

# CHRONIC PAIN: THEIR PAIN OR YOURS?



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## Why Us? The Role of Emergency Physicians in the Care of Chronic Pain

Managing chronic pain is a challenge in the ED. Finding the right balance between too much and too little is key to good patient management.



by JIM DUCHARME, MD, CM, FRCP

The figures are well-established: more than a quarter of people will suffer from chronic pain during their lifetime. It is the disease state with the highest economic impact on society in terms of lost workdays. The average annual family income of patients with chronic pain is less than \$25,000, which is below the poverty line. But why do emergency physicians need to know about chronic pain?

Few physicians among us understand the myriad of pain conditions that fall under the label “chronic pain.” Fewer still recognize the pathologic changes in personality associated with chronic pain as being part of the disease symptom complex, just as peripheral neuropathy is a manifestation of diabetes. Most family physicians are ill-equipped to provide the multidisciplinary care required; most patients cannot afford the paramedical care provided by physiotherapists, psychologists, social workers, etc. Pain management is further complicated by the issues related to opioids—opiophobia, diversion, and addiction—even though only one-third of chronic-pain patients require opioids as part of their care.

The consequence? Chronic-pain patients are poorly understood and poorly treated. As a result of not having their pain properly controlled and not having been taught adequate coping skills, these patients modify their behavior in an attempt to get the physician to provide the necessary care—aberrant behaviour called *pseudoaddiction*. Distinguishing aberrant behavior linked to pseudoaddiction from that associated with true addiction is difficult at best; it may take a pain-medicine expert months to identify the underlying reason for the aberrant behavior. It is almost never possible to do so in an isolated visit to the emergency department.

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**Table 1: Opioid Risk Tool from the Canadian Opioid Guideline**

ITEM	MARK EACH BOX THAT APPLIES	ITEM SCORE IF FEMALE	ITEM SCORE IF MALE
<b>Family History of Substance Abuse</b>			
Alcohol	<input type="checkbox"/>	1	3
Illegal Drugs	<input type="checkbox"/>	2	3
Prescription Drugs	<input type="checkbox"/>	4	4
<b>Personal History of Substance</b>			
Alcohol	<input type="checkbox"/>	3	3
Illegal Drugs	<input type="checkbox"/>	4	4
Prescription Drugs	<input type="checkbox"/>	5	5
<b>Age ( mark box if 16-45)</b>	<input type="checkbox"/>	1	1
<b>History of Preadolescent Sexual Abuse</b>	<input type="checkbox"/>	3	0
<b>Psychological Disease</b>			
Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia	<input type="checkbox"/>	2	2
Depression	<input type="checkbox"/>	1	1
<b>TOTAL</b>			
<b>Total Score Risk Category</b>			
<b>Low Risk:</b> 0 to 3			
<b>Moderate Risk:</b> 4 to 7			
<b>High Risk:</b> 8 and above			

More information is available at <http://nationalpaincentre.mcmaster.ca/opioid>.

**Source:** Furlan AD, Reardon R, Wepler C, for the National Opioid Use Guideline Group (NOUGG). *Opioids for chronic noncancer pain: a new Canadian practice guideline*. CMAJ. 2010;182: 923-930.

The emergency department is the safety net of our system—impoverished patients in pain receiving inadequate (or no) care from a primary-care provider have nowhere else to turn. In the Pain and Emergency Medicine Initiative (PEMI) study involving 18 academic centers across Canada and the United States, 20 percent of patient visits had chronic pain as the *primary* reason for their visit to the emergency department. That is the largest percentage of visits to the emergency department for any one pathology; paradoxically, it is decried by most emergency physicians as a condition that is “not part of emergency medicine.” It is clear the emergency department cannot provide ongoing care to chronic-pain patients any more than it can do so for patients with diabetes. It is equally clear that we must be involved in their care to some degree, just as we are involved to some degree in the care of many patients with a chronic disease—that is the nature of our horizontal specialty. What is our role?

**Caring for patients with chronic pain is part of the ED mandate. Distinguishing them from patients with problems of addiction is difficult, but they are not the same patients and should not be treated similarly.**

**Acute Flare-up of Chronic Pain**

Certain conditions, such as fibromyalgia (FM) or complex regional pain syndrome (CRPS), generate new pain or acute worsening of that pain state. Our role is to first ensure that patients are not suffering from a new acute condition unrelated to their chronic pain condition—the latter does not make them immune to other pathology. Intervening with ketamine in analgesic doses can abort the acute flare-up in CRPS. For patients with FM, reassurance they do not have a new medical problem will usually result in their returning home satisfied, reluctantly accepting that their new pain is, indeed, part of their FM.

**Acute New Pain Pathology**

Patients who take medications for chronic pain (including opioids) require proper pain management just like everyone else when they suffer, for example, an acute fracture. If they already take opioids, they will require their usual daily dose *plus* dosing for their new pain;

often, identifying what their usual PRN dose is will give a starting point for the first dose of opioids in the emergency department, with titration after that. Physicians have to recognize that the doses of opioids required to provide adequate analgesia in chronic-pain patients taking long-term opioids will almost always be higher than the doses we use for patients not taking such opioids.

**Medication Requests**

Patients receiving care from pain physicians require a minimum of two to three *months* to get their pain controlled. Emergency physi-

cians should, therefore, not feel an obligation to provide or initiate a medication for someone’s chronic pain during a single emergency department visit, nor should they feel any urgent need to manage that chronic pain in the emergency department. Patients receiving long-term opioids have an agreement or contract with a primary provider wherein only that provider will prescribe their opioids. If patients were to go to their primary provider and say they had “run out” a few days early, the provider would reiterate that the patients are responsible for their medication usage and not renew the prescription until the next scheduled time

interval. In the emergency department, the physician should restate this “single provider” principle and feel very comfortable declining to provide opioids, all the while offering to help patients in any other way possible.

**Adverse Events or Drug-Drug Interactions**

Most emergency physicians are unfamiliar with either the medications prescribed or the (high) doses prescribed for chronic-pain management. While most physicians will not exceed 75 mg of amitriptyline, for example, patients with neuropathic pain

**Request samples at [Xifaxan550.com/samples](http://Xifaxan550.com/samples)**

**Hepatic Encephalopathy: ARE YOUR PATIENTS LIVING ON THIN ICE?**

Overt hepatic encephalopathy (HE) should be considered in any patient with cirrhosis.<sup>1</sup> Once a cirrhotic patient has developed HE, experts in hepatology recommend maintenance drug therapy to reduce the risk of unpredictable recurrences.<sup>2</sup>

**Treat continuously with a Xifaxan 550 mg pill twice daily**

**58%** proven reduction in the risk of overt HE breakthrough<sup>3\*</sup>

**50%** proven reduction in the risk of HE-related hospitalizations<sup>3††</sup>

The most common adverse reactions occurring (≥12% incidence) in the clinical trial with Xifaxan 550 mg were peripheral edema, nausea, dizziness, and fatigue.<sup>3</sup>

**Xifaxan 550**  
rifaximin 550 mg tablets  
Prescribe. Protect. Repeat.

\*Over a 6-month period; P<0.0001 vs placebo.<sup>3</sup>  
†Over a 6-month period; P=0.0129 vs placebo.<sup>3</sup>  
††HE-related hospitalization defined as hospitalization directly caused by HE or a hospitalization during which an HE event occurred.<sup>3</sup>

**Indication for XIFAXAN 550 mg**  
XIFAXAN® (rifaximin) 550 mg is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients ≥18 years of age.

