratification is completed. In these cases, pretreatment evaluation may include a risk assessment using the previously described ORT or SOAPP®-R, urine toxicology testing to assess for the presence of unreported drugs, and documentation of clear functional treatment goals and informed consent, among other steps. Other practice workflows to consider may include (a) refill request policies (e.g., not after 4:30 pm on a Friday or no earlier than 5 days before the next refill is due), (b) after hours and weekend opioid prescribing rules, and (c) the practice-wide requirement to use safety monitoring and risk-reduction tools such as controlled substance agreements, urine drug screening tests, etc. These interventions are described in more detail in the sections that follow.

## Controlled Substance Agreements

Using a controlled substances agreement (CSA) can be helpful, is required in some states, and is reported to give providers greater mastery and comfort with opioid prescribing [28]. Many will call these pain "contracts," but the preferred term is "treatment agreement" or something similar since the word "contract" is misleading, not legally enforceable, and may be unethical and erode trust [29]. These agreements have four commonly identified justifications: (1) to improve adherence, (2) to provide informed consent, (3) to meet legal risk-management requirements, and (4) to improve practice efficiency and outline office prescribing policies [30]. A recent systematic review showed that the use of treatment agreements along with urine drug testing modestly reduced opioid misuse [31], although other sources have called their efficacy into question [32]. Another benefit of using a CSA is that it allows the resident to review clinic policies and opioid prescribing expectations at the onset of opioid use.

Employing shared decision-making is essential so that the patient and the provider have a full appreciation of the relative risks and benefits of opioid therapy and can make an informed decision together. The best agreements will outline expectations for both the patient and provider regarding how to use and prescribe the medication safely, as well as reasons why opioids may need to be discontinued. Importantly, for shared decision-making to occur, the agreement must be written at a literacy level that is accessible to most patients [33]; many CSAs do not consider this. Thankfully, programs to assess readability statistics exist (including Microsoft Word), and a tool such as an estimated Flesch-Kincaid grade level can be used in addition to spelling and grammar checks when drafting a CSA or adopting one for use.

Importantly, CSAs should strive to present information in terms of safety and should avoid using stigmatizing language whenever possible. One ongoing point of controversy is the use of the term "narcotic" in CSAs. Clinically, the word narcotic is imprecise and may refer to substances other than opioids; the US Controlled Substances Act incorrectly lists cocaine as a narcotic [34]. Furthermore, the term is typically used to refer to drug control efforts or substance use disorders such as with police "Narcotic Task Force" divisions or "narcotic treatment programs." Not surprisingly, there is a great deal of stigma associated with the word, and we strongly discourage its routine use. However, few patients will understand what an "opioid" is, and it may be appropriate to include the term in a limited way.

A quick Internet search for controlled substance agreements will bring up many examples of variable quality, including some that clearly do not adhere to the standards described above. Rather than simply adopting an existing agreement wholesale, we encourage Clinic Directors to consider the content, tone, and word choice of the CSA they use. One of the chapter authors recently wrote a paper that explored these issues and offered a template for low health literacy CSAs based on principles of shared decision-making; readers are encouraged to review that document for more information [30].

## State Prescription Monitoring Programs

Since 2002, Congress has provided funding to the US Department of Justice to support the development of state-specific Prescription Drug Monitoring Programs (PDMPs) [35]. In general, these programs require pharmacies to report the dispensing of controlled substances to a central database including information about both the prescription and the prescriber. As of May 2017, every state has its own functional PDMP except for Missouri (which has introduced legislation to create a PDMP at the time this chapter was written), although the design and functionality of the programs are variable. In some states, registration with and use of the PDMP are required by state law.

Prior to initiating opioid therapy and periodically thereafter, we strongly recommend that residents be required as a matter of clinic policy (regardless of law) to check their PDMP for a patient's refill history and to document this in the medical record. When used consistently, this very powerful tool can be extremely helpful at detecting evidence of doctor shopping and other scams.

