Chronic Back Pain With Possible Prescription Opioid Misuse

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DR LIBMAN: Mr O is a 71-year-old man who had been treated for chronic low back pain since 1981 when he underwent surgery for a herniated lumbar disk. He continued to have pain, which was unsuccessfully managed with acetaminophen and tricyclic antidepressants. Nonsteroidal anti-inflammatory drugs were not used because of a history of gastritis and Barrett esophagus. Steroid injections offered temporary relief. For more than a decade he achieved reasonable pain control by taking oxycodone-acetaminophen 3 times a day as needed (84 tablets every month). He signed a controlled substance agreement. However, urine drug testing (UDT) found no oxycodone on 2 occasions. He explained that he occasionally drinks alcohol and does not take his oxycodone-acetaminophen when doing so. His oxycodone-acetaminophen was discontinued for this violation of his agreement. Since then, he reports that his pain is inadequately controlled and his function has decreased.

His medical history is notable for hypertension, hyperlipidemia, chronic obstructive pulmonary disease, dyspepsia, Barrett esophagus, anxiety, and depression. He is under psychiatric care.

His medications include atorvastatin, hydrochlorothiazide, bupropion, alprazolam, venlafaxine, esomeprazole, gabapentin, and fluticasone, albuterol, and ipratropium inhalers.

Mr O is divorced and lives alone. He receives long-term disability due to chronic back pain. He drinks beer occasionally (remote history of heavy drinking) and smokes 2 to 3 packs of cigarettes a day. There is no history of illicit substance use.

MR O: HIS VIEW

I had a ruptured disk in 1981. Since then I have had back injections and pain medication. One doctor said I had sciatic nerve root damage and ever since I have been suffering. I started on Percocet and it was doing its job. I would still get pain and it was still tough walking, but the Percocet helped the pain. I still get injections, which help for 2 weeks only.

The Percocet was stopped when I took a blood test, and they did not see it in my system. There was no Percocet in my system because I had just gone to the city club and had a few drinks. When I have a few drinks I don’t take the Percocet. I guess they assumed that I was selling it.

I needed the Percocet. I don’t think they ever should have taken me off it. I lay down most of the time and don’t go anywhere because I cannot walk far. When I started on the narcotics, they gave me a form to sign where I wasn’t going to overdo it. I never raised the dosage.

I believe that there are people that do sell Percocet. I have seen a lot out there, but I am not going to sell what I need, so I don’t think that applies to me. I am 71 years old. I don’t know...
what addiction really is. Addiction to me is when you take something you cannot get off and it is bad for you. I was so mad I wanted to see a different doctor but I ended up not.

**SCOPE OF THE PROBLEM**

**Dr Alford:** Approximately 100 million Americans have chronic pain.1 The safe and effective use of opioids for the management of chronic pain is complex. Clinicians must balance the goals of relieving pain and suffering while not harming the patient (eg, addiction or overdoses). Because of the lack of pain medicine specialists, even the most complex patients with chronic pain are primarily managed in primary care.2 This is compounded by the lack of pain management curricula3,4 in medical training. This results in some clinicians overprescribing and others underprescribing. In a survey5 of community clinicians, the 2 most common opioid prescribing concerns were patients becoming addicted or diverting (eg, selling) the opioid. Unrealistic expectations regarding the potential benefits of opioids and an underappreciation for the potential harms also complicate opioid prescribing. As opposed to acute pain, not all chronic pain improves while taking opioid therapy.6 For those patients who do not respond, uncontrolled dose escalation often ensues, all in a desperate, yet futile, attempt to obtain pain relief.