**Important Safety Information About XIFAXAN 550 mg**  
XIFAXAN® (rifaximin) 550 mg tablets are contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis.

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued.

There is increased systemic exposure in patients with more severe hepatic dysfunction. The clinical trials were limited to patients with MELD scores <25.

Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh C).  
Based on animal data, XIFAXAN may cause fetal harm. Discontinue in nursing mothers after taking into account the importance of the drug to the mother.  
The most common adverse reactions occurring in ≥10% of patients and at a higher incidence than placebo in the clinical study were peripheral edema (15%), nausea (14%), dizziness (13%), fatigue (12%), and ascites (11%).  
Xifaxan 550 mg is not available for sale outside the U.S.  
Xifaxan 550 mg is licensed by Alfa Wassermann S.p.A. to Salix Pharmaceuticals, Inc.

**Please see brief summary on reverse.**

References: 1. Starr SP, Raines D. Cirrhosis: diagnosis, management, and prevention. *Am Fam Physician*. 2011;84(12):1353-1359. 2. Khungar V, Poordad F. Management of overt hepatic encephalopathy. *Clin Liver Dis*. 2012;16(1):73-89. 3. Xifaxan [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc.; 2011.

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may require up to 250 mg. Higher than normal dosing carries a higher risk of adverse events. Another example of risk is seen in patients prescribed methadone for pain or addiction. These patients will have a markedly prolonged QT interval from the methadone. Multiple case reports of sudden death have been reported after patients taking methadone were prescribed a fluoroquinolone. It is critical during the emergency visit that we ensure patients will not suffer from such an adverse event.

Why is abnormally high dosing often required when medications are used to manage

pain? For many patients in pain, their nervous system has undergone “plastification” as a result of the pain. Functional MRI often shows multiple areas of the brain with abnormal function. Be it the development of tolerance with opioids or the higher doses of non-opioid medications required to deactivate abnormal synaptic transmissions, patients with chronic pain often require dosing higher than what may be considered therapeutic for other conditions. These higher doses should not lead to suspicion of misuse or drug dependency but should lead to careful evaluation to identify possible adverse effects.

## Providing Support

In chronic-pain patients who have been properly screened for addiction risk using the Opioid Risk Tool (see Table 1, p. 9), the risk of addiction for those who are scored at low risk is less than 0.2 percent—60 times lower than the general public rate of addiction. When these patients arrive in our emergency departments, they do not know where else to turn. Simply saying “no” is not a solution. Guiding them to support services, advising them of community resources, demonstrating understanding, and educating them on the role of the emergency department in their care are all key roles for emergency phy-

sicians to play. We advise smokers to stop smoking and guide them to programs; we encourage alcoholics to get into detox programs; we advise diabetics about diet, exercise, and community programs—surely, we can do the same for patients with chronic pain.

**Higher than normal dosing carries a higher risk of adverse events. Another example of risk is seen in patients prescribed methadone for pain or addiction. These patients will have a markedly prolonged QT interval from the methadone. Multiple case reports of sudden death have been reported after patients taking methadone were prescribed a fluoroquinolone.**

# Xifaxan 550

rifaximin 550 mg tablets

The following is a brief summary; see complete Prescribing Information at [www.Xifaxan550.com](http://www.Xifaxan550.com).

## INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of XIFAXAN and other antibacterial drugs, XIFAXAN when used to treat infection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## Hepatic Encephalopathy

XIFAXAN 550 mg is indicated for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients  $\geq$  18 years of age.

In the trials of XIFAXAN for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed.

XIFAXAN has not been studied in patients with MELD (Model for End-Stage Liver Disease) scores  $>$  25, and only 8.6% of patients in the controlled trial had MELD scores over 19. There is increased systemic exposure in patients with more severe hepatic dysfunction [see Warnings and Precautions (5.4), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

## CONTRAINDICATIONS

### Hypersensitivity

XIFAXAN is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in XIFAXAN. Hypersensitivity reactions have included exfoliative dermatitis, angioneurotic edema, and anaphylaxis [see Adverse Reactions (6.2)].

## WARNINGS AND PRECAUTIONS

### Travelers' Diarrhea Not Caused by *Escherichia coli*

XIFAXAN was not found to be effective in patients with diarrhea complicated by fever and/or blood in the stool or diarrhea due to pathogens other than *Escherichia coli*. Discontinue XIFAXAN if diarrhea symptoms get worse or persist more than 24-48 hours and alternative antibiotic therapy should be considered.

XIFAXAN is not effective in cases of travelers' diarrhea due to *Campylobacter jejuni*. The effectiveness of XIFAXAN in travelers' diarrhea caused by *Shigella* spp. and *Salmonella* spp. has not been proven. XIFAXAN should not be used in patients where *Campylobacter jejuni*, *Shigella* spp., or *Salmonella* spp. may be suspected as causative pathogens.

### *Clostridium difficile*-Associated Diarrhea

*Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including XIFAXAN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon which may lead to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

## Development of Drug Resistant Bacteria

Prescribing XIFAXAN for travelers' diarrhea in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

## Severe (Child-Pugh C) Hepatic Impairment

There is increased systemic exposure in patients with severe hepatic impairment. Animal toxicity studies did not achieve systemic exposures that were seen in patients with severe hepatic impairment. The clinical trials were limited to patients with MELD scores  $<$  25. Therefore, caution should be exercised when administering XIFAXAN to patients with severe hepatic impairment (Child-Pugh C) [see Use in Specific Populations (8.7), Nonclinical Toxicology (13.2) and Clinical Studies (14.2)].

