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'The Sound and the Fury': Patients in Pain Need Compassion, Not Regulations

It is imperative that the United States finds more effective ways to deal with the growing availability and utilization of opiates and other drugs for pain that is compassionate and grounded in medicine rather than criminalizing such use, said Ethan Nadelmann, JD, PhD, founder and Executive Director of the Drug Policy Alliance, a New York City-based nonprofit organization.

In presenting the Keynote Address at PAINWeek 2014, "The Sound and the Fury: What Ending the Drug War Looks Like," Dr. Nadelmann outlined harm ensuing from the US government's "War on Drugs," pointing to the highest per capita incarceration rate in the world, a 10-fold increase in drug law violations over the past 30 years, and the $50-$100 billion spent annually to treat drugs as a criminal problem.

> It is imperative that the United States finds more effective ways to deal with the growing availability and utilization of opiates that is compassionate and grounded in medicine.

Most remarkable, he said, is the growing movement to end marijuana prohibition, with recent surveys showing more than half of Americans are now in favor of legalizing marijuana. Colorado and Washington, the first states to legalize marijuana use, may soon be joined by Oregon, Alaska, and the District of Columbia; and Florida is the 24th state considering legalizing marijuana for medical purposes. This makes sense, he said, when one realizes that half of all US drug arrests are for marijuana use, costing taxpayers untold billions of dollar as "offenders" are arrested, prosecuted, and even jailed.

He pointed to a recent article in *JAMA Internal Medicine* that found states with medical cannabis laws had a 25% lower mean annual opioid overdose mortality rate when compared with states where medical marijuana is illegal. While no causal relationship has been established, this is certainly a piece of evidence worth considering, he said, and underscores that different types of medications work for different people and different medical conditions, perhaps in a synergistic way.

He exhorted attendees to become powerful advocates for people in pain who need opiates—and protection against overdoses. Specifically, Dr. Nadelmann asked all who write prescriptions for opioids to ensure patients have access to naloxone, which he believes should be available over-the-counter, and that they promote "Good Samaritan 911" immunity laws in their states to protect those who report witnessed overdoses and fear being arrested or prosecuted themselves for drug possession.

All of this requires a deeper understanding of the nature of pain in society and a greater—and more creative—investment in educating consumers about pain and how to manage it.

According to the Drug Policy Alliance's website, the organization "envisions a just society in which the use and regulation of drugs are grounded in science, compassion, health and human rights, in which people are no longer punished for what they put into their own bodies but only for crimes committed against others, and in which the fears, prejudices and punitive prohibitions of today are no more." In addition, the group's "mission is to advance those policies and attitudes that best reduce the harms of both drug use and drug prohibition, and to promote the sovereignty of individuals over their minds and bodies."

Dr. Nadelmann asks PAINWeek 2014 attendees to become powerful advocates for people in pain who need opiates.

'Harm Reduction Strategies' Can Help Avoid Legal Headaches When Prescribing Controlled Medications

When prescribing controlled medications, what type of conduct leads to legal trouble?

Helping providers understand such conduct, and how to use these lessons learned to "enhance current prescribing compliance protocols in a manner that preserves patient access to controlled medication where clinically appropriate" was the focus of a course presented by Jennifer Bolen, JD, of The Legal Side of Pain, a division of the J. Bolen Group, LLC, Nashville, Tennessee.

Bolen provided snapshots of court documents and extracted references from published case law and administrative decisions to illustrate today's clinical standard of care expectations. This included an understanding of the influence of medical expert testimony on pain management prosecutions and the overall direction of pain management regulatory compliance issues.

Included were cases representative of federal prosecutions (federal criminal court, DEA administrative cases) and state prosecutions (state criminal authorities and state licensing boards). She also provided typical, simplified prosecution chronologies for federal and DEA cases. Intentionally omitted were civil (negligence, wrongful death) and financial (payor financial investigations and overpayment audits) cases.

What the federal and DEA cases have in common are that they are expensive and disruptive, involve the use of experts, require documentation, and involve reputation. Common substantive issues are that the cases are document intensive, with the potential for undercover and other surveillance, with a focus on pill quantity, patients per day, and office hours. Patients and staff are interviewed. Common failures among prescribers include:

- Failure to document
- Failure to perform according to standard of care
- Treating everyone the same way
- Failure to stay involved with the patient
- Failure to account for dose and combination prescribing
- Failures in risk evaluation and monitoring.

Under the Controlled Substances Act (CSA), the DEA has the authority to deny, suspend, or revoke a DEA registration upon a finding that the registrant has:

- Materially falsified any application filed
- Been convicted of a felony relating to a controlled substance or a List I chemical
- Had their state license or registration suspended, revoked, or denied
- Committed an act which would render the DEA registration inconsistent with the public interest
- Been excluded from participation in a Medicaid or Medicare program.

Typical investigation tactics include inspection warrants, search warrants, and medical record review. Others may involve undercover work or "follow the money." Bolen provided one example of what she called a "bad idea": "two diversion investigators go out to talk to a physician. Physician opens the door and denies his identity."

"Expert witnesses" is another investigation tactic, with different types of medical experts having specific roles—and an impact in the courtroom (*Table 1*).

Also outlined were topics medical experts frequently address in the courtroom.

Early factors of inappropriate prescribing were described in the 1978 case, US v. Rosen:

1. Inordinately large quantity of controlled substances was prescribed.
2. Large numbers of prescriptions were issued.
3. No physical examination was given.