Since the 1980s when the medical literature began to support opioid therapy for chronic noncancer pain, there has been a 4-fold increase in opioid prescribing.7,8 During the same period, unintentional opioid overdose deaths has increased 4-fold9 and substance abuse treatment admissions for prescription opioid addiction has increased 5-fold.10 In the United States, nonmedical use of prescription opioids is the second most prevalent type of illicit drug use after marijuana.11 Data on the effectiveness of long-term opioids are limited12-16 (Table 1). Most of the published studies are uncontrolled case series. The randomized clinical trials are of short duration, less than 8 months. Studies find statistically better analgesia with opioids than controls, but the pain relief is modest. Whether function and quality of life improves is inconclusive. In a systematic review17 of opioid treatment for chronic back pain, the study quality was considered weak and there was no significant benefit of opioid therapy. Because of the poor quality of evidence, it remains unclear whether long-term opioid therapy is effective. However, it is not uncommon in clinical practice to have patients like Mr O with apparent benefit from long-term opioids.

Allergies to opioids are extremely rare, but adverse effects such as nausea, sedation, and constipation are common. Patients will develop tolerance to most adverse effects over time; however, constipation can be a persistent problem.17 Respiratory depression is a concern because opioids have also been linked to both central and obstructive sleep apnea.18 Unlike other analgesics—nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen—organ toxicity to opioids is rare. Opioids can suppress the hypothalamic-pituitary-gonadal axis resulting in opioid-induced hypogonadism19 leading to sexual dysfunction, fatigue, and poor bone health. A study found that higher-dose opioids (>50 mg of morphine equivalent dose) are associated with a 2-fold increase in fracture risk.20 Another concern is the development of a paradoxical increase in pain sensitivity due to opioid-induced hyperalgesia.21 The mechanism for this hyperalgesia is unclear.

Opioid addiction and opioid induced overdoses are 2 major concerns. The true rate of opioid addiction in patients prescribed opioids for chronic pain is unclear but is reported from 0% up to 50%.22 This uncertain incidence results from different populations studied and different definitions of addiction used. Annually, patients taking opioids long term have a 1.8% risk of overdosing.23 Recent observational studies have shown a correlation between opioid dose and risk of fatal overdoses and adverse events24-26 with a 9-fold increase in fatal overdoses for morphine equivalent doses of more than 100 mg/d and a 2-fold increase in substance-related health services utilization for morphine

### Table 1. Effectiveness of Opioids for Chronic Pain

<table>
<thead>
<tr>
<th>Systematic Reviews</th>
<th>Study Objective</th>
<th>Summary</th>
<th>Major Findings</th>
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<tr>
<td>Noble et al,6 2010</td>
<td>Long-term opioid management for noncancer pain</td>
<td>26 Prospective studies with at least 6 mo of treatment included 4893 participants; 25 case series studies or uncontrolled trials and 1 randomized controlled trial comparing 2 opioids</td>
<td>Many participants discontinued opioids due to adverse effects (up to 23%) or insufficient pain relief (up to 10%); all studies showed clinically significant reductions in pain; improvement in quality of life and functional status were inconclusive</td>
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<tr>
<td>Martell et al,16 2007</td>
<td>Opioid treatment for chronic back pain</td>
<td>Meta-analysis of 4 studies assessing opioids compared with placebo or a nonopioid control and 5 studies comparing the efficacy of different opioids</td>
<td>No significant reduction in pain with opioids was found; study quality was weak overall</td>
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Opioids are powerful analgesics that act peripherally by inhibiting activation of nociceptors and act centrally by turning off descending inhibitory pain pathways and by preventing ascending transmission of pain signals.12 Patients’ response to and ability to tolerate different opioids is influenced by genetic variations in μ-opioid receptor binding and opioid metabolism.13-15 Therefore, a trial of several opioids may be needed to find an acceptable balance between analgesia and tolerability.
equivalent doses of more than 120 mg/d. Because Mr O was prescribed a low dose of oxycodone, he was at a lower risk of experiencing these opioid-related complications.