## ADVERSE REACTIONS

### Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### Hepatic Encephalopathy

The data described below reflect exposure to XIFAXAN 550 mg in 348 patients, including 265 exposed for 6 months and 202 exposed for more than a year (mean exposure was 364 days). The safety of XIFAXAN 550 mg taken two times a day for reducing the risk of overt hepatic encephalopathy recurrence in adult patients was evaluated in a 6-month placebo-controlled clinical trial (n = 140) and in a long term follow-up

study (n = 280). The population studied had a mean age of 56.26 (range: 21-82) years; approximately 20% of the patients were  $\geq$  65 years old, 61% were male, 86% were White, and 4% were Black. Ninety-one percent of patients in the trial were taking lactulose concomitantly. All adverse reactions that occurred at an incidence  $\geq$  5% and at a higher incidence in XIFAXAN 550 mg-treated subjects than in the placebo group in the 6-month trial are provided in Table 2. (These include adverse events that may be attributable to the underlying disease).

**Table 1: Adverse Reactions Occurring in  $\geq$  5% of Patients Receiving XIFAXAN and at a Higher Incidence Than Placebo**

MedDRA Preferred Term	Number (%) of Patients	
	XIFAXAN Tablets 550 mg TWICE DAILY N = 140	Placebo N = 159
Edema peripheral	21 (15%)	13 (8%)
Nausea	20 (14%)	21 (13%)
Dizziness	18 (13%)	13 (8%)
Fatigue	17 (12%)	18 (11%)
Ascites	16 (11%)	15 (9%)
Muscle spasms	13 (9%)	11 (7%)
Pruritus	13 (9%)	10 (6%)
Abdominal pain	12 (9%)	13 (8%)
Abdominal distension	11 (8%)	12 (8%)
Anemia	11 (8%)	6 (4%)
Cough	10 (7%)	11 (7%)
Depression	10 (7%)	8 (5%)
Insomnia	10 (7%)	11 (7%)
Nasopharyngitis	10 (7%)	10 (6%)
Abdominal pain upper	9 (6%)	8 (5%)
Arthralgia	9 (6%)	4 (3%)
Back pain	9 (6%)	10 (6%)
Constipation	9 (6%)	10 (6%)
Dyspnea	9 (6%)	7 (4%)
Pyrexia	9 (6%)	5 (3%)
Rash	7 (5%)	6 (4%)

The following adverse reactions, presented by body system, have also been reported in the placebo-controlled clinical trial in greater than 2% but less than 5% of patients taking XIFAXAN 550 mg taken orally two times a day for hepatic encephalopathy. The following includes adverse events occurring at a greater incidence than placebo, regardless of causal relationship to drug exposure.

### Ear and Labyrinth Disorders: Vertigo

**Gastrointestinal Disorders:** Abdominal pain lower, abdominal tenderness, dry mouth, esophageal variceal bleed, stomach discomfort

**General Disorders and Administration Site Conditions:** Chest pain, generalized edema, influenza like illness, pain NOS

**Infections and Infestations:** Cellulitis, pneumonia, rhinitis, upper respiratory tract infection NOS

**Injury, Poisoning and Procedural Complications:** Contusion, fall, procedural pain

**Investigations:** Weight increased

**Metabolic and Nutritional Disorders:** Anorexia, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hyponatremia

**Musculoskeletal, Connective Tissue, and Bone Disorders:** Myalgia, pain in extremity

**Nervous System Disorders:** Amnesia, disturbance in attention, hypoesthesia, memory impairment, tremor

**Psychiatric Disorders:** Confusional state

**Respiratory, Thoracic, and Mediastinal Disorders:** Epistaxis

**Vascular Disorders:** Hypotension

## Postmarketing Experience

The following adverse reactions have been identified during post approval use of XIFAXAN. Because these reactions are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to XIFAXAN.

### Infections and Infestations

Cases of *C. difficile*-associated colitis have been reported [see Warnings and Precautions (5.2)].

### General

Hypersensitivity reactions, including exfoliative dermatitis, rash, angioneurotic edema (swelling of face and tongue and difficulty swallowing), urticaria, flushing, pruritus and anaphylaxis have been reported. These events occurred as early as within 15 minutes of drug administration.

## DRUG INTERACTIONS

*In vitro* studies have shown that rifaximin did not inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 at concentrations ranging from 2 to 200 ng/mL [see Clinical Pharmacology (12.3)]. Rifaximin is not expected to inhibit these enzymes in clinical use.

An *in vitro* study has suggested that rifaximin induces CYP3A4 [see Clinical Pharmacology (12.3)]. However, in patients with normal liver function, rifaximin at the recommended dosing regimen is not expected to induce

CYP3A4. It is unknown whether rifaximin can have a significant effect on the pharmacokinetics of concomitant CYP3A4 substrates in patients with reduced liver function who have elevated rifaximin concentrations.

An *in vitro* study suggested that rifaximin is a substrate of P-glycoprotein. It is unknown whether concomitant drugs that inhibit P-glycoprotein can increase the systemic exposure of rifaximin [see Clinical Pharmacology (12.3)].

## USE IN SPECIFIC POPULATIONS

### Pregnancy

#### Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Rifaximin has been shown to be teratogenic in rats and rabbits at doses that caused maternal toxicity. XIFAXAN tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of rifaximin to pregnant rats and rabbits at dose levels that caused reduced body weight gain resulted in eye malformations in both rat and rabbit fetuses. Additional malformations were observed in fetal rabbits that included cleft palate, lumbar scoliosis, brachygnathia, interventricular septal defect, and large atrium.

The fetal rat malformations were observed in a study of pregnant rats administered a high dose that resulted in 16 times the therapeutic dose to diarrheic patients or 1 times the therapeutic dose to patients with hepatic encephalopathy (based upon plasma AUC comparisons). Fetal rabbit malformations were observed from pregnant rabbits administered mid and high doses that resulted in 1 or 2 times the therapeutic dose to diarrheic patients, based upon plasma AUC comparisons.

Post-natal developmental effects were not observed in rat pups from pregnant/lactating female rats dosed during the period from gestation to Day 20 post-partum at the highest dose which resulted in approximately 16 times the human therapeutic dose for travelers' diarrhea (based upon AUCs) or approximately 1 times the AUCs derived from therapeutic doses to patients with hepatic encephalopathy.

### Nursing Mothers

It is not known whether rifaximin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from XIFAXAN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

The safety and effectiveness of XIFAXAN 200 mg in pediatric patients with travelers' diarrhea less than 12 years of age have not been established. The safety and effectiveness of XIFAXAN 550 mg for HE have not been established in patients  $<$  18 years of age.

### Geriatric Use

Clinical studies with rifaximin 200 mg for travelers' diarrhea did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger subjects. In the controlled trial with XIFAXAN 550 mg for hepatic encephalopathy, 19.4% were 65 and over, while 2.3% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### Renal Impairment

The pharmacokinetics of rifaximin in patients with impaired renal function has not been studied.

