Los Angeles Times Versus Purdue Pharma: Is 12-Hour Dosing of OxyContin Appropriate?

In a provocative article, writers for the *Los Angeles Times* stated they have evidence that the 12-hour dosing schedule indicated for OxyContin is ineffective in many people and fosters addiction.[1] Purdue Pharma is said to have known about this problem yet continued to promote the 12-hour dosing schedule for financial reasons.

Purdue responded that the *LA Times* disregarded clinical evidence provided to the reporters (by Purdue) supporting 12-hour dosing of OxyContin, and stated that the article was "long on anecdote and short on facts."[2] *LA Times* countered all of the points raised by Purdue.[3]

Practical Pain Management presents excerpts of the claims and responses from both sides (Table, page 20). In addition, our resident opioid expert, Jennifer Schneider, MD, PhD, culled through the *LA Times* article and describes her reaction to the claims made (see Commentary, page 18).

FDA Calls for an Individualized Approach to OxyContin Dosing Schedule

The *LA Times* article included a written statement from Food and Drug Administration (FDA) spokesperson Sarah Peddicord stating, "It should be well understood by physicians that there will be some individual variability in the length of time that patients respond to this drug....While the labeled dosing regimen is a reasonable starting point, physicians should carefully individualize their approach to patients based on how quickly they metabolize the drug."

Practical Pain Management contacted the FDA for a response to article, and was told, "The FDA has no additional comment on this topic."

—Kristin Della Volpe

References

1. Ryan H, Girion L, Glover S. "You want a description of hell?" OxyContin's 12-hour problem. *Los Angeles Times*. http://static.latimes.com/oxycontin-part1/#nt=oft12aH-1gp2. Published May 5, 2016. Accessed May 5, 2016.
2. Purdue Pharma. Setting the record straight on OxyContin's FDA-approved label. May 5, 2016. http://www.purduepharma.com/news-media/get-the-facts/setting-the-record-straight-on-oxycontins-fda-approved-label. Accessed May 6, 2015.
3. Ryan H. Purdue Pharma issues statement on OxyContin report; L.A. Times responds. *Los Angeles Times*. http://static.latimes.com/purdue-response/. Published May 6, 2016. Accessed May 6, 2016.

My Experience With OxyContin 12-Hour Dosing

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Purdue has known for decades that some patients need more frequent dosing of extended-release OxyContin. As a pain specialist, I too have known this for decades. I have certainly observed it in my practice, as have other pain medicine physicians. Many years ago, I learned from other specialists that at least 25% of patients require 8-hour dosing of OxyContin, and at least 25% of those prescribed a Duragesic patch (which contains fentanyl, an opioid that is almost 100 times as powerful as oxycodone) require every-48-hour dosing, rather than the FDA-approved 72-hour dosing interval.[1]

A retrospective chart review presented as a poster at the 2002 annual meeting of the American Pain Society described the dosing intervals at pain clinics for OxyContin, MS Contin, Duragesic, and other opioids. It showed that MS Contin was dosed 3 times a day in 68% of patients, and Duragesic patches were dosed every 48 hours in 23.4% of patients.[2]

The current Purdue package insert for OxyContin demonstrates clearly that the company is aware that OxyContin works in some patients for less than 12 hours and requires additional dosing. It says, "Patients who experience breakthrough pain may require a dosage increase of OxyContin or may need rescue medication with an appropriate dose of an immediate-release analgesic.…There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours."[3]

What this means is that this subgroup of patients either needs to be prescribed an additional immediate-release version of the drug to get them through until the next 12-hour dose is due; an increased dose of OxyContin, which often does last for the longer time frame; or the drug at a shorter interval. None of this is news! The biggest problem for physicians and patients is when insurance plans won't cover every-8-hour dosing of OxyContin or every-48-hour dosing of the Duragesic patch.