TERMINOLOGY

The use of opioids to treat chronic pain is complicated by misunderstood terminology. Physical dependence is a predictable physiological response to chronic opioid exposure resulting in a withdrawal syndrome with abrupt cessation or rapid dose reduction. Most patients who are receiving long-term daily opioid therapy will become physically dependent. Mr O was not physically dependent because he did not complain of withdrawal symptoms when not taking his opioids for days. Physical dependence does not indicate maladaptive behaviors and does not meet the diagnostic criteria of opioid dependence, without, for example, loss of control or continued use despite negative consequences. Criteria for opioid addiction were developed to better address the need to identify problems in patients with chronic pain. Addiction is characterized by behaviors that include one or more of the 4Cs: impaired Control over drug use, Compulsive use, Continued use despite harm, and Craving. Although the term pseudoaddiction is based on a single case report, it describes behavior suggestive of addiction that is triggered by unrelieved pain. Patients seeking pain relief should be focused on pain relief and be willing to try nonopioid therapies while the addicted patient is solely focused on obtaining more opioid. Prescription drug misuse refers to drug use in a way different from that prescribed or for reasons other than for which it was prescribed. Diversion is when opioids are shared or sold. Federal surveillance programs have shown an increase in prescription opioid diversion due to their significant street value. Aberrant medication-taking behavior describes a spectrum of behaviors that may reflect drug misuse. Although Mr O’s behavior was not suggestive of opioid addiction, that his urine drug tests results were negative for his prescribed opioid raises concern for diversion.

Before Prescribing an Opioid

Prior to starting opioids for chronic pain, it is important to review what the patient’s experience has been with non-opioid and nonpharmacotherapies. Because all patients taking opioids long term have potential for prescription opioid misuse, “Universal Precautions for Pain Medicine” are now recommended. That is, all patients should be assessed for risk before starting opioids and monitored for harm and benefit while taking opioids. Although this recommendation is not evidence based, it is increasingly used. Specific risk factors for prescription opioid misuse include younger age (16-45 years), mental illness, personal or family history of substance abuse, or legal history of substance abuse.

Numerous risk assessment tools have been developed to risk stratify patients including the Screener and Opioid Assessment for Patients with Pain (SOAPP) and the Opioid Risk Tool (ORT). The ORT is a brief 5-item self-report that classifies patients as low, moderate, and high risk. The risk level can help determine the intensity of monitoring that will be required of the patient. Some patients with a history of prescription opioid addiction may not be suitable candidates for prescription opioids and ideally should be referred to specialty care (ie, pain medicine, addiction medicine).

Patient education regarding realistic treatment goals and opioid risks is critical. Patients must understand that the initial and subsequent opioid prescriptions are a test and not necessarily a commitment to long-term opioids. This discussion is often aided by using a risk-benefit framework. This framework, not dissimilar to what clinicians use with other treatments for chronic diseases, focuses attention on judging the treatment (ie, opioid therapy), not the patient. This serves to clarify the clinician’s role as a caregiver and not as a police officer or a judge.

Patient education is enhanced by the use of a standardized patient-prescriber agreement. The agreement articulates the rationale for and risk of long-term opioid therapy and the monitoring strategies (eg, UDT, pill counts) and consequence of aberrant medication taking behavior (eg, unsanctioned dose escalation). When a patient, such as Mr O, exhibit behavior for opioid misuse (eg, UDT negative for the prescribed opioid), the clinician should first confirm that the urine result is accurate. If confirmed, the clinician should interview the patient considering the full differential diagnoses for the behavior of concern. Once the etiology has been determined, a change in treatment plan (eg, medication change, increased monitoring, or both) should occur.