### Hepatic Impairment

Following administration of XIFAXAN 550 mg twice daily to patients with a history of hepatic encephalopathy, the systemic exposure (i.e., AUC<sub>0-24</sub>) of rifaximin was about 10-, 13-, and 20-fold higher in those patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively, compared to that in healthy volunteers. No dosage adjustment is recommended because rifaximin is presumably acting locally. Nonetheless, caution should be exercised when XIFAXAN is administered to patients with severe hepatic impairment [see Warnings and Precautions (5.4), Clinical Pharmacology (12.3), Nonclinical Toxicology (13.2), and Clinical Studies (14.2)].

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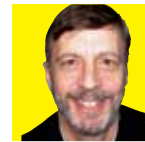
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# A Rational Approach to the Opioid-Seeking Patient

by JIM DUCHARME, MD, CM, FRCP

## Drug Diversion and Abuse Is a Major Societal Problem

In 2012, an estimated 23.9 million Americans age 12 or older—or 9.2 percent of the population—had used an illicit drug or abused a psychotherapeutic medication (such as a pain reliever, stimulant, or tranquilizer) in the past month ([www.drugabuse.gov/publications/drug-facts/nationwide-trends](http://www.drugabuse.gov/publications/drug-facts/nationwide-trends)). Marijuana is the gateway drug. Despite being declared by many to be a benign recreational drug, the odds of going on to addictive drugs such as opioids or methamphetamine are 140 times greater for those having used marijuana than having not used it. Despite the publicity of the rise in misuse of prescription opioids, the 25 percent increase in marijuana use since 2007 is the largest increase for any category of drugs of abuse. Nevertheless, prescription opioids are now fourth behind marijuana, alcohol, and cigarettes in prevalence of abuse among adolescents. They rank second behind marijuana in terms of

rate of abuse in society. Given their much greater risk of morbidity and mortality, as well as the association with organized crime, the growing misuse of prescription opioids has created ever-increasing concern.

## Chronic Non-Cancer Pain Management Is Failing Miserably

It is the complex disease state with the highest prevalence in society, has the highest economic impact on the workforce, and results in poverty-level existence for the average family that has someone suffering from it. Unable to pay for the multidisciplinary care required, more than 90 percent of patients with chronic non-cancer pain (CNCN) receive inadequate care for their pain. Lacking any other resource, many CNCN patients turn to the ED. This specific issue was addressed in the previous article, “Why Us? The Role of Emergency Physicians in the Care of Chronic Pain” (*ACEP Now*, January 2014, p. 9).

**Emergency physicians believe we can identify people coming to the ED for addiction or diversion, but this is not true.**

## Oligoanalgesia Rampant Across Health Care

Education in medical schools about pain management is less than one-third of similar training in veterinary schools. There is even less education about addiction and how to interact with people suffering from personality disorders. The average physician enters practice undereducated and

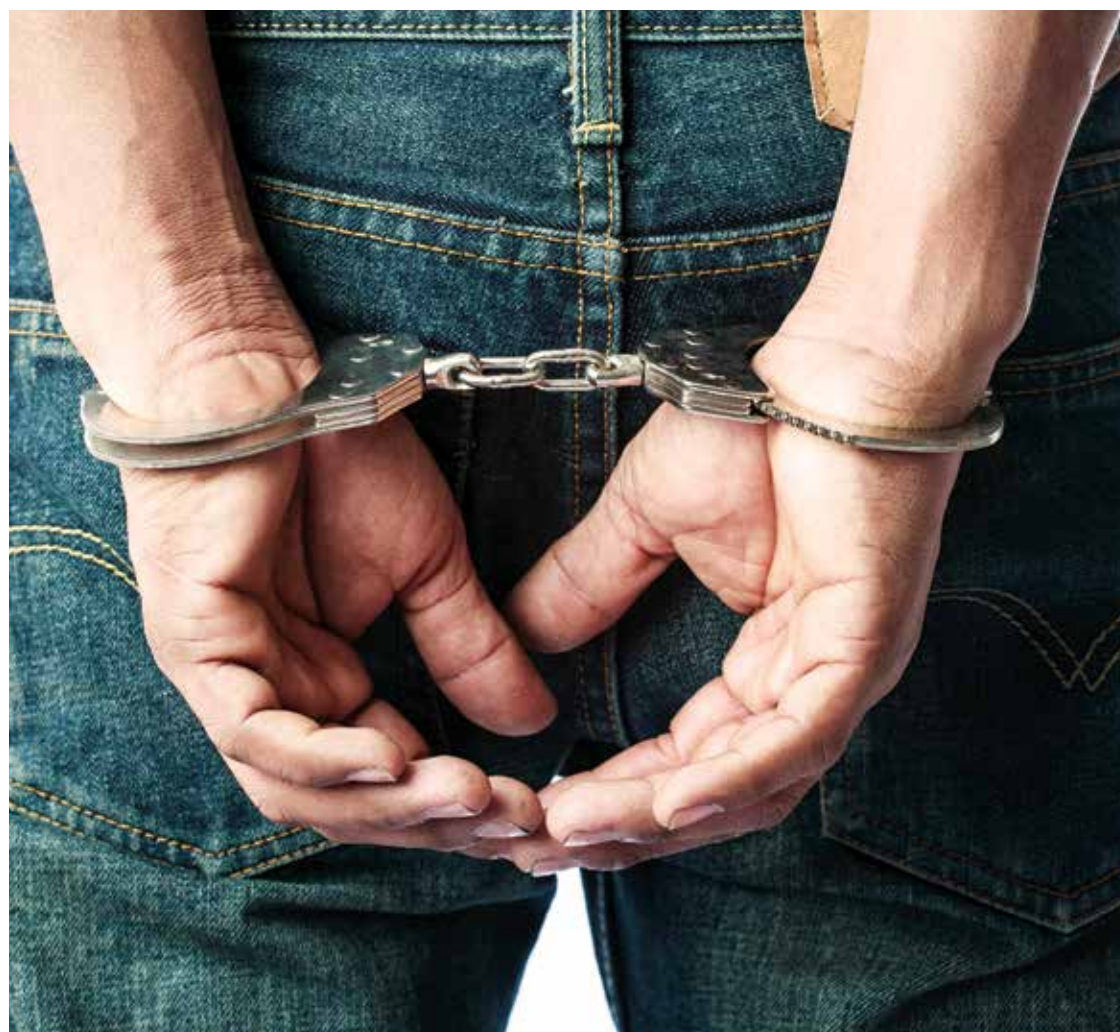
ill-equipped to deal with any of the very difficult situations described above. The natural reaction to this lack of preparation is to be defensive and overly suspicious and find encounters with patients seeking opioids to be emotional and stressful. It's hoped this article can provide some suggestions about a rational approach to such patients to minimize that stress and avoid confrontations while meeting patient needs.