TABLE 1. Medical Experts

Type	Their Job	Courtroom Impact
• Medical • Pharmacy • Toxicology • Medical Examiner • DEA Agent • Financial	• Review records • Give opinion • Assist with case development (consulting expert v. testifying expert issue)	• May have history of prior testimony • May or may not understand legal standards applicable to cases. May not understand objective/subjective aspects of prescribing standard • May or may not be good at describing prescribing in the usual course of professional practice and legitimate medical purpose.

4. Prescriber warned the patient to fill the prescriptions at different drug stores.
5. Prescriber gave prescriptions to patient despite knowing (or having reason to know) that patient was diverting the medication.
6. Medication prescribed at intervals inconsistent with legitimate medical treatment.
7. Prescriber uses street slang to refer to commonly prescribed controlled medications.
8. No logical relationship between the drugs prescribed and the condition treated.
9. Prescriber wrote more than one prescription in order to spread them out.

In the case of Iyer, a 2009 DEA Administrative Case, the three points of which physicians should be aware were 1) responsibility to issue prescriptions for a legitimate medical purpose while acting in the usual course of professional practice; 2) responsibility to monitor patients (as a part of routine clinical practice) for warning signs that they are personally abusing or diverting their medications; and 3) failure to fulfill these responsibilities constitutes acts inconsistent with the public health and safety.

Attendees were encouraged to use the cases Bolen presented to evaluate their own practices and create checklists of areas for improvement. "Harm reduction strategies" that providers can embrace to head off potential lawsuits include patient and staff education; addressing CNS issues and related medical conditions (sleep apnea, multiple CNS depressants in medication therapy, sleep hygiene); weight loss and smoking cessation; alcohol education and compliance measures; safe use, storage, and disposal education, and coordination of care issues.

Transdermal Creams Can Reduce Oral Pain Medication Use in Elderly Patients

Nonsystemic transdermal (NST) therapy can significantly reduce pain, improve quality of life, and reduce and replace use of oral pain medications in patients 65 years and older with a variety of chronic pain conditions.

That was the conclusion of a presentation at PAINWeek 2014 that explored patient-reported outcomes of the effect of the use of customized nonopiate-based creams in reducing the use of specific classes of oral pain medications.

Dean Juge, PharmD, of the University of Alabama at Birmingham, and Chief Science Officer at DeTOURE, a patient-reported outcomes-focused research company specializing in chronic pain management, and colleagues used an institutional review board survey that incorporated the MD Anderson Brief Pain Inventory to capture pain severity levels and quality of life metrics at baseline, week 1, and week 4 from 925 elderly patients.

Specifically, they were asked to indicate whether their use of oral pain medication had decreased, increased, or stayed the same while undergoing NST pain therapy. If decreased, they were asked to indicate the drug class and specific drugs whose uses were decreased while on NST.

This group represented a subpopulation of 3587 patients prescribed nonopioid-based transdermal pain creams who agreed to participate in the study.

BUT JUST HOW EFFECTIVE IS IT?

The data showed that NST pain creams reduced pain severity by 21%, improved physical and emotional qualify of life metrics by 23% and 25%, respectively, and reduced the use of oral pain medications in 38% of the population.

Of the 38% of patients, 55% reported reduction in use of antiinflammatory agents; 38% in use of opioids; 28%, nutritional supplements; 21%, anticonvulsants; 18%, antidepressants; and 17%, topical agents.

Among the 38% who reported a reduction in opioid use, 45% reduced hydrocodone use; 35%, tramadol; 18% oxycodone; 5%, codeine compounds; 5%, fentanyl; 5%, morphine; and 3%, hydromorphone.

Minor adverse events were reported in less than 5% of patients, and no severe adverse events were observed.

Dr. Juge pointed to the American Geriatric Society statement on the use of opioids in the treatment of persistent pain in older adults, which notes that persistent pain is undertreated in the elderly, leading to many adverse outcomes. In addition, because of alterations in drug absorption, distribution, metabolism, and excretion, resulting from age-related changes—including in CNS, hepatic, and renal functions—treating chronic pain in patients who are elderly with oral pain medications is a less attractive option.

Pharmacogenomic Testing Helps Personalize Pain Medicine, Improving Outcomes

"How do we know how a patient will respond to a certain medication or if they will have an adverse effect to that medication?" Brett B. Snodgrass, MSN, APRN, FNP-C, asked. The answer, she said, is that we couldn't – until now.

Pharmacogenomic testing can identify how genetic variations affect drug responses, and help guide treatment strategies for patients suffering from chronic pain, according to Snodgrass.

Genomics offers "improved diagnostic and prescribing accuracy and speed," Snodgrass said, decreasing healthcare costs and better personalizing treatment plans. On the research front, pharmacogenomics also promises to hasten rational drug design and the development of gene therapies, she added.

For example, more than 50 enzymes in the cytochrome P450 (CYP450) super-family have been identified in humans. These enzymes are found in the liver, mucosal surfaces and intestines, and play "important roles in the biosynthesis and metabolism of endogenous and exogenous compounds," she explained. Seven of these metabolize more than 90% of the clinically most-important drugs, Snodgrass noted.

"CYP2D6 is involved in the metabolism of 25% to 30% of all prescribed drugs," she said. "CYP2C19 is involved in metabolizing 15%." Gene variations in CYP2D6 and CYP2C19 genes "result in markedly increased or decreased drug metabolism, leading to wide variations in clinical effect," she explained. In addition to allelic variation, there are gene copy-number polymorphisms that may affect drug metabolism, she reported.