## Prescribing Tips to Reduce the Risk of Misuse, Diversion, and Overdose

The way a prescription is generated and the choice of medication can affect risk of misuse. For example, prescription forgery risk can be reduced by using secure electronic prescribing when available and tamper-resistant prescription paper that resists alteration when it is not; tamper-resistant prescription paper is already required for Medicaid patients [36], and we recommend implementing this for all clinic patients, regardless of insurance type. Other good prescribing habits include writing out the number of pills dispensed instead of using numbers and avoiding trade-name-only prescriptions whenever possible; generic opioids typically have equal efficacy to their branded counterparts while also having a lower street value when the medication is diverted since it is less recognizable as "the real thing."

Diversion can be challenging to prevent, but providers should directly counsel patients that opioids must never be used differently than prescribed and should never be shared with or sold to another person. This warning should also be included in the practice controlled substance agreement. State prescription drug monitoring programs should be checked before opioids are prescribed and then periodically thereafter to look for evidence of doctor shopping. Additionally, patients should be counseled to safely store their medications in a locked container that is out of sight and out of reach from children, housemates, and guests.

As previously mentioned, we also recommend using opioids only in conjunction with other non-opioid treatments as part of a comprehensive multimodal pain management plan, which is beyond the scope of this chapter. When used, coach trainees to prescribe the lowest dose of the least potent opioid that can sufficiently achieve

therapeutic goals. Additionally, analgesic goals and evaluation of potential adverse effects should be fastidiously reassessed at each visit. When it becomes clear that the risk of ongoing opioid use exceeds observed benefits, prescribers should carefully discontinue them.

There is no evidence that one opioid is consistently superior to others, but regardless of opioid choice, only short-acting opioid analgesics should be used in opioid-naïve patients to reduce the risk of overdose [20]. Prescribers should reserve long-acting opioids for patients with poorly controlled chronic (not acute or intermittent) pain syndromes despite the regular use of around-the-clock short-acting opioids. Safe use of extended-release/long-acting opioids is of such concern that the FDA developed a Risk Evaluation and Mitigation Strategy (REMS) program as part of a multifaceted effort to reduce the risk of harm [37]. However, even when using short-acting opioids, residents must consider their relative potency, half-life, and onset of action and should "go low and slow" when in doubt. Possible drug-drug and drug-disease interactions (e.g., long QT syndrome, respiratory depression, etc.) need to be considered as well, and most experts strongly caution against co-prescribing opioids and benzodiazepines because of the increased risk for overdose.

Additionally, when overdose risk is elevated (e.g., patients taking greater than 50 MMEs of opioids per day, patients using benzodiazepines with opioids, and patients with a history of prior overdose), the CDC advises prescribers to consider co-prescribing the opioid reversal agent naloxone, which can be lifesaving [38]. Residency Clinic Directors may consider requiring naloxone co-prescribing for patients on COT as clinic policy. Naloxone is not itself a controlled substance, doctors do not require any special certification to prescribe the drug, and in some states naloxone can be prescribed to patients and their families by trained pharmacists even without a doctor's prescription. Prescribers are strongly advised to review the CDC guidelines for additional opioid prescribing best practices.

## Urine Drug Screening (UDS)

Urine drug testing is an indispensable tool when prescribing opioid medications. Some have expressed concern that UDS testing will negatively affect the patient-doctor relationship, but this is considered standard of care in pain medicine. When utilized for all patients on controlled substances and normalized as an expected part of safety monitoring, much of the stigma of urine testing can be mitigated.

The purpose of UDS testing is to detect illicit drug use and to confirm the presence of the prescribed medication. Drugs are concentrated in the urine, so UDS testing is an easy way to test for their presence in the body. However, the window of detection is limited to several days for most drugs, and urine is susceptible to adulteration or dilution. Unless directly observed, tampering may occur, and in some cases, other types of testing (e.g., hair, nails, oral fluid, and blood) can be used instead. However, urine drug testing is far more common.