## Distinguishing People in Pain Seeking Opioids from People Seeking Opioids for Addiction or Diversion

Patients with pain as their primary complaint represent up to 75–80 percent of emergency patients. After 7 p.m., up to 70 percent of motor vehicle collisions are related to alcohol use. Similarly, the prevalence of patients with addiction as a medical disorder rises in patients presenting to the ED after 7 p.m. Even in inner-city hospitals at night, the ratio of patients in pain to those with addiction or diversion issues remains greater than three-to-one. The age of the patient is not of value; people visiting the ED for opioid abuse come from all age groups, including young children (Center for Behavioral Health Statistics and Quality, SAMHSA, Drug Abuse Warning Network, 2009).

Emergency physicians believe we can identify people coming to the ED for addiction or diversion, but *this is not true*. In a case-controlled study, 21 percent of patients requesting analgesia and 13 percent of controls tested positive for drug addiction using the DAST-20 survey (of those who agreed to participate). There was no correlation between the pain score and the DAST score. Almost one-half of patients scoring positive for addiction had a history of multiple ED visits and requests for specific opiates or “allergies” to opiates—but *more than half did not*. (*California J EM*. 2005;6:3-8). This inability to identify such patients usually results in labeling all patients seeking pain relief or requesting analgesics as “opioid seekers” for diversion rather than people suffering from inadequate pain management.

In my next column, I will discuss standardizing the ED approach to patients seeking opioids. ☛



## CHRONIC PAIN: THEIR PAIN OR YOURS?



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# Standardizing Our Approach to Patients Seeking Opioids: Part 2

A test positive for cocaine is a true positive for that drug—and no patients testing positive for cocaine should receive opioids. Patients stating they have a prescription for an opioid but who test negative for that opioid should raise concern about diversion.

by JIM DUCHARME, MD, CM, FRCP

Last time, we explored the research and statistics on pain management and opioid addiction (ACEP Now March, p. 22). In this column, we will explore some standard strategies to use when patients seek opioids in the ED.

In the management of chronic non-cancer pain (CNCP), the current recommendation is to use “universal precautions” for all patients. Just as we assume in the ED that any patient might have a blood-borne pathogen and so we take universal precautions, the baseline assumption in chronic pain is that anyone can be at risk for diversion or addiction. This does not mean that no patients receive an opioid for pain care; rather, it means that a standardized approach is used for all patients. This type of approach can be used in the ED.

A 37-year-old male presents at 2 am on a Saturday complaining of dental pain and insisting on getting some “Percs” for his pain. What to do?

- **Offer a valid alternative.** Dental pain can be severe, and it cannot tell time. During working hours, such patients can get to a dentist, but such service is not available in the middle of the night. Rates of addiction are higher, and there is no way to test objectively for pain. To ensure pain is addressed while also allaying any concerns over diversion, the best option is to offer a dental block with bupivacaine. The anesthetic will last six to eight hours and allow patients to see a dentist in the morning; it is a valid analgesic approach to opioids. You should raise, in a nonconfrontational manner, your suspicions of nonmedical use of opioids with any patients who refuse such therapy and offer to provide support for substance abuse if they admit to that problem. Invalidated concerns of misuse do not mean no management of pain; they mean that the pain should be properly managed with alternatives to opioids. Do not allow patients to suffer because of our (unjustified) suspicions.



- **Establish the risk of abuse or diversion.** The Opioid Risk Tool is an excellent screening tool for establishing risk of abuse and can be done in one to two minutes. Low-risk patients have less than 0.2 percent risk of abuse.

- **Consider a urine drug screen.** While urine drug screening has many limitations in assessing patients with psychiatric disorders or with altered mental status, it can be of value in patients seeking opioids. A test positive for cocaine is a true positive for that drug—and no patients testing positive for cocaine should receive opioids. Patients stating they have a prescription for an opioid but who test negative for that opioid should raise concern about diversion. Further discussion is required before any consideration of opioids for such patients.

A 44-year-old woman with 10 years of low-back pain and who states she takes a sustained-release morphine preparation (and has done so for four years) comes to the ED saying she has “run out” and needs some pills for the next three days until her doctor gets back in town.

- **Avoid giving a short-acting opioid in the ED.** Injections of short-acting opioids can lead to acceleration of tolerance and create institutional dependency, worsening catastrophizing. There is no upside to this prac-

tice. If patients who take opioids for chronic pain have a new pathology requiring additional opioids, the best approach is a PCA pump that is locked—inadequate pain relief in these situations increases risk of abuse in previously stable patients.

- **Do not prescribe opioids at discharge.** Patients on long-term opioids have an identified primary prescriber and should have their opioids prescribed only by that provider. They should not receive a prescription to “hold them over” until they see their caregiver; they would receive the identical response from their primary prescriber if they presented before their scheduled appointment and asked for additional opioids. Several guidelines suggest that if you do choose to provide opioids at discharge, it should be a dose with which you are comfortable in a quantity that suffices until the next business day. Even if this option is chosen, it should never be repeated a second time.
- **Make use of any existing state drug database.** This is the only practical way to identify double doctoring and dates of prescriptions. This has had a dramatic effect on physicians’ ability to identify patients seeking additional prescriptions and allows for a “level playing field” in the discussion with patients.

### Avoid Labelling Patients or Turning Them Away

Patients with addiction disorders have a medical condition requiring care, just as do alcoholics and smokers. It is part of our mandate to identify this condition and offer support. Patients who use drugs intravenously are at high risk for serious infections; addicts are always at risk for overdose or acute withdrawal. Placing signs in the waiting room advising patients that opioid prescriptions are not renewed not only breaches EMTALA regulations but risks turning away very sick patients (with an addiction disorder) who feel they will not be cared for. It also encourages patients in severe pain to leave without receiving care.

Patients with an addiction disorder are not immune to painful conditions. They are not mutually exclusive. Identifying patients as addicts or “drug seeking” often precludes any further consideration of comorbidity. Addiction is but one medical condition, just as is diabetes, and does not prevent the presence of a second illness. To the contrary, they are *more* at risk because of their primary condition.