Blood Levels

Regarding the cycle of addiction diagram in the *LA Times* article, the variation in blood levels can be prevented if the drug is given at appropriate intervals, which, as stated above, can vary. In fact, providing smoother blood levels rather than the ups and downs shown in that diagram is precisely the benefit of the extended-release formulations of various opioids.

What causes euphoria in the brain is not the quantity of opioid in the bloodstream, but rather how quickly the concentration in the brain's blood vessels increases. It's the rapid increase that causes a high, and in turn makes it more likely that the patient will want more. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, states, "Routes of administration that produce more rapid and efficient absorption into the bloodstream (for example, intravenous injections, smoking, and snorting) tend to result in a more intense intoxication and an increased likelihood of an escalating pattern of substance use leading to withdrawal."[4]

Everyone knows this about marijuana, for example. People using marijuana for its brain effects prefer to smoke it rather than eat marijuana brownies because the active chemical THC (tetrahydrocannabinol) gets into the lungs' blood vessels faster with smoking, and thence into the brain much faster, and produces more psychological effects. The same is true of

immediate-release versus extended-release opioids: immediate-release oxycodone has a much higher street value than does OxyContin (same chemical, but released more slowly into the blood stream, and thus gets into the brain more slowly).

In 2010, when the formulation of OxyContin was changed to a formula that can't be crushed, inhaled, or injected, its street value dropped enormously.[5] In addition, declines in abuse and therapeutic error exposures decreased by 39% and 25%, respectively.

In a 2009 paper on this topic, Charles Argoff, MD, and Daniel I. Silvershein, MD, wrote that there are no high-quality studies showing that at the same total daily dose, extended-release opioids are more effective in reducing pain compared with immediate-release opioids.[6] However, extended-release agents have better adherence, less dose-watching, and result in improved sleep.[6] Immediate-release opioids and extended-release opioids that can be crushed to produce immediate release have greater appeal to abusers[6]

This is exactly why the extended-release formulations are preferred for around-the-clock dosing for chronic pain. Other experts have concurred with this. For example, Richard L. Rauck, MD, stated, "The body of data that supports the role of LAOs [long-acting opioids] in chronic pain management and their beneficial effects on function, as well as quality of life and sleep, is more robust than that for SAO [short-acting opioids]. Whenever possible, it is this author's opinion that LAOs should be considered because less frequent dosing and more consistent pain relief may be associated with better functional outcomes."[7]

It is absolutely not true that the shorter dosing schedule is safer, nor that the 12-hour dosing "fosters" addiction. If a patient reports that efficacy wears off at 8 hours, the next step would be to try an 8-hour dosing regimen. One can start by prescribing the same total daily dose split into 3 doses per day (every 8 hours) rather than 2 per day (every 12 hours). On the contrary, the relatively greater street value of immediate-release formulations than extended-release versions makes the immediate-release drugs much more attractive to abuse and divert.

Too many articles on opioids assume that it's all about addiction and diversion. Health care providers have to do appropriate risk assessment for every chronic pain patient. This should include performing urine drug screens when the patient doesn't expect them; checking each state's online Prescription Drug Monitoring Program, which lists every controlled drug (such as an opioid) that the patient has been prescribed; and checking for "red flags," such as when the patient reports the prescription was lost or stolen or that the patient needs an early refill.

Don't Confuse Addiction With Dependence

It's very common, as it was in the *LA Times* article, to confuse 2 separate concepts: addiction and physical dependence. It's important to note that withdrawal symptoms do not mean the person is addicted; rather, they mean his body has adapted to the drug so that he is physically dependent.

Almost everyone who is on a more than minimal opioid dose for more than a few weeks becomes physically dependent, meaning they will experience withdrawal symptoms. The same thing happens for other drugs that are used a lot in medicine (including corticosteroids such as prednisone, and antidepressants such as paroxetine [Paxil]), and no one thinks that patients on those drugs are addicts if they stop the prednisone or paroxetine suddenly and experience withdrawal symptoms.