### *Types of Urine Drug Tests*

Most screening tests are immunoassays and are highly sensitive but can have limited specificity. Advantages of screening immunoassays include their wide availability (often as point-of-care testing), versatility (can test for numerous substances at once), and generally low expense. However, they provide qualitative results only and are susceptible to both false-positive and false-negative results, and most immunoassays for "opiates" will fail to detect synthetic opioids such as oxycodone, which must be ordered separately. For example, the commonly used CEDIA Opiate Assay cross-reacts with oxycodone at a concentration of 10,000 ng/mL only 3.1% of the time [39]. In contrast, confirmatory testing utilizing gas chromatography (GC) or liquid chromatography and mass spectroscopy (LC/MS) provide results that are quantitative and highly specific. However, they are more expensive, take longer to process, and are often "send-out" tests to reference labs.

If you are not an expert in the interpretation of UDS testing, consider scheduling an appointment with the director of the medical toxicology laboratory at your hospital. This person will be an invaluable resource in interpreting unexpected results and reviewing the limitations of the assays used at your institution. Ask them to review their testing protocol and their spec sheet for drug testing.

### *How Often to Test*

One could argue that testing frequency be risk-based so that very low-risk patients may need testing only 1–2 times per year, and a very high-risk patient may need testing monthly. However, as previously mentioned, providers are very poor at predicting which patients will have abnormal/unexpected UDS results, and therefore this approach is limited [11]. Additionally, in resident clinics, the need for UDS testing can be easily overlooked or delayed due to inexperience, poor record keeping, or other factors; in some cases, the UDS is never checked. UDS testing should be done at the start of therapy and whenever aberrant behavior is suspected, but it needs to be done randomly and periodically after that as well. A reasonable compromise is to set a minimum frequency so that all patients must get a UDS at least once every 90 days. If your patient panel is moderately high risk, then this may be appropriate. In our experience, a rule to test approximately every 90 days typically results in three to five tests per year.

### *Collecting Urine Samples*

In general, resident clinics do not have a dedicated UDS bathroom (i.e., no sink in the room, toilet water has blue dye added) as may exist for legal purposes (e.g., at the start of a new job). Instead, the staff and providers need to maintain a reasonable

index of suspicion for tampering so that it will not be missed. Medical assistants and/or nurses should be trained to ask patients to leave bags and coats outside the bathroom and to ensure that the patient is alone in the bathroom when the sample is collected.

To be valid, samples should be obtained without notice, and a patient should not be allowed to leave the office and return to provide the sample later. The patient should be asked when they took their last dose of the opioid and if they have missed any doses in the last few days. In addition, the patient should be asked if they have taken any other pain medications and if they have used any other prescription or over-the-counter (OTC) drugs in the last week; a patient may not think to tell us about a prescription containing codeine from their dentist. Importantly, the process of labeling the specimen cup must be clear. Many patients confronted with a positive UDS will claim that the samples were mixed up and the urine tested was not their own.

## *Evidence of Urine Tampering*

Is the sample provided actually urine? Short answer: if it looks and smells like water, it probably is water. However, this should be confirmed by sending the sample for a urine creatinine. In most labs, a value of 5–20 mg/dL is consistent with a very dilute specimen, but a value less than 5 mg/dL is not consistent with urine [40]. Other tests including measures of temperature and pH can also be helpful. Some clinics have also purchased cups with a built-in thermometer to confirm the specimen is freshly voided. Many commercial labs perform validity testing by measuring the sample for urine creatinine, for specific gravity, and for oxidizing adulterants. Labs that do this will have rules to reject samples based on these results.

## *What Drugs to Test and When to Order Confirmatory Testing*

Most commercial UDS tests for drugs of abuse include amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates, and phencyclidine. As noted previously, most screening immunoassays will provide qualitative results only, and synthetic or semisynthetic opioids such as oxycodone, methadone, fentanyl, and buprenorphine need to be ordered separately. Heroin is not detected directly but is quickly metabolized to 6-acetylmorphine which is then rapidly metabolized to morphine. Most labs include 6-acetylmorphine in their assay, but due to its short half-life, often only morphine will be detected. Thus, patients prescribed morphine but using heroin can be difficult to identify.

Depending on the reason why testing is being done, providers may have the option to order reflex confirmatory testing. In this case, if the screen tests positive for a class of drug, then confirmatory testing will automatically be performed. In gen-

eral, assays for cocaine and cannabinoids are highly specific with few false positives, so additional testing for those substances may not be necessary. In contrast, amphetamines and opiates may have false-positive and complex results plagued by cross-reactions, so confirmation testing is critical. If reflex confirmatory testing is not ordered, the resident will need to keep on top of the immunoassay results and order confirmatory testing promptly as samples may only be valid for a couple of days.