Box 1. Differential Diagnosis for Unexpected Urine Drug Test Results

<table>
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<tr>
<th>Unexpected Positive</th>
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<tr>
<td>Illicit drug use</td>
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<td>Metabolic conversion of prescribed medication</td>
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<table>
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<tr>
<th>Unexpected Negative</th>
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<tr>
<td>Drug is absent (not taken in past 72 hours)</td>
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<tr>
<td>Hoarding</td>
</tr>
<tr>
<td>Diverting</td>
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<tr>
<td>Pharmacologic induction causing rapid metabolism</td>
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<table>
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<tr>
<th>Specimen manipulation (dilution or adulteration)</th>
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<tbody>
<tr>
<td>Drug is present but below assay cutoff</td>
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<tr>
<td>Wrong assay ordered</td>
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Laboratory issues
- Incorrect specimen
- Cross-reaction causing interference

Adapted from Reisfield et al.

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though the efficacy of agreements in decreasing opioid misuse has not been well established, they are increasingly being used. Mr O’s so-called violation of his agreement was the basis of discontinuation of his opioids. Because of the inherent risks of opioids, clinicians should obtain informed consent from patients. This should include a description of the patient’s responsibilities (eg, safe storage and disposal and not diverting) and potential opioid risks including adverse effects (short- and long-term), physical dependence, risk of drug (eg, sedatives) interactions resulting in central nervous system and respiratory depression, addiction, and overdose. It is particularly important to warn the patient about the elevated risk of driving and overdose when the opioid is started and titrated. The risk for overdose seems greatest shortly after the initial opioid prescription or after a refill. Despite Mr O’s being on a low-dose opioid, his concurrent benzodiazepine use puts him at higher risk of adverse outcomes (eg, central nervous system depression).

SAFE OPIOID PRESCRIBING

Safe opioid prescribing practices from expert-derived clinical guidelines have been published (Box 2).

Selecting an Opioid

Opioid therapy should be individualized based on its onset and duration of action as well as the patient’s prior experience. Although there are efforts to develop abuse-resistant opioids, currently all opioids and opioid formulations are potentially abusable. Clinical guidelines recommend long-acting (extended-release) opioids for treating chronic persistent pain and short-acting (immediate-release) opioids for intermittent or incidental pain. However, there is insufficient evidence in the literature to determine whether long-acting opioids are more effective or safer than short-acting opioids in treating chronic pain. It is prudent to start with less potent opioids (eg, codeine) before prescribing higher potency opioids (eg, morphine). A trial of several opioids may be necessary before an acceptable balance between efficacy and adverse effects is achieved. If an opioid loses efficacy or has intolerable adverse effects, switching from one opioid to another (ie, opioid rotation) may improve clinical outcomes at lower opioid doses. When switching from one opioid to another, equivalent analgesic tables should be used cautiously because they do not take into consideration individual variability in metabolism, receptor polymorphisms, and drug-drug interactions. To improve clinical outcomes and to decrease the total amount of opioid required, multimodal analgesia (eg, NSAIDs, tricyclic antidepressants, gabapentin) should be considered.

To eliminate the need for weekend refills and to ensure that the patient taking opioids daily will be due for a refill on the same day of the week every month, clinicians can give a 28-day rather than 30-day opioid prescription.

Monitoring for Benefit and Harm

Much of what is recommended for monitoring is based on expert opinion rather than on research. When starting opioids, frequent face-to-face visits (eg, weekly to every 2 weeks) are prudent. In managing chronic pain all measures of benefit and harm are subjective. Despite this limitation, clinicians must evaluate the efficacy and safety of the opioid therapy they have started or are continuing. All patients prescribed opioids should be agreeable to having their opioid use closely monitored for benefit and harm.

Monitoring for benefit includes measuring improvement in pain, function and quality of life. Most of the validated instruments to measure benefit (eg, Brief Pain Inventory) are too cumbersome for primary care settings. A validated 3-question pain, enjoyment, general activity (PEG) scale now makes this assessment practical in primary care. Monitoring for harm includes detecting opioid misuse including addiction and diversion. It includes UDT, pill counts, use of state prescription drug monitoring programs (PDMPs), and identifying and documenting instances of aberrant medication-taking behaviors. As mentioned earlier, this monitoring should be implemented for all patients.