### A Final Suggestion

Most people with personality disorders have less refined interpersonal social skills. They succeed in getting what they want through more obvious manipulation, such as overpraising or creating feelings of guilt or anger. Every physician has to recognize that such feelings are not normal during a patient encounter and should be recognized for what they are: manipulation by the patient. Rather than reacting to those emotions, the physician should recognize them as a sign of a personality disorder and respond accordingly with no emotional responses and the establishment of limits for that encounter. A typical response could be: “I understand that you say you are in a lot of pain. I am going to do everything I can to help you get that pain under control now and after discharge. What I am not able to do, however, is provide opioids for this particular situation. I am certain that we will still be able to take steps to get your pain better controlled.” ☺

# CHRONIC PAIN: THEIR PAIN OR YOURS?



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## Decriminalizing Chronic Pain: How to Approach Those Without Adequate Follow Up

by JIM DUCHARME, MD, CM, FRCP

**SCENARIO 1:** Mr. Smith is a 42-year-old male who has come to the ED because he is in severe pain from a chronic low back condition lasting at least 10 years. He cannot stand upright. He moved into town when his company closed two months ago so he could stay with his sister. He is unemployed. He says his meds—duloxetine, tramadol, and celecoxib—are running out. There is no pain clinic in the community, and he has no family physician.

**SCENARIO 2:** Mrs. Smith is a 51-year-old female with 15 years of chronic neuropathic leg pain. She has been discharged by her family physician because her urine tested positive for cocaine twice—she admits this because she is desperate to get care. The physician rapidly tapered her off opioids (in 10 days), and she has just finished a horrible week of withdrawal. She comes into the ED with severe pain and has no analgesic prescriptions.

These types of scenarios are not rare in emergency medicine. After all, we are the safety net for health care. Patients with varying types of chronic medical conditions and nowhere else to go end up in the

emergency department and are routinely seen in county hospitals. Emergency physicians have had no training in any chronic medical condition, including chronic pain with its inherent biases and risks of opioid misuse. Just as we do not provide ongoing care for patients with insulin-dependent diabetes, we should not provide ongoing care for patients with chronic pain. There is a difference, however: patients with the former can continue to receive insulin and can often be cared for in hospital or community clinics, whereas the latter are shunned. Further, emergency phy-

sicians have received zero training in chronic pain and so often have a starting viewpoint that this is “not our problem.”

When you talk to patients with chronic pain who have been successfully managed, they will usually state how they have learned to deal with their problem and how their coping skills have improved. They will tell you that medications ultimately played a minor role—essential for getting the pain under control at the start but less important as other steps are taken. The American Pain Society will tell you that mindfulness is an essential primary aspect of care for

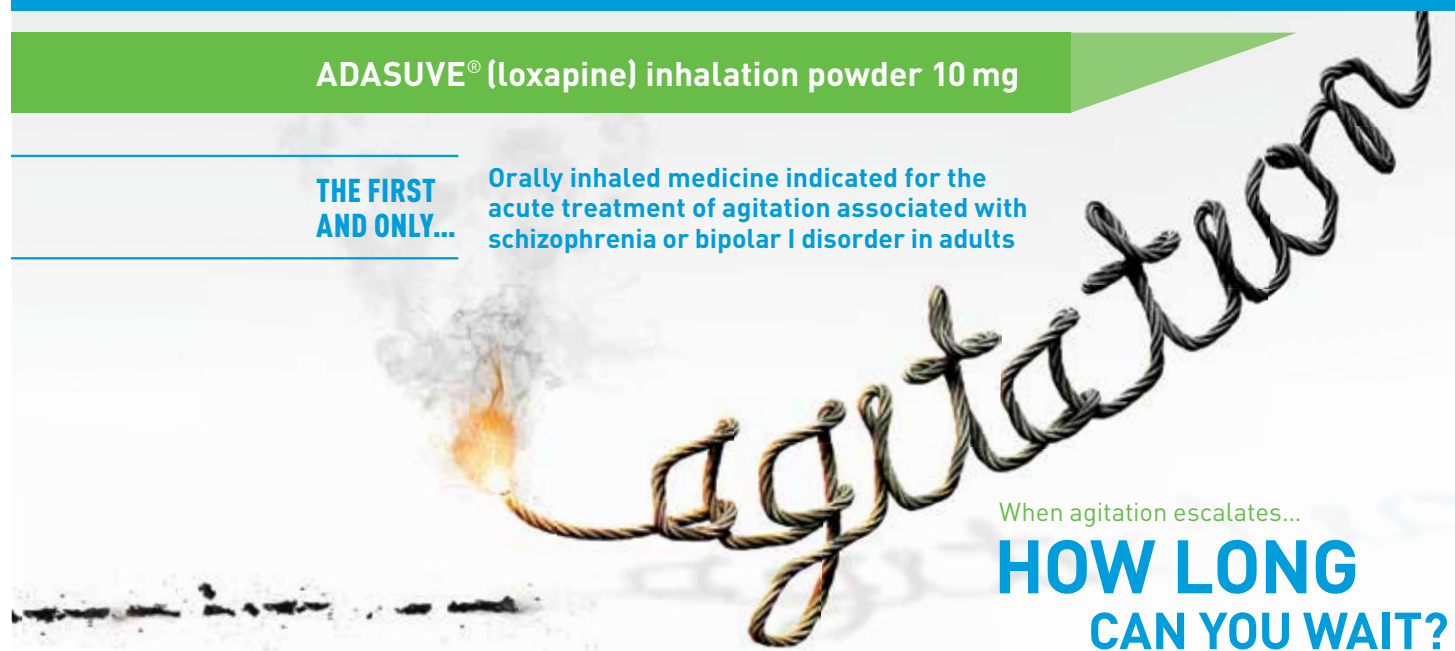
these patients. Patients with fibromyalgia will experience a 75 percent decrease in pain if they complete and maintain a four-day-a-week exercise program for at least four to six weeks. How does this help us in the ED? We need to sit down with these patients and help them review how they are in charge of their illness; dependency on others is a sign of failure. Specifically, areas patients need to work on include:

1. Learning about their illness/condition. We need to help educate them about the (minimal) role of the ED as well as what their condition is and why they have pain.

### ADASUVE® (loxapine) inhalation powder 10 mg

THE FIRST AND ONLY...

Orally inhaled medicine indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults



When agitation escalates...

**HOW LONG CAN YOU WAIT?**

#### INDICATIONS AND USAGE

ADASUVE® (loxapine) inhalation powder, for oral inhalation use, is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Efficacy was demonstrated in 2 trials in acute agitation: one in schizophrenia and one in bipolar I disorder.

**Limitations of Use:** As part of the ADASUVE Risk Evaluation and Mitigation Strategy (REMS) Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility.