## *How to Handle a Positive UDS for a Non-prescribed Drug*

The presence of a non-prescribed controlled drug on a UDS can be unexpected and needs to be carefully considered in each case; human or lab error is always possible, and identification of a metabolite or a false-positive result from another substance can occur. For an unexpected result that may result in a major change in treatment (e.g., discontinuation of the opioids), retesting of the same sample by the lab may be performed. Most labs will hold the specimen for a few days and should be able to duplicate the initial result with retesting. In our experience, the lab will only rarely find that a technical error had occurred. If there is continued uncertainty, the sample can also be sent to an outside reference lab. Except under unusual circumstances, we generally do not recommend requesting another sample of urine when results are unexpected because advanced notice of testing may allow a patient to defeat the test through a variety of scams.

If the sample repeatedly tests positive for a non-prescribed drug, the patient should be questioned about the finding. Most addiction experts recommend that evidence of current high-risk illicit drug use (e.g., cocaine, methamphetamine, PCP, or heroin) result in discontinuation of prescribed opioids, although practices vary in their approach and may sometimes allow for an isolated episode of misuse with increased monitoring and/or treatment of an underlying substance use disorder. Clinic Directors should consider the best approach for their practice and may want to codify it in a practice policy to improve prescribing consistency, although variability between specific patient cases and circumstances may make this challenging.

Sometimes when confronted with urine test results that indicate the presence of a non-prescribed or illicit drug, patients will offer a variety of creative excuses. We list some below along with a brief analysis of the provided excuse:

1. *Amphetamine*: “I bought a weight loss pill on the internet” or “I borrowed a pill to help me concentrate at work/school.” Both responses, if true, represent unsafe use of non-prescribed substances and make the ongoing use of prescribed opioids far riskier. A well-written controlled substance agreement will outline this.
2. *Barbiturates*: “Someone gave me something to settle my stomach” (e.g., Donnatal—atropine/hyoscyamine/scopolamine/phenobarbital) or “I borrowed a friend’s headache medication” (e.g., Fioricet—butalbital/acetaminophen/caffeine). Using other people’s medications is very dangerous and risks

sometimes-fatal drug interactions and overdose. Opioids cannot be used safely in this circumstance. This too should be outlined in a controlled substance agreement.

3. *Benzodiazepines*: "I borrowed something from a relative to help me sleep." Same analysis as above.
4. *Cocaine*: "I was in an apartment when someone was smoking crack." Very intense exposure to secondhand cocaine will result in detectable but low levels in the urine. Typically, these have been reported to be below the screening cutoff of the immunoassay. If the assay is positive, it is likely they used the cocaine themselves.
5. *Marijuana (cannabinoids)*: (1) "I was in a room when someone was smoking marijuana," (2) "I used to smoke marijuana but haven't in a few weeks and we just started my pain pill last week," or (3) "medical marijuana is legal in my state anyway." There are several studies that show even heavy secondhand exposure will not cause the usual assay cutoff of 50 ng/mL to be positive, and this excuse is not acceptable for workplace testing [41–43]. If positive, assume the patient inhaled. Importantly, heavy habitual users of marijuana can have urine that tests positive for weeks or even months after their last use, so the excuse given in the second example is possible. Finally, medical marijuana typically requires either a prescription or physician's certification, and without those, use remains illegal. Unless the patient lives in a state where recreational marijuana is legal, this is an invalid excuse.
6. *Opiates*: "I had some left-over cough syrup with codeine," or "I was visiting my relative and they offered me one of their pain medications because my back was hurting more than usual." As with the above examples, using other people's medications is dangerous. Using previously prescribed medications that contain opioids is a more challenging circumstance, but at a minimum, the patient needs to be reeducated about the risks for drug interactions and the importance of safely discarding leftover medication. If the decision is made to continue opioid therapy, in most cases, patients should be advised that further episodes of non-prescribed drug use will result in stopping their opioids.