Genotyping patients allows identification of those likely to respond normally

Identifying Small Fiber Neuropathies Key to Improved Treatment Approaches

Suspect small fiber neuropathies for unexplained neuropathic pain

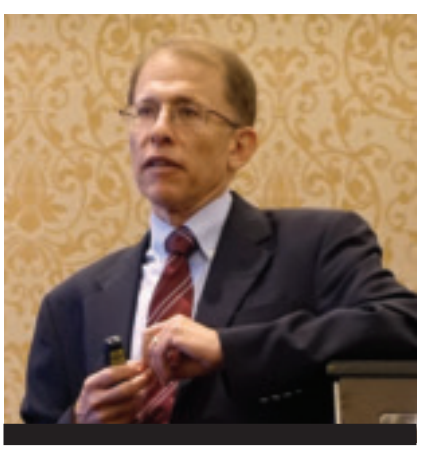
Recognizing the existence of small fiber neuropathies (SFNs) and their association with more conditions than previously identified may lead to improved treatment approaches, said Charles E. Argoff, MD, Professor of Neurology, Albany Medical College and Director, Comprehensive Pain Center, Albany Medical Center, Albany, New York.

Approximately 40 million people experience peripheral neuropathy, many with both large and small fiber involvement. Common neuropathic pain diagnoses range from postherpetic and trigeminal neuralgia, to spinal cord injury, post-stroke pain, and HIV-related neuropathy.

Increasingly recognized is specific involvement of small myelinated or unmyelinated fibers resulting from damage to the peripheral nerves. Thermal perception, nociception, and enteric function are all subserved by small fibers.

Most SFNs occur in a length-dependent fashion, first with stocking distribution changes and later, glove distribution. "Rarely, non-length dependent SFN can result in symptoms involving the face, trunk, proximal limbs, or other more localized areas," he said. The pathogenesis of injury to small fibers is not well understood, and SFN can progress to involve large fibers.

Numerous disorders are associated with SFN, from diabetes to HIV to restless leg syndrome (see *Box*). Symptoms vary widely in severity, with affected individuals often describing a gradual onset of vague distal sensory disturbances. Examples include a sock feeling



A detailed diagnosis is vital to making a diagnosis of small fiber neuropathy, said Dr. Argoff.

as if it has pebbles in it, pins and needles or cold painful sensations. Burning pain in the extremities, sometimes severe, may occur; socks or bed sheets may be painful; and symptoms are often worse at night. Autonomic and enteric dysfunction may include dry eyes, dry mouth, lightheadedness with changes in posture, syncope, abnormalities

to a given drug therapy, and those who are less likely to benefit or who might be at increased risk for toxic adverse events, she said.

"For example, codeine is metabolized into the active morphine," she explained. "Poor metabolizers would not achieve a full therapeutic response. Ultra-rapid metabolizers metabolize codeine quickly into morphine, potentially leading to a toxic effect." Among nursing mothers, ultra-rapid codeine metabolism could lead to morphine overdose in their breast-fed infants. Similarly, patients may metabolize hydrocodone into hydromorphone too quickly or too inefficiently, risking significant side effects or poor pain relief, respectively, she said.

> Pharmacogenomic tests should be considered before prescribing when patients say that "nothing works" to alleviate their pain or that "everything makes me feel horrible."

"If a patient is complaining about a drug not being effective, or about side effects, genomics testing can guide your therapy," Snodgrass said. Pharmacogenomic tests should be used in pain management when pharmacotherapies fail to relieve pain at an appropriate dose, or when a patient complains of significant side-effects and pain is not controlled, she advised.

Pharmacogenomic tests should be considered before prescribing when patients say that "nothing works" to alleviate their pain or that "everything makes me feel horrible," Snodgrass added. Genetic analyses for pain management planning are available for genes affecting metabolism of codeine, fentanyl, oxycodone, methadone, morphine, and tramadol.

Results of such tests are probabilistic; a smaller or larger number of patients with a particular gene variation are likely to be non-responders for a particular drug, for example. That information can significantly improve the odds that a particular treatment strategy will help a patient, Snodgrass concluded.

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of sweating, erectile dysfunction, GI symptoms and changes in urinary frequency, including nocturia.

Dr. Argoff said a detailed diagnosis is vital to making a diagnosis of SFN, since patients will primarily have a normal basic physical and neurological examination. Possible findings included decreased pin prick, diminished thermal sensation, hyperalgesia, and dry skin. Diagnostic studies include blood tests, X-ray, CT, MRI, quantitative sensory testing, and epidermal skin biopsy. Although electromyography and nerve conduction velocity may also be used, he said limitations include that they are insensitive in acute injury, a normal result does not rule out neuropathic pain, and they cannot assess function of small-fiber nerves involved in most neuropathic pain.

Skin biopsy has become widely accepted as a technique to evaluate the structure of small nerve fibers, with the standard being a 3-mm skin punch biopsy that can be taken from anywhere over the body; however, due to the need to compare to normal values, the lower extremity is most commonly assessed (and because length-dependent SFN is more common). Results are expressed as the number of intraepidermal fibers per mm; the sensitivity (78%-92%) and specificity (65%-90%) is fairly high for this technique.