About the Author: *Jennifer P. Schneider, MD, PhD, is a physician certified in Internal Medicine, Addiction Medicine, and Pain Management. She is the author of 9 books and numerous articles in professional journals. She is a compassionate professional committed to educating others in her fields of specialty. She is a nationally recognized expert in 2 addiction-related fields: addictive sexual disorders and the management of chronic pain with opioids. For more information on opioid prescribing, please read the following articles in* Practical Pain Management *written by Dr. Schneider:*

- *A Practical Guide for the Use of Opioids in Chronic Pain*
- *Ask the Expert: Pain Persists in Spite of High-Dose Opioids*
- *Opioid Prescribing Part 1: A Practical Guide to Appropriate Documentation*
- *Ask the Expert: Dependence vs. Addiction.*

References

1. Duragesic [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2009.
2. Royal M, Jenson M, Bhakta B, Movva V, Ward S. Retrospective assessment of frequency of dosing of sustained release opiate preparations in chronic pain patients. Poster presented at: 21st Annual Scientific Meeting of the American Pain Society; March 14-17 2002; Baltimore, MD.
3. OxyContin [package insert]. Stamford, CT: Purdue Pharma LP; 2015.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, VA: American Psychiatric Association; 2013:486.
5. Severtson SG, Bartelson BB, Davis JM, et al. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *J Pain*. 2013;14(10):1122-1130.
6. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc*. 2009;84(7):602-612.
7. Rauck RL.What is the case for prescribing long-acting opioids over short-acting opioids for patients with chronic pain? A critical review. *Pain Pract*. 2009;9(6):468-479.

Table. *Los Angeles Times* Versus Purdue Pharma: Excerpts of Responses on Key Issues

Issue	*LA Times* wrote:[1]	Purdue Pharma responded:[2]
Is the evidence reviewed in the article sufficient?	"The *Times* investigation is based on thousands of pages of confidential Purdue documents and other records," in addition to records from the US Food and Drug Administration, Patient Office files, medical journal articles, and interviews with experts.	"Purdue Pharma provided the *LAT* with more than a dozen hours of briefings and discussions regarding the clinical evidence supporting OxyContin's 12-hour dosing and the regulatory requirement that we promote the product as such. Unfortunately, the paper disregarded this information, instead publishing a story that's long on anecdote and short on facts."
Does the 12-hour dosing "problem" referred to by the *LA Times* put patients at risk?	"OxyContin's stunning success masked a fundamental problem: The drug wears off hours early in many people, a *Los Angeles Times* investigation found."	"Nearly a decade ago, the FDA cited a lack of clinical evidence when it formally rejected the 'fundamental premise' that patients receiving OxyContin at intervals more frequent than twice-daily are at increased risk of 'side effects and serious adverse reactions.' In doing so, the agency reinforced the twice-daily labeling for OxyContin. The *LAT* omitted the findings of this report from its story."
Is 12-hour dosing of OxyContin adequate?	"In study after study, many patients given OxyContin every 12 hours would ask for more medication before their next scheduled dose."	"Scientific evidence amassed over more than 20 years, including more than a dozen controlled clinical studies, supports the FDA's approval of 12-hour dosing for OxyContin. The OxyContin label has been updated more than 30 times and at no point did FDA request a change to the dosing frequency. In fact, the FDA-approved label clearly states, 'There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours.'"
Purdue cited that the *LA Times* article claimed, "Purdue should tell physicians to prescribe OxyContin for eight-hour use."	—	"The FDA prohibits pharmaceutical companies from promoting their products for uses, including dosing, not approved by the agency. Given FDA has not approved OxyContin for eight-hour use, we do not recommend that dosing to prescribers. In fact, a state attorney general recently cited a peer company for falsely claiming that OxyContin was an eight-hour drug. The *LAT* omitted this piece of information from its story."
Purdue cited that the article claimed "It's rare for patients to take extended-release drugs at different intervals."	—	"In a 2008 report on OxyContin dosing, the FDA recognized there may be significant 'patient variability' when it comes to opioid-based treatment of pain. The agency also noted that 'it is important that physicians individualize the treatment and dosing for each patient.' The *LAT* omits this finding specific to the use of OxyContin."
Was new information uncovered in this investigation?	"The internal Purdue documents reviewed by the *Times* come from court cases and government investigations and include many records sealed by the courts…. "They remain sealed to this day. The *Times* reviewed thousands of pages of them."	"The *LAT's* claims have not only been publicly voiced, they've been directly rejected by regulatory authorities. This story not only fails to provide the public with the facts about a complex topic, it risks creating more confusion around our national opioid epidemic. For more than a decade, Purdue Pharma has sought to play a constructive role in the fight against opioid abuse, including by reformulating OxyContin with abuse-deterrent properties and leading our industry in this area of innovation. That may be an inconvenient fact for the *LAT*, but it's a fact nonetheless."