Sometimes urine drug tests will be unexpectedly positive for a non-prescribed drug because of normal metabolism. Prescription opioids are heavily metabolized, and the UDS will often detect not only original drug but also its metabolites. In contrast, as noted previously, heroin is not directly detected by urine testing and is very quickly metabolized to morphine. Unless the intermediate metabolite 6-acetylmorphine is detected, it can be extremely difficult to discriminate between heroin and morphine use. The interpretation of positive urine drug test findings can be very challenging; the previously mentioned resource TOPCARE developed at Boston Medical Center offers an excellent drug interpretation support tool that can be accessed at http://mytopcare.org/udt-calculator/ (Table 2).

**Table 2** Examples of detectable urine metabolites

| Parent drug | Metabolite(s) |
|---|---|
| Codeine | Morphine, hydrocodone, hydromorphone |
| Heroin | 6-acetylmorphine, morphine |
| Hydrocodone | Hydromorphone |
| Methamphetamine | Amphetamine |
| Morphine | Hydromorphone |
| Oxycodone | Oxymorphone |

## *How to Handle an Unexpectedly Negative UDS*

An unexpectedly negative UDS can be due to several factors, and interpretation of results can be tricky.

For example, very low doses of some opioids may lead to a level measured in the urine that is below the threshold required for a qualitatively "positive" test. Sometimes the laboratory will be able to provide additional information or testing when this is in question. In some labs, this can be a particular problem with oxycodone since certain assays have a much higher cutoff level for a positive result with oxycodone than for other opioids.

Another reason why the UDS can be unexpectedly negative is that the wrong test was ordered. As noted above, synthetic and semisynthetic opioids are not typically detected in an opiate immunoassay, and therefore oxycodone, fentanyl, and other such drugs may need to be ordered separately. One potential solution is to work with your institution's laboratory and electronic medical record teams to develop "bundled" order sets that include naturally occurring opiates along with common synthetic and semisynthetic drugs into a single screening panel.

Sometimes the UDS is negative because the substance is not in the patient's body, but even in those cases, interpretation can be challenging. Did the patient use up the medication sooner than directed? Is the patient using the medication on an "as needed" basis and had not taken the medication in several days? Is the patient worried that you will discontinue their prescription and is inappropriately hoarding their medication? Is the medication being illegally diverted? Trainees need to consider all these possibilities and personalize their approach to each patient.

## *UDS Special Circumstances*

1. *Methamphetamine*: In some parts of the country, methamphetamine use is very common. Although methamphetamine is available as a prescription drug, it is very rarely prescribed. If a patient were taking this as a prescription, a careful

history before prescribing opioids should discover this. In general, a UDS positive for methamphetamine will also confirm the presence of amphetamine, its metabolite, and this result should be interpreted as methamphetamine misuse. There is one uncommon exception! Over-the-counter Vicks Vapor Inhaler has the active ingredient levomethamphetamine which is the L-enantiomer of methamphetamine. The L (levo) isomer is felt to have no addictive potential and no central nervous system effects. However, repeated use of this nasal inhaler may result in a urine level that confirms the presence of methamphetamine. Most commercial assays will not discriminate the D (dextro) and L (levo) forms, although there is an assay available to do this. If a patient unexpectedly has a UDS positive for methamphetamine, the patient should be asked if he/she is using any other OTC medications. We have discovered two patients this way that had started to use Vicks Vapor Inhaler and had a false-positive UDS.

2. *Heroin*: Heroin is very rapidly metabolized (in minutes) to 6-acetylmorphine (sometimes reported as 6-monoacetylmorphine) and then to morphine. For this reason, UDS assays do not test for heroin but should test for the metabolite 6-acetylmorphine. The confirmed presence of 6-acetylmorphine is absolute proof of heroin use unless there has been a lab error. Beyond this very brief window, only morphine will be detected.
3. *Poppy seeds*: Poppy seeds contain small amounts of morphine and much smaller amounts of codeine. Eating usual amounts of foods with poppy seeds will not typically cause a UDS to detect morphine, but this rarely may occur with unusual diets. A large amount of morphine in the urine would probably not be explained by even excessive poppy seed consumption.
4. *Methadone*: Methadone may be prescribed for pain. Not all UDS assays will include a test for methadone, and the immunoassay screen for opiates will not typically detect methadone. Thus, a patient only on methadone for pain should be "opiate" negative on most assays and methadone positive when tested separately.