#### ▲ IMPORTANT SAFETY INFORMATION

##### WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

###### Bronchospasm

**ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation). Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE. Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS.**

###### Increased Mortality in Elderly Patients With Dementia-Related Psychosis

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of patients with dementia-related psychosis.**

- ADASUVE is contraindicated in patients with the following:
  - Current diagnosis or history of asthma, chronic obstructive pulmonary disease (COPD), or other lung disease associated with bronchospasm
  - Acute respiratory signs/symptoms (eg, wheezing)
  - Current use of medications to treat airways disease, such as asthma or COPD
  - History of bronchospasm following ADASUVE treatment
  - Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine
- ADASUVE must be administered only by a healthcare professional
- Prior to administration, all patients must be screened for a history of pulmonary disease and examined (including chest auscultation) for respiratory abnormalities (eg, wheezing)
- Administer only a single 10 mg dose of ADASUVE within a 24-hour period by oral inhalation using the single-use inhaler

2. Developing coping skills. Catastrophizing, social isolation, and despair all lead to marked worsening of the pain. Dealing with flare-ups in their pain by coming to the ED demonstrates a failure to understand their condition and how to deal with the worse days. You might want to ask a social worker to get involved for this discussion, as well.

3. Learning what the community has to offer. That means the staff in the ED needs to know what is available: social work, support groups for fibromyalgia, etc.

It is my experience that this type of discussion rarely takes more than 10 to 15 minutes and is worth every minute. If we do not take the time to explain their responsibilities and

**We are all responsible for every script we write. No physician in the ED should initiate opioids for patients with chronic pain, renew prescriptions of opioids for such patients, or provide short-acting opioids to “get them out of the ED.”**



the role of the ED, these patients will keep returning, expecting to get a prescription and developing an ever-increasing institutional dependency—a poor coping trait and a growing burden on the ED.

#### Managing Medications

We are all responsible for every script we write. No physician in the ED should initiate opioids for patients with chronic pain, renew prescriptions of opioids for such patients,

or provide short-acting opioids to “get them out of the ED.” The latter creates institutional dependency and also accelerates tolerance. There is no positive for patients other than

**CONTINUED** on page 14

**ADASUVE® (loxapine) inhalation powder**  
**HELP DEFUSE THE SITUATION BEFORE**  
**AGITATION ESCALATES FURTHER**



#### ORAL INHALATION

Breath-actuated, single-use, ready-to-use inhaler<sup>1</sup>



For more information about ADASUVE, visit [ADASUVE.COM](http://ADASUVE.COM)

For REMS Program information, visit [ADASUVEREMS.COM](http://ADASUVEREMS.COM) or call 855-755-0492



#### FAST ONSET

Statistically significant reduction in agitation at **2 hours**, with improvement rapidly achieved at **10 minutes** post-dose<sup>1</sup>

Reduction from baseline in agitation symptoms<sup>2,3</sup>

ENDPOINT	SCHIZOPHRENIA		BIPOLAR I DISORDER	
	ADASUVE	PLACEBO	ADASUVE	PLACEBO
AT 2 HOURS (PRIMARY)	49%	33%	53%	27%
AT 10 MINUTES (SECONDARY)	19%	10%	23%	10%

The mean baseline PEC scores in all treatment groups were 17.3 to 17.7.

**PEC**—Positive and Negative Syndrome Scale—Excited Component. Intent-to-treat population with last observation carried forward. Agitation symptoms measured: tension, excitement, poor impulse control, uncooperativeness, hostility. Each item is scored on a scale from 1 to 7 (1=absent, 4=moderate, 7=extreme). Patient total PEC scores ranged from 14 to 31 out of a possible 35. The efficacy of ADASUVE 10 mg in the acute treatment of agitation associated with schizophrenia or bipolar I disorder was established in a short-term (24-hour), randomized, double-blind, placebo-controlled, fixed-dose trial including 344 patients who met DSM-IV criteria for schizophrenia and in another study, 314 patients who met DSM-IV criteria for bipolar I disorder, manic or mixed episodes with or without psychotic features.

#### ▲ IMPORTANT SAFETY INFORMATION (continued)

- After ADASUVE administration, patients must be monitored for signs and symptoms of bronchospasm at least every 15 minutes for at least 1 hour
- ADASUVE can cause sedation, which can mask the symptoms of bronchospasm
- Antipsychotic drugs can cause a potentially fatal symptom complex called Neuroleptic Malignant Syndrome (NMS), manifested by hyperpyrexia, muscle rigidity, altered mental state, irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia. Associated features can include escalated serum creatine phosphokinase (CPK) concentration, rhabdomyolysis, elevated serum and urine myoglobin concentration, and renal failure. If NMS occurs, immediately discontinue antipsychotic drugs and other drugs that may contribute to the underlying disorder, monitor and treat symptoms, and treat any concomitant serious medical problems
- ADASUVE can cause hypotension, orthostatic hypotension, and syncope. Use with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that would predispose patients to hypotension. In the presence of severe hypotension requiring vasopressor therapy, epinephrine should not be used
- Use ADASUVE with caution in patients with a history of seizures or with conditions that lower the seizure threshold. ADASUVE lowers the seizure threshold. Seizures have occurred in patients treated with oral loxapine and can also occur in epileptic patients
- Use caution when driving or operating machinery. ADASUVE can impair judgment, thinking, and motor skills
- The potential for cognitive and motor impairment is increased when ADASUVE is administered concurrently with other CNS depressants
- Treatment with antipsychotic drugs caused an increased incidence of stroke and transient ischemic attack in elderly patients with dementia-related psychosis; ADASUVE is not approved for the treatment of patients with dementia-related psychosis
- Use of ADASUVE may exacerbate glaucoma or cause urinary retention
- The most common adverse reactions (incidence ≥2% and greater than placebo) in clinical studies in patients with agitation treated with ADASUVE were dysgeusia, sedation, and throat irritation
- Pregnancy Category C. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk of extrapyramidal and/or withdrawal symptoms after delivery. ADASUVE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
- Nursing mothers: Discontinue drug or nursing, taking into account the importance of the drug to the mother
- The safety and effectiveness of ADASUVE in pediatric patients have not been established

**References:** 1. ADASUVE [package insert]. Horsham, PA: Teva Select Brands, a division of Teva Pharmaceuticals USA, Inc.; December 2013.  
2. Data on file. Clinical Study Report 004-301. Teva Pharmaceuticals. 3. Data on file. Clinical Study Report 004-302. Teva Pharmaceuticals.

Please see Brief Summary of Prescribing Information, including Boxed Warnings, on following pages.



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**adasuve**  
(loxapine) inhalation powder

perhaps a two-hour decrease in pain, a pain they have had for years. Opioids should be reserved in opioid-dependent patients for acute breakthrough pain or for acute new injuries or conditions, such as a new fracture.