Urine drug testing confirms therapeutic adherence (ie, the medication prescribed is detected in the urine) and detects use of illicit or nonprescribed drugs. Urine drug testing is increasingly used in clinical practice because self-reported illicit drug use is unreliable and because observing patients for aberrant medication-taking behavior detects only some problems and because it may improve treatment adherence (eg, decreased illicit drug use). Although UDT is recommended, a major barrier is the lack of skill clinicians have interpreting the results. Although UDT detects use of illicit drugs or nonuse of prescribed opioids, it does not diagnose prescription opioid abuse, addiction, or diversion. To accurately interpret UDT results, clinicians must order the correct assay (eg, immunoassay, gas chromatography/mass spectrometry), understand the major and minor opioid metabolic pathways, and know expected drug detection times and potential causes of false-positive and false-negative results.
negative results (Box 1). Before sending a UDT, it should be documented when the patient last took the medication being tested for. If the patient has not taken the opioid in 72 hours, it will not be detected. It does not appear that Mr O was asked when he last took his oxycodone-acetaminophen prior to his test. The level of concern and next steps would be different if Mr O disclosed that he had not taken his opioid prior to his test rather than in response to the unexpected test results. The rationale of requiring a UDT should always be discussed openly with patients. It is less about catching patients doing something wrong and more about assessing increased prescription opioid misuse risk. Mr O seemed unaware of the UDT based on his statement: “I took a blood test, and they did not see it in my system.” Because of the complexity of UDT interpretation, clinicians need access to a laboratory toxicologist to help with both UDT ordering and assessment.55

**Pill counts** can be used to monitor patients for medication adherence and to detect possible diversion. If a patient “forgets” to bring in the remaining pills, it is useful to have the patient return later that week for a pill count. Conducting pill counts would have been helpful in determining how Mr O was taking or not taking his opioids prior to the unexpected UDT result.

**Prescription-Drug Monitoring Programs** are statewide electronic databases that serve to help clinicians identify patients obtaining controlled substances from multiple prescribers (ie, “doctor shopping”). Currently 42 states have an operational program.66

### TO CONTINUE OR DISCONTINUE OPIOIDS

Decisions to continue or discontinue opioids should be based on the risk:benefit ratio. Does the opioid therapy benefit more than harm Mr O? If there is benefit in the absence of harm, then opioid therapy can be continued. If there is a small benefit in the absence of harm, then a dose increase may be warranted. Although opioids do not appear to have an analgesic ceiling effect, it is now known that higher opioid doses are associated with increased risk.53-20 Therefore, clinicians should ensure that patients take the lowest effective opioid dose possible.

If there is no benefit and no harm, then the clinician should consider trying a different opioid (ie, opioid rotation). If there remains no benefit and the patient is not meeting treatment goals, then the treatment benefit cannot outweigh risks and the clinician should stop or taper (should the patient be physically dependent) the opioid therapy. When there is a lack of benefit, the clinician should reiterate his/her belief that the patient’s pain is real and express frustration at the lack of benefit from opioid therapy. The clinician should show commitment to continue caring for the patient. The clinician is not abandoning the patient but rather abandoning an ineffective treatment.

If the patient is engaging in aberrant medication-taking behavior, the clinician should consider the complete differential diagnoses for that behavior; eg, is the patient treatment seeking for unrelieved symptoms, drug seeking due to addiction, or a combination of both (Table 2). If the behavior is because of addiction (ie, loss of control, compulsive use, continued use despite harm), the clinician should give specific and timely feedback to the patient for why the behaviors raise concern for possible addiction. In cases of suspected addiction, the benefits can no longer outweigh risks and the patient should be referred to addiction treatment.

### RECOMMENDATIONS FOR MR O

It is unclear how Mr O is taking his opioid. With negative UDT results, he has not taken his oxycodone-acetaminophen for at least 48 to 72 hours on multiple occasions despite being prescribed enough medication to be
taken 3 times a day. Lack of physical withdrawal also suggests that Mr O does not take his opioid daily. I would perform pill counts to better assess his opioid use.