## Stopping Opioids, Discharging Patients, and Discarding Unused Medication

Some providers wrongly assume that stopping opioids also means the patient should be discharged from the clinic. A decision to discontinue opioid therapy because the benefits no longer outweigh the risks should not equate to reflexive termination from the practice. Threats of violence and other inappropriate behaviors toward providers and staff may warrant discharge, but this should be evaluated distinctly from whether opioids are still safe to prescribe. In some circumstances of inappropriate but less egregious behaviors, an experienced clinic manager can meet with the patient and review what behavior is acceptable. Such efforts should be well documented, and a formal letter of warning to the patient should be issued.

Problematic behaviors surrounding opioid prescribing are often driven by addiction. The management of addiction is rapidly becoming a problem that can be treated in the primary care setting [44]. However, even if your clinic is not equipped to treat addiction, residents should continue to provide primary care and refer patients to appropriate addiction treatment. Once an active addiction is identified, prescription opioids for chronic pain management should be stopped except under very unusual circumstances.

It should be noted that evidence shows approximately 65% of those who are started on COT will still be on opioids years later [45]. In the study, this was especially true when high-dose opioids were prescribed (greater than 120 morphine milligram equivalents per day). One should strongly consider this before starting opioids in the first place.

## *How to Discontinue Opioids*

There are many factors to consider when deciding when and how to discontinue opioids, but in general a taper of 10% of the original dose per week is usually well tolerated with minimal physiologic adverse effects [46]. However, more rapid tapers are sometimes appropriate, and in some circumstances, opioids should be abruptly discontinued. We offer a few specific examples below:

1. *Use of high-risk illicit drugs*: When deciding to stop opioids because the patient is actively using high-risk illicit drugs such as cocaine, heroin, and methamphetamine, it is reasonable to rapidly taper the patient off opioids. If the prescribed opioid is not detected in the urine (presumably due to diversion), then there would be no indication to taper at all. This discussion should take place face to face, and referral for addiction treatment should be offered. Primary care should still be provided, and non-opioid analgesics can be used to manage chronic pain.
2. *Use of lower-risk illicit drugs (i.e., marijuana)*: Your clinic should decide on a policy regarding how to handle patients who test positive for lower-risk illicit drugs such as marijuana. You will need to decide on your threshold for allowing a second chance, but this should be standardized across the practice and applied uniformly. Remember too that former heavy marijuana users may have a UDS positive for cannabinoids weeks to months after they no longer use as previously described. When discontinuing opioids because of lower-risk illicit drug use, we recommend a slow taper of approximately 10% per week as described above. Non-opioid pain medications should be optimized.
3. *Diversion*: When diversion is detected, opioids must be stopped immediately, and there is no need for a taper or additional prescription. Knowing diversion is taking place but continuing to prescribe risks violating federal and/or state law [47].
4. *Aberrant behaviors*: These include refusal to provide a urine for drug testing, missed appointments, frequent emergency department visits for chronic pain, refusal to take any medication other than opioids, repeatedly losing their

prescription, etc. Many of these behaviors in isolation appear minor, but in some patients, a pattern emerges. Repeated aberrant behaviors that do not correct with direct feedback may warrant discontinuation of COT. *Plan –: Meet with the patient. Explain that the clinic will no longer be able to continue the opioids due to the repeated aberrant behaviors despite corrective warnings. An opioid taper is often appropriate. Maximize pain treatment with non-controlled medications.*

5. *Poor risk-benefit ratio*: There will be patients with poor pain control despite continued and often escalating doses of chronic opioids. In some cases, no improvement in day-to-day function can be documented. Many of these patients will demonstrate tolerance with escalating doses over time. Others develop progressive pain suggestive of opioid-induced hyperalgesia. If you assess that the benefit to the patient appears to be less over time or the benefits no longer outweigh the risks, a decision to stop the opioids should be considered. Since the patient will be dependent on opioids, any suggestion of stopping will likely be met with great resistance. They may have had prior episodes of running out of medication, experienced withdrawal symptoms, and may be fearful this will happen again. *Plan: Meet with the patient to review your concerns that the benefits of opioid use no longer clearly outweigh the risks. Discuss options to maximize pain treatment with non-controlled medications. Outline a plan to taper off opioids slowly enough to avoid withdrawal symptoms, and treat any withdrawal symptoms that occur with clonidine or other adjunctive medications.*

When opioids are discontinued, it is very important that they be discarded in a safe manner. Leftover supply should not be stored because this increases the risk for theft, diversion, and future overdose. Instead, unused drug supply should be disposed of in accordance with various federal, state, and local recommendations. The FDA suggests flushing unused supply down the toilet, while some states and municipalities prohibit this practice for fear that the drug will enter the water supply [48]. Instead, the unused medication can be adulterated with an unappealing substance (e.g., soil, coffee grounds, used kitty litter), the container sealed, and the bottle placed in the trash. Many police stations and some other facilities also offer a place to securely deposit leftover medications for incineration, and some pharmacies also provide a process by which unused medications can be returned for safe disposal. Clinic Directors are encouraged to become familiar with the regulations and resources in their area.

Importantly, the decision to discontinue opioid therapy can be emotionally difficult for some patients, and there is a high risk for confrontation during this time. However, by approaching the conversation with empathy, avoiding stigmatizing language, explaining decision-making in clear and transparent terms, and adhering to a risk-benefit framework, these can be successful encounters. These issues were explored in more depth in a recent article written by one of the chapter authors, and readers are advised to review that source for additional information [9].

## Final Opioid Checklist

1. *Are opioids indicated?* Opioids should be used in the treatment of chronic severe pain that results in functional disability and has not responded to other non-opioid treatment options. Opioids should be part of a multimodal treatment plan, and the underlying diagnosis should be fully evaluated. In general, avoid opioids in the treatment of fibromyalgia and other functional pain amplification syndromes since the benefits rarely outweigh the risks.
2. *Are opioids contraindicated or unacceptably risky?* Screen for evidence of untreated depression, suicidality, and active addiction. Consider using validated risk-screening tools such as the Opioid Risk Tool to assess for the risks of misuse. Do not use opioids when the risks outweigh the benefits. Validate test results and outside medical records before starting opioid therapy. Check your state's prescription drug monitoring program before prescribing opioid therapy, and document this in the patient's chart, particularly in states where checking the PDMP is required by law.
3. *Establish informed consent and clear practice policies*. Utilize controlled substance agreements and shared prescribing expectations across the practice and for all patients receiving controlled substances. Make certain that the patient understands the relative risks and benefits of opioid use, and engage in shared decision-making to establish functional goals of use.
4. *Monitor safety*: Utilize state prescription drug monitoring programs, urine drug testing, pill counts, and other tools to be sure that opioids are being used only as prescribed and as safely as possible.
5. *Know when to stop*: Stop prescribing when the benefits no longer outweigh the risks. Abandon the treatment option, not the patient. Refer or implement addiction treatment protocols when appropriate.

## Conclusion

Opioid therapy is a very powerful tool in the management of chronic pain that can offer relief to selected patients but is also fraught with danger, particularly when used differently than prescribed. Opioids should only be prescribed when the perceived benefits are assessed to outweigh evidence of risks and harms, at the lowest effective dose, and for the shortest duration that is medically necessary. However, when carefully used as part of a multimodal approach to pain management that also includes nonpharmacologic and non-opioid therapy, patients may benefit. Careful, rational, and deliberate prescribing is critical, as is the use of risk-management tools and thoughtful documentation in the medical record. Clinic Directors must work with their trainees, faculty, and clinic staff to develop an organized approach to opioid prescribing and should remain vigilant for inconsistent opioid use patterns

among their providers. Faculty development, resident education, and awareness of the ever-evolving regulatory environment are of utmost importance, as is keeping abreast of the medical literature as our understanding of safe opioid use continues to evolve.

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