Other medications for pain, such as a tricyclic or gabapentinoid for new zoster-related neuropathic pain, may be of benefit and worth initiating. A SSRI, such as duloxetine for chronic osteoarthritis or low back pain, combined with acetaminophen or a NSAID may provide valid relief. Patients can follow up in a medical clinic without fear of bias and start on the long road to stabilization. We do the same for patients with hypertension, so why not for chronic pain? To do so, however, means we

## It is not our role to care for them on an ongoing basis but to educate them and start them in the right direction.

have to learn more about chronic pain conditions and the medications and doses required. Dosing for chronic pain may be very different than for other indications, for example:

- 300 mg gabapentin a day for seizure disorders but up to 3,600 mg for pain
- 25–75 mg nortriptyline for depression but

up to 250 mg for neuropathic pain. Still, all patients with chronic pain are treated the same way with medications: “start low and go slow,” avoiding adverse effects and identifying the lowest effective dose possible. The starting dose you are comfortable prescribing will be the same starting dose a

pain physician would use, but they then take up to three months to get to the right dose and combination of medications.

It is up to the ED group as a whole to work with the hospital and community to identify potential resources for patients with chronic pain; that way, the nursing staff and the physicians can guide the patients properly. It is not our role to care for them on an ongoing basis but to educate and start them in the right direction. We are also there for acute worsening of their pain and to identify other pathologies as causes of new or worsening pain. In the end, our role for patients with chronic pain is almost the same as for every other chronic medical condition. ☛

### BRIEF SUMMARY

#### ADASUVE® (loxapine) inhalation powder, for oral inhalation use

The following is a brief summary only; see full prescribing information, included Boxed Warnings for complete product information.

#### WARNING: BRONCHOSPASM and INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

##### Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [see Warnings and Precautions (5.1, 5.2)]. Prior to administering ADASUVE, screen patients regarding a current diagnosis, history, or symptoms of asthma, COPD and other lung diseases, and examine (including chest auscultation) patients for respiratory signs. Monitor for signs and symptoms of bronchospasm following treatment with ADASUVE [see Dosage and Administration (2.2, 2.4) and Contraindications (4)].

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ADASUVE REMS [see Warnings and Precautions (5.2)].

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**  
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ADASUVE is not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.3)].

### 1 INDICATIONS AND USAGE

ADASUVE is a typical antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. “Psychomotor agitation” is defined in DSM-IV as “excessive motor activity associated with a feeling of inner tension.” Patients experiencing agitation often manifest behaviors that interfere with their care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior), leading clinicians to the use of rapidly absorbed antipsychotic medications to achieve immediate control of the agitation [see Clinical Studies (14)]. The efficacy of ADASUVE was established in one study of acute agitation in patients with schizophrenia and one study of acute agitation in patients with bipolar I disorder [see Clinical Studies (14)].

#### Limitations of Use:

As part of the ADASUVE REMS Program to mitigate the risk of bronchospasm, ADASUVE must be administered only in an enrolled healthcare facility [see Warnings and Precautions (5.2)].

### 4 CONTRAINDICATIONS

ADASUVE is contraindicated in patients with the following:

- Current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm [see Warnings and Precautions (5.1)]
- Acute respiratory symptoms or signs (e.g., wheezing) [see Warnings and Precautions (5.1)]
- Current use of medications to treat airways disease, such as asthma or COPD [see Warnings and Precautions (5.1)]
- History of bronchospasm following ADASUVE treatment [see Warnings and Precautions (5.1)]
- Known hypersensitivity to loxapine or amoxapine. Serious skin reactions have occurred with oral loxapine and amoxapine.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Bronchospasm

ADASUVE can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest [see Adverse Reactions (6.1)]. Administer ADASUVE only in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation and mechanical ventilation) [see Boxed Warning and Warnings and Precautions (5.2)].

Prior to administering ADASUVE, screen patients regarding a current diagnosis or history of asthma, COPD, and other lung disease associated with bronchospasm, acute respiratory symptoms or signs, current use of medications to treat airways disease, such as asthma or COPD; and examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing) [see Dosage and Administration (2.2) and Contraindications (4)]. Monitor patients for symptoms and signs of bronchospasm (i.e., vital signs and chest auscultation) at least every 15 minutes for a minimum of one hour following treatment with ADASUVE [see Dosage and Administration (2.4)]. ADASUVE can cause sedation, which can mask the symptoms of bronchospasm.

Because clinical trials in patients with asthma or COPD demonstrated that the degree of bronchospasm, as indicated by changes in forced expiratory volume in 1 second (FEV1), was greater following a second dose of ADASUVE, limit ADASUVE use to a single dose within a 24 hour period. Advise all patients of the risk of bronchospasm. Advise them to inform the healthcare professional if they develop any breathing problems such as wheezing, shortness of breath, chest tightness, or cough following treatment with ADASUVE.

#### 5.2 ADASUVE REMS to Mitigate Bronchospasm

Because of the risk of bronchospasm, ADASUVE is available only through a restricted program under a REMS called the ADASUVE REMS. [see Boxed Warning and Warnings and Precautions (5.1)] Required components of the ADASUVE REMS are:

- Healthcare facilities that dispense and administer ADASUVE must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site access to equipment and personnel trained to provide advance airway management, including intubation and mechanical ventilation.
- Wholesalers and distributors that distribute ADASUVE must enroll in the program and distribute only to enrolled healthcare facilities.

Further information is available at [www.adasuverems.com](http://www.adasuverems.com) or 1-855-755-0492.

#### 5.3 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the cases of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies can be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ADASUVE is not approved for the treatment of elderly patients with dementia-related psychosis [see Boxed Warning].

#### 5.4 Neuroleptic Malignant Syndrome

Antipsychotic drugs can cause a potentially fatal symptom complex termed Neuroleptic Malignant Syndrome (NMS). Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Associated features can include elevated serum creatine phosphokinase (CPK) concentration, rhabdomyolysis, elevated serum and urine myoglobin concentration, and renal failure. NMS did not occur in the ADASUVE clinical program.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to consider the presence of other serious medical conditions (e.g., pneumonia, systemic infection, heat stroke, primary CNS pathology, central anticholinergic toxicity, extrapyramidal symptoms, or drug fever).

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs that may contribute to the underlying disorder, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

#### 5.5 Hypotension and Syncope

ADASUVE can cause hypotension, orthostatic hypotension, and syncope. Use ADASUVE with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, or treatment with antihypertensive medications or other drugs that affect blood pressure or reduce heart rate).

In the presence of severe hypotension requiring vasopressor therapy, the preferred drugs may be norepinephrine or phenylephrine. Epinephrine should not be used, because beta stimulation may worsen hypotension in the setting of ADASUVE-induced partial alpha blockade.

In short-term (24-hour) placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar I disorder, hypotension occurred in 0.4% and 0.8% in the ADASUVE 10 mg and placebo groups, respectively. There were no cases of orthostatic hypotension, postural symptoms,