The differential diagnosis for his unexpected UDTs (ie, medication not detected) is broad (Box 1). It includes that he does not take his opioids daily as prescribed. Does he only skip doses when he is drinking as he states? If so, then it appears that he is drinking for extended periods of time (48–72 hours) and thus is at risk for the negative health consequences of unhealthy alcohol use. If he is not taking his opioids daily, which may be clinically appropriate, what is he doing with his extra medication? Is he hoarding them or diverting them? Alternatively, is he taking more than prescribed on certain days and running out of medication early?

Is the UDT assay insufficiently sensitive to detect the medication at the concentration present, that is, there is oxycodone present but it is below the laboratory set cutoff (50 ng/mL)? Has he adulterated or substituted the sample to avoid detection of illicit drug use? A laboratory error is always possible in clinical laboratories that don’t use chain of custody procedures, but this is less likely in this case because it was confirmed negative in 2 separate specimens. I would express my concern about his unexpected test results and ask him in a nonjudgmental way to explain the results.

If he were benefiting but taking less than prescribed, I would inquire about the status and safe storage of his extra medication. I would decrease his dose and schedule close follow-up with random pill counts and UDTs. Prior to sending each urine sample to the laboratory, I would document when he took his last opioid dose.

If there was too much risk (eg, misuse such as diversion) despite benefit, I would discontinue his opioid therapy as was done in this case. There would be no need for an opioid taper in the absence of physical dependence.

QUESTIONS AND COMMENT

QUESTION: How do pill counts work when the patient comes back on the 28th day so by definition they have run out?

DR ALFORD: Follow-up visits with me are not necessarily at the same time that refills are due. Although inconvenient for some patients it’s the best way to ensure medication adherence. Refills are processed in between physician visits with the help of our nursing staff.

QUESTION: How do you respond to patients who say, “It’s not working because you are not giving me enough?”

DR ALFORD: I remind them that not all chronic pain responds to opioids. Initially, if there is inadequate response, I might increase the dose once or twice. Keep in mind that some patients may not report benefit because of fears that the dose will be decreased or stopped or the workup for the cause of their pain will stop. Remind the patient that your goal is not necessarily to stop the medication if it is helping. Another level of complexity is determining how much benefit—pain relief and functional improvement—is enough to justify continued opioid therapy for any given patient. There are times when I believe there is insufficient benefit but the patient disagrees. These uncomfortable conversations go much smoother when I am able to be specific about why I believe there is insufficient benefit based on what the patient has been telling me.

QUESTION: What tips can you offer for treating the patient with addiction and pain?

DR ALFORD: For the patient addicted to nonopioids such as cocaine or marijuana, I discuss how treating them with opioids is too risky because studies show that they are at higher risk of opioid misuse. I recommend that they seek addiction treatment. Although addiction treatment may be hard to access, mutual help groups such as Narcotics Anonymous are effective, widely available, and free. I emphasize that I will only prescribe opioids if the patient is abstinent from illicit drugs. For patients with active opioid addiction, it is too risky to prescribe opioids, so I recommend managing them with nonopioids only. One other option is to refer the patient to a physician qualified to treat opioid addiction (and pain) with buprenorphine.

QUESTION: So even when opioids are given appropriately, the magnitude of improvement is not that big. How do you introduce that to the patient?

DR ALFORD: Setting realistic goals is extremely important before starting (or continuing) opioids and must be readied during therapy. Unrealistic expectations foster repeated requests for limitless dose escalations. Although opioids do not have an analgesic ceiling effect, there seems to be a point of diminishing return at higher doses and the risks such as overdose seem to increase. Unfortunately, patients hold out hope that if the current dose is not helping, they just need more. Educating patients about the limitations of opioids and the risks including opioid-induced hyperalgesia is a difficult yet critical conversation that needs to be reinforced.

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