Dr. Argoff advised attendees to "treat the treatable," and, if an underlying cause of SFN can be determined, optimal treatment of the causative condition may lessen SFN symptoms. Although few studies and no guidelines have examined pharmacologic treatment of the pain associated with SFN, gabapentin and tramadol have shown efficacy. One emerging treatment: intravenous immunoglobulin, study of which is warranted in larger studies.

Disorders Associated with SFN

- Diabetes
- Impaired glucose tolerance
- Metabolic syndrome
- Sarcoidosis
- Thyroid dysfunction
- HIV
- Vitamin B12 deficiency
- Chemotherapy drugs
- Antiviral agents
- Celiac disease
- Sjögren's syndrome
- Paraneoplastic syndromes
- Paraproteinemia
- Rheumatoid arthritis
- Idiopathic (up to 50%)
- Guillain-Barre syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Restless leg syndrome
- Hepatitis C
- Systemic lupus erythematosus
- Amyloidosis
- Fabry's disease
- Hereditary sensory neuropathies
- Hereditary autonomic neuropathies

For Refractory Migraine, Consider Ketamine

Ketamine infusions show efficacy as alternative therapy for refractory migraine

When first- and second-line drugs fail in the treatment of refractory migraine, ketamine may be a suitable option.

In fact, the US Headache Consortium recommended treatment of migraine includes ketamine, was well as triptans and ergot and its derivatives, antiemetics, NSAIDs and nonnarcotic analgesics, and narcotic opiate analgesics, said Natalie H. Strand, MD, Chief Medical Officer at Freedom Pain Hospital, Scottsdale, Arizona.

She reviewed the diagnostic criteria for migraine, clinical presentation of migraine, ketamine pharmacology, and the clinical application of ketamine for migraine.

Paroxysmal episodes of headache, with associated symptoms of nausea, vomiting, visual changes, photophobia, and phonophobia, are the hallmarks of migraine, which may be precipitated by a trigger and last from 4 to 72 hours. Phases of migraine are prodrome, aura, headache, and postdrome. Migraine may occur with or without aura and may be chronic. Status migrainosus is a migraine attack that lasts more than 72 hours, causing intense pain and disability and often refractory to usual outpatient treatments.

CANDIDATES FOR KETAMINE THERAPY

Of the 28 million people in the US who suffer from migraine, 75% are adult women. In fact, migraine prevalence is 18.2% among females, nearly three times that of 6.5% among males. Migraine causes an estimated $15.5 billion in lost revenue annually due to loss of work house and use of medical facilities.

Common migraine comorbidities include sleep disturbance, depression, anxiety, panic disorder, bipolar disorder, epilepsy, obsessive-compulsive behavior, fibromyalgia, and cognitive impairment.

Ketamine is a noncompetitive NMDA receptor antagonist that blocks the release of excitatory neurotransmitter glutamate, providing anesthesia, amnesia, and analgesia. It works by decreasing central sensitization and the "wind-up" phenomenon. Ketamine is also a serotonin and norepinephrine reuptake inhibitor, and is lipophilic, crossing the blood-brain barrier. If administered intravenously, onset of action is 1 to 5 minutes; subcutaneously, 15 to 30 minutes; and orally, 30 minutes.

TABLE. Contraindications to Ketamine

Pregnancy (placental transfer)
Substance abuse
Glaucoma
Thyrotoxicosis
Significant psychiatric comorbidities including bipolar disorder and schizophrenia
Active post-traumatic stress syndrome
Uncontrolled hypertension or hypotension
Cardiac failure
Renal failure
Liver failure
Prolonged QT syndrome
Neurogenic bladder or urinary retention
Known elevated CSF
Methadone usage
Daily opioid dose > a morphine equivalent of 120mg
History of stroke unless cleared by cardiology and neurology
Significant cognitive dysfunction

OPTIMIZING DOSAGES AND ADMINISTRATION

In clinical use for more than 30 years as a rapid-acting general anesthetic, ketamine can be administered intravenously, intramuscularly, subcutaneously, orally, rectally, nasally, transdermally, epidurally, or intrathecally, and appears to be most effective for nociceptive and/or neuropathic pain.

Dr. Strand reviewed studies using ketamine in varying dosages. Clinical experience has shown that anxious and apprehensive patients are more likely to have psychomimetic side effects, which may be prevented if they are pretreated with a benzodiazepine. Contraindications to ketamine are summarized in the *Table*.

USE CAUTION WITH KETAMINE

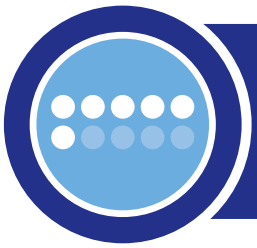
Due to the duration of ketamine, patients should be educated to avoid driving a car, operating hazardous machinery, or engaging in hazardous activities for a minimum of 24 hours after administration. They should also contact their clinician if they experience severe confusion, hallucinations, unusual thoughts, extreme fear, dream-like feeling, double vision, jerky muscle movements, dizziness, drowsiness, nausea, vomiting, loss of appetite, or insomnia.

RELISTOR®
methylnaltrexone bromide
subcutaneous injection

NOW APPROVED

FOR THE TREATMENT OF OPIOID-INDUCED CONSTIPATION IN ADULT PATIENTS WITH CHRONIC NON-CANCER PAIN.

In a clinical study of patients with chronic non-cancer pain who suffered from opioid-induced constipation:



6 out of 10 RELISTOR® (methylnaltrexone bromide) patients had at least 3 SBMs* per week[1]

33% of patients taking RELISTOR experienced an SBM* within 4 hours of their first dose[1]

- RELISTOR targets the underlying cause of opioid-induced constipation without affecting analgesia[2]
- RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction[2]
- In the clinical study in adult patients with opioid-induced constipation and chronic non-cancer pain, the most common adverse reactions (≥ 1%) were abdominal pain (21%), nausea (9%), diarrhea (6%), hyperhidrosis (6%), hot flush (3%), tremor (1%), and chills (1%).

*Spontaneous Bowel Movement occurring without the use of rescue laxatives.

Indication

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

Important Safety Information about RELISTOR

RELISTOR® (methylnaltrexone bromide) Subcutaneous Injection is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom.

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia and should be monitored for adequacy of analgesia and symptoms of opioid withdrawal.

Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

RELISTOR may precipitate opioid withdrawal in a fetus and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In nursing mothers, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

In the clinical study in adult patients with opioid-induced constipation and chronic non-cancer pain, the most common adverse reactions (≥ 1%) were abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills.

In clinical studies in adult patients with opioid-induced constipation and advanced illness, the most common adverse reactions (≥ 5%) were abdominal pain, flatulence, nausea, dizziness, and diarrhea.

Please see Brief Summary of complete Prescribing Information for RELISTOR on the adjacent page.

References

1. Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain: a randomized controlled study. *J Pain*. 2011;12(5):554-562.
2. RELISTOR® (methylnaltrexone bromide) Prescribing Information, Salix Pharmaceuticals, Inc.

www.salix.com
8510 Colonnade Center Drive, Raleigh, NC 27615
For additional information, call: 1-866-669-SLXP (7597)
To report adverse events, call: 1-800-508-0024

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RELISTOR®
methylnaltrexone bromide
subcutaneous injection

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

Limitation of use: Use of RELISTOR beyond four months has not been studied in the advanced illness population.

CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom.

Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their healthcare provider.

Opioid Withdrawal

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using RELISTOR in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients.

ADVERSE REACTIONS

Clinical Trial 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 clinical practice.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The safety of RELISTOR was evaluated in a double-blind, placebo-controlled trial in adult patients with opioid-induced constipation and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 4-week, double-blind, placebo controlled period in which adult patients were randomized to receive RELISTOR 12 mg once daily (150 patients) or placebo (162 patients). After 4 weeks of double-blind treatment, patients began an 8-week open-label treatment period during which RELISTOR 12 mg was administered less frequently than the recommended dosage regimen of 12 mg once daily.

Adverse reactions in adult patients with opioid-induced constipation and chronic non-cancer pain receiving RELISTOR are shown in the following table. The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR in Adult Patients with Opioid-Induced Constipation and Chronic Non-Cancer Pain

Adverse Reaction	RELISTOR 12 mg once daily n = 150	Placebo n = 162
Abdominal Pain	21%	6%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	< 1%
Chills	1%	0%

*Adverse reactions occurring in ≥ 1 % of patients receiving RELISTOR 12 mg once daily and at an incidence greater than placebo.

During the 4-week double-blind period, in patients with opioid-induced constipation and chronic non-cancer pain that received RELISTOR 12 mg every other day, there was a higher incidence of adverse reactions, including nausea (12%), diarrhea (12%), vomiting (7%), tremor (3%), feeling of body temperature change (3%), piloerection (3%), and chills (2%) as compared to daily RELISTOR dosing. Use of RELISTOR 12 mg every other day is not recommended in patients with OIC and chronic non-cancer pain. The rates of discontinuation due to adverse reactions during the double-blind period (Study 1) were higher in the RELISTOR once daily (7%) than the placebo group (3%). Abdominal pain was the most common adverse reaction resulting in discontinuation from the double-blind period in the RELISTOR once daily group (2%).

The safety of RELISTOR was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with opioid-induced constipation and chronic non-cancer pain (Study 2). Patients were allowed to administer RELISTOR 12 mg less frequently than the recommended dosage regimen of 12 mg once daily, and took a median of 6 doses per week. A total of 624 patients (60%) completed at least 24 weeks of treatment and 477 (46%) completed the 48-week study. The adverse reactions seen in this study were similar to those observed during the 4-week double-blind period of Study 1. Additionally, in Study 2, investigators reported 4 myocardial infarctions (1 fatal), 1 stroke (fatal), 1 fatal cardiac arrest and 1 sudden death. It is not possible to establish a relationship between these events and RELISTOR.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in adult patients with opioid-induced constipation and advanced illness receiving palliative care: Study 3 included a single dose, double blind, placebo-controlled period, whereas Study 4 included a 14-day multiple dose, double-blind, placebo-controlled period.

The most common (≥5%) adverse reactions in adult patients with opioid-induced constipation and advanced illness receiving RELISTOR are shown in the following table.

Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR in Adult Patients with Opioid-Induced Constipation and Advanced Illness*

Adverse Reaction	RELISTOR n = 165	Placebo n = 123
Abdominal Pain	29%	10%
Flatulence	13%	6%
Nausea	12%	5%
Dizziness	7%	2%
Diarrhea	6%	2%

*Adverse reactions occurring in ≥ 5 % of patients receiving all doses of RELISTOR (0.075, 0.15, and 0.30 mg/kg/dose) and at an incidence greater than placebo.

The rates of discontinuation due to adverse events during the double-blind placebo controlled clinical trials (Study 3 and Study 4) were comparable between RELISTOR (1%) and placebo (2%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RELISTOR. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal

Perforation, cramping, vomiting

General Disorders and Administrative Site Disorders

Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported.

DRUG INTERACTIONS

Other Opioid Antagonists

Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

Drugs Metabolized by Cytochrome P450 Isozymes

In healthy subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with RELISTOR in pregnant women. The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of intravenous methylnaltrexone during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. RELISTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether RELISTOR is present in human milk. However, methylnaltrexone bromide is present in rat milk. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of RELISTOR have not been established in pediatric patients.

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing were observed, and the juvenile rats were found to be more sensitive to the adverse effects of methylnaltrexone bromide when compared to adult animals. Juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks had a toxicity profile similar to adult dogs.

Geriatric Use

In the double-blind studies, a total of 118 (14%) patients aged 65-74 years (79 methylnaltrexone bromide, 39 placebo) and a total of 108 (13%) patients aged 75 years or older (64 methylnaltrexone bromide, 44 placebo) were enrolled. No overall differences in safety or effectiveness were observed between these patients and younger patients, 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.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dose adjustment based on age is recommended.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose reduction by one-half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault).

Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment.

OVERDOSAGE

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus. Monitor for signs or symptoms of orthostatic hypotension and initiate treatment as appropriate.

If a patient on opioid therapy receives an overdose of RELISTOR, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration

Advise all patients to:

- Inject RELISTOR subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
- Safely dispose of needles by following the sharps disposal recommendations described in the RELISTOR Instructions for Use.
- Be within close proximity to toilet facilities once RELISTOR is administered.
- Discontinue RELISTOR if treatment with the opioid pain medication is also discontinued.

Advise chronic non-cancer pain patients receiving RELISTOR for opioid-induced constipation to:

- Discontinue all maintenance laxative therapy prior to initiation of RELISTOR. Laxative(s) can be used as needed if there is a suboptimal response to RELISTOR after three days.
- Inject one dose every day.
- Inform their healthcare provider if their opioid regimen is changed, to avoid adverse reactions, such as diarrhea.

Advise patients with advanced illness receiving RELISTOR for opioid-induced constipation to:

- Inject one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

Gastrointestinal Perforation

Advise patients to discontinue RELISTOR and to promptly seek medical attention if they develop unusually severe, persistent, or worsening abdominal pain.

Severe or Persistent Diarrhea

Advise patients to discontinue RELISTOR if they experience severe or persistent diarrhea.

Opioid Withdrawal

Advise patients that symptoms consistent with opioid withdrawal may occur while taking RELISTOR, including sweating, chills, diarrhea, abdominal pain, anxiety, and yawning.

Pregnancy

Advise females of reproductive potential, who become pregnant or are planning to become pregnant that the use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood brain barrier.

Nursing

Advise females who are nursing against breastfeeding during treatment with RELISTOR due to the potential for opioid withdrawal in nursing infants.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

To report adverse events, a product complaint, or for additional information, call: 1-800-508-0024.

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Quantifying Catastrophizing About Pain

Higher catastrophizing is a risk factor for long-term pain and for disproportionately negative consequences of pain

Research increasingly is focusing on whether negative cognitive and emotional factors, such as catastrophizing, can predict patient response to pain, said Robert R. Edwards, PhD, MSPH, of Brigham and Women's Hospital Department of Anesthesiology, Boston, Massachusetts.

The goal: by improving assessment and targeting of pain-related catastrophizing, healthcare providers can offer more effective pain management to patients with many different persistent pain conditions, such as fibromyalgia, osteoarthritis, and postoperative pain.

"Variability in pain is the rule rather than the exception," he said, and this is related to its biopsychosocial aspects.

Catastrophizing, considered one of the most important psychological factors that shape pain perception, is defined as a set of negative cognitions, emotions, attitudes, and beliefs related to pain that include magnification, rumination, and helplessness.

Catastrophizing can easily be assessed in patients using the PCS, or Pain Catastrophizing Scale, which asks patients to rate 13 questions beginning with, "When I'm in pain…", on a scale of 0 (not at all) to 4 (all the time). Examples include:

- *I worry all the time about whether the pain will end.*
- *I feel I can't stand the pain anymore.*
- *I wonder whether something serious may happen.*

Overall, Dr. Edwards said, higher catastrophizing is a risk factor for long-term pain and for disproportionately negative consequences of pain, including worsening physical disability, medication misuse, and higher healthcare costs.

Catastrophizing appears to exert its effects via numerous pathways, including amplifying pain processing in the brain, increasing distress. For example, a higher percentage of patients with chronic pain who rated themselves as "high catastrophizing" (versus low or average), embraced active suicidal ideation and intent.

In addition, studies in patients with musculoskeletal pain conditions have found catastrophizing to be the most important pretreatment risk factor that impairs the effectiveness of pain-relieving interventions.

He described familial catastrophizing, a phenomenon in which early parent catastrophizing predicted chronic postoperative pain in children undergoing major surgery.

In one study in which 83 children were followed for 12 months, parent and child catastrophizing became more strongly linked over time.

In a second study of 107 families of children with chronic pain, after controlling for children's pain duration and intensity, parental catastrophizing was associated with parental stress, parental anxiety, a child's functional disability, and school attendance.

> Catastrophizing is defined as a set of negative cognitions, emotions, attitudes, and beliefs related to pain that include magnification, rumination, and helplessness.

Catastrophizing is one of the most important psychological factors that shape pain perception, said Dr. Edwards.

Although to date no genetic factors have been linked to catastrophizing, emotional—but not physical—abuse in childhood has been found to predict adult catastrophizing.

One of the most effective nonpharmacological treatment approaches to the treatment of catastrophizing is cognitive behavioral therapy (CBT), he said. Recently, a pilot study has found that CBT reduces catastrophizing in patients with fibromyalgia and high PCS scores, with a short-term change in catastrophizing at posttreatment prospectively associated with reduction in pain severity at 6 months.

Screen Chronic Pain Patients for Depression, Sleep Disorders, Suicidal Ideation

Chronic pain frequently is associated with suicide ideation, according to behavioral psychologist Martin D. Cheatle, PhD, Clinical Associate Professor of Psychology in Psychiatry at the University of Pennsylvania and Director of Behavioral Medicine at Penn Pain Medicine Center in Philadelphia.

Possible mediators of the relationship between pain and suicide risk include insomnia, depression, family history of suicide, substance use disorder, poor stress-coping abilities, and catastrophizing.

Clinics should have action plans for interventions for patients identified as being actively suicidal or at high-risk for suicide, said Dr. Cheatle.

During his presentation, he cited various studies linking chronic pain with suicide ideation. In a study of 113 chronic pain patients published in *Pain Practice* in 2012, researchers found that perceived burdensomeness was the sole predictor of suicidal ideation. Researchers who studied 51 patients with noncancer chronic pain found that 24% of them reported suicidal ideation and endorsed higher levels of sleep-onset insomnia, pain intensity, medication usage, pain-related interference, and depressive symptoms, according to a paper published in 2004 in the *Clinical Journal of Pain*. A study of 1512 chronic pain patients found that 32% of subjects reported some form of suicidal ideation, with results showing that two predictors of the presence and severity of suicidal ideation were the magnitude of depressive symptoms and the degree of pain-related catastrophizing, researchers reported in 2006 in *Pain*.

"I think people get into the cycle of developing pain, having a mood disorder, developing a sleep disorder, and it just feeds on itself," Dr. Cheatle said, adding that all 3 problems must be tackled aggressively at the same time to control patients' chronic pain.

Behaviors suggestive of an increased risk of suicide include giving away personal property, lack of future goals, making a will, and experiencing recent loss, he said. He noted that urine drug screens also have a role in risk assessment. If a patient has been prescribed opioids or benzodiazepines, but the drugs do not show up in urine drug tests, the patient may be hoarding the medications. They may be hoarding because they do not trust that their physician will prescribe more pain medication or they be saving up the drugs to kill themselves when their circumstances get worse.

Dr. Cheatle noted that a biopsychosocial approach to pain has been shown to improve treatment outcomes significantly. This approach has 5 main components: cognitive behavioral therapy (CBT), exercise, nutrition (eg, weight control), evidence-based rational pharmacotherapy, and social support. The objective of CBT is to guide patients in recognizing and reconceptualizing their personal view of pain, identifying their role in the healing process, and getting the patient to be proactive. CBT has been found to be effective in treating the chronic pain associated with a number of disorders, including arthritis, lupus, and low back pain.

Major Depression and Pain are a Major Treatment Challenge

Major depression is pervasive among pain clinic patients, with reported rates varying from clinic to clinic but commonly exceeding 50%, compared to 4% among the general population. But treating major depression in the context of pain is a complex challenge, said Mark D. Sullivan, MD, PhD, Professor of Psychiatry at the University of Washington.

Worldwide and across cultures, the WHO reports that patients with persistent pain (>6 months) are 4.14 times more likely than others to have anxiety or depressive disorder. Pain can cause depression but treatment of pain does not necessarily make depression vanish, Dr. Sullivan reported.

Among patients receiving chronic opioid therapy, depression was the strongest predictor of ambivalence about opioids. "Depression reduces response to pain treatment," he said. "Acute pain is lessened with opioid treatment but depression is associated with reduced response to acute opioid treatment. Depression complicates pain treatment, but the converse is also true: chronic pain reduces responses to depression treatment, further complicating treatment.

The risk of poor SSRI (selective serotonin reuptake inhibitor) treatment response in those with mild pain is 25%, he noted; 30% among patients with moderate pain, and 14% among patients with severe pain.

Antidepressants with norepinephrine reuptake inhibition like TCAs (tricyclic antidepressants) and SNRIs

Continued on page 16

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INTRODUCING

Hysingla™ ER

(Hydrocodone Bitartrate) CII

EXTENDED-RELEASE TABLETS

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WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

PURDUE

A8970-APP-A 11/2014

Hysingla™ ER

(Hydrocodone Bitartrate) CII

EXTENDED-RELEASE TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the Full Prescribing Information and Medication Guide.)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

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Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

4 CONTRAINDICATIONS

HYSINGLA ER is contraindicated in patients with: • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected paralytic ileus and gastrointestinal obstruction • Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS 5.1 Addiction, Abuse, and Misuse HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9.1)]*. As extended-release products such as HYSINGLA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient. Abuse or misuse of HYSINGLA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death *[see Drug Abuse and Dependence (9.1), and Overdosage (10)]*. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product. **5.2 Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10.2)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases. To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential *[see Dosage and Administration (2.1, 2.2)]*. Overestimating the HYSINGLA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone. **5.3 Neonatal Opioid Withdrawal Syndrome** Prolonged use of HYSINGLA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. **5.4 Interactions with Central Nervous System Depressants** Hypotension, profound sedation, coma, respiratory depression, and death may result if HYSINGLA ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of HYSINGLA ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin HYSINGLA ER is made, start with a lower HYSINGLA ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*. **5.5 Use in Elderly, Cachectic, and Debilitated Patients** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating HYSINGLA ER and when HYSINGLA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. **5.6 Use in Patients with Chronic Pulmonary Disease** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with HYSINGLA ER, as in these patients, even usual therapeutic doses of HYSINGLA ER may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible. **5.7 Use in Patients with Head Injury and Increased Intracranial Pressure** In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury. Avoid the use of HYSINGLA ER in patients with impaired consciousness or coma. **5.8 Hypotensive Effect** HYSINGLA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose of HYSINGLA ER. In patients with circulatory shock, HYSINGLA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of HYSINGLA ER in patients with circulatory shock. **5.9 Gastrointestinal Obstruction, Dysphagia, and Choking** In the clinical studies with specific instructions to take HYSINGLA ER with adequate water to swallow the tablet, 11 out of 2476 subjects reported difficulty swallowing HYSINGLA ER. These reports included esophageal obstruction, dysphagia, and choking, one of which had required medical intervention to remove the tablet *[see Adverse Reactions (6)]*. Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen. **5.10 Decreased Bowel Motility** HYSINGLA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of HYSINGLA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis. **5.11 Cytochrome P450 CYP3A4 Inhibitors and Inducers** Since the CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations. The clinical results with CYP3A4 inhibitors show an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects, which could be more pronounced with concomitant use of CYP3A4 inhibitors. The expected clinical result with CYP3A4 inducers is a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration is necessary, caution is advised when initiating HYSINGLA ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.1)]*. **5.12 Driving and Operating Machinery** HYSINGLA ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16 hours (range 6 – 30 hours) after initial dosing of HYSINGLA ER tablet administration. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated-dose administration. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of HYSINGLA ER and know how they will react to the medication *[see Clinical Pharmacology (12.3)]*. **5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics** Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including HYSINGLA ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. **5.14 QTc Interval Prolongation** QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg *[see Clinical Pharmacology (12.2)]*. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing HYSINGLA ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. HYSINGLA ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

6 ADVERSE REACTIONS The following serious adverse reactions are described elsewhere in the labeling: • Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]* • Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]* • Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]* • Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]* • Hypotensive Effects *[see Warnings and Precautions (5.8)]* • Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]* **6.1 Clinical Trial 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. A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical trials. Five hundred patients were treated for 6 months and 364 patients were treated for 12 months. The clinical trial population consisted of opioid-naïve and opioid-experienced patients with persistent moderate to severe chronic pain. The common adverse reactions (≥2%) reported by patients in clinical trials comparing HYSINGLA ER (20-120 mg/day) with placebo are shown in Table 2 below:

Table 2: Adverse Reactions Reported in ≥2% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

	Open-label Titration Period	Double-blind Treatment Period	
MedDRA Preferred Term	(N=905) (%)	Placebo (N=292) (%)	HYSINGLA ER (N=296) (%)
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common (≥5%), common (≥1% to <5%), and less common (<1%).

The most common adverse reactions (≥5%) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common (≥1% to <5%) adverse events reported by patients treated with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Ear and labyrinth disorders	tinnitus
Gastrointestinal disorders	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux disease
General disorders and administration site conditions	chest pain, chills, edema peripheral, pain, pyrexia

Infections and infestations	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
Injury, poisoning and procedural complications	fall, muscle strain
Metabolism and nutrition disorders	decreased appetite
Musculoskeletal and connective tissue disorders	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
Nervous system disorders	lethargy, migraine, sedation
Psychiatric disorders	anxiety, depression, insomnia
Respiratory, thoracic and mediastinal disorders	cough, nasal congestion, oropharyngeal pain
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash
Vascular disorders	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS **7.1 Drugs Affecting Cytochrome P450 Isoenzymes** *Inhibitors of CYP3A4* Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inducers of CYP3A4* CYP3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with HYSINGLA ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. **7.2 Central Nervous System Depressants** The concomitant use of HYSINGLA ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and HYSINGLA ER for signs of respiratory depression, sedation and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Warnings and Precautions (5.4)]*. **7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics** Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist analgesics (buprenorphine) may reduce the analgesic effect of HYSINGLA ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving HYSINGLA ER. **7.4 MAO Inhibitors** HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. **7.5 Anticholinergics** Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs. **7.6 Strong Laxatives** Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Pregnancy Category C Risk Summary* There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Clinical Considerations* Fetal/neonatal adverse reactions Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*. *Data* Animal Data No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in in rabbit at 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons. **8.2 Labor and Delivery** Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. **8.3 Nursing Mothers** Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. **8.4 Pediatric Use** The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established. Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*. HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*. **8.5 Geriatric Use** In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone *[see Clinical Pharmacology (12.3)]*. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received HYSINGLA ER. Hydrocodone may cause confusion and oversedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion. **8.6 Hepatic Impairment** No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*. **8.7 Renal Impairment** No dose adjustment is needed in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE **9.1 Controlled Substance** HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse. **9.2 Abuse** All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build up