LAT, *Los Angeles Times*

	***LA Times* countered:[3]**
	"Purdue executives declined to speak to the *Times* on the record. The company arranged two phone briefings on 12-hour dosing with a Purdue executive, on condition the executive not be quoted and the information not be attributed to Purdue. The *Times* fully considered that information and included in its article the parts that were relevant and could be verified independently. Purdue provided a one-page, on-the-record statement, portions of which are quoted in the story."
	"The Food and Drug Administration decision cited by Purdue did not focus on whether OxyContin lasts 12 hours…. In a petition to the FDA, the Connecticut attorney general said that some doctors were prescribing OxyContin for use every 8 hours, and that this was unsafe and was fueling black-market sales of the drug. The state asked the FDA to add a warning to OxyContin's product label prohibiting prescriptions for anything less than 12 hours. "Purdue opposed the warning. Company lawyers acknowledged…that eight-hour dosing could 'optimize treatment' for some patients and should not be prohibited. Still, the lawyers said, the company planned to continue marketing the painkiller as a 12-hour drug. Among the reasons the company cited was the 'competitive advantage' over painkillers that have to be taken more frequently…. "The FDA rejected the Connecticut petition in 2008. It said physicians should retain the option to prescribe OxyContin at less-than-12-hour intervals to suit patients' needs."
	"Purdue's statement that scientific evidence and clinical studies support 12-hour dosing was included in the article. The *Times* report also describes clinical trials conducted by Purdue that found patients given OxyContin requested more pain medication in between 12-hour doses. In the first clinical trial, more than a third of patients who took OxyContin complained about pain within eight hours, and about half had asked for more medication by the 12-hour mark."
	"The article does not say Purdue should tell physicians to prescribe OxyContin for eight-hour use. Rather, it details evidence that OxyContin does not last 12 hours in many patients, and it describes the potential consequences: withdrawal symptoms and an increased risk of addiction. The article makes clear that Purdue sought and received FDA approval of the painkiller as a 12-hour drug. It also notes that Purdue did not test OxyContin on other dosing schedules, although it could have."
	"The article does not state that it is rare for patients to take extended-release drugs at different intervals. In fact, it makes the opposite point: Many physicians prescribe OxyContin for intervals shorter than 12 hours when patients complain that the effects wear off sooner. The article explained that narcotic painkillers work differently in different people. It included an FDA spokeswoman's statement that 12-hour dosing of OxyContin 'is a reasonable starting point" and that "physicians should carefully individualize their approach to patients based on how quickly they metabolize the drug.'"
	"Much of the information in the article had not previously been published. The article drew on thousands of pages of internal Purdue records, many of which had been sealed by courts at Purdue's request. The article acknowledges instances in which scientists or litigants raised questions about whether OxyContin lasts 12 hours. "Regarding Purdue's efforts to deter abuse of OxyContin by reformulating the pill and funding anti-theft programs, they are described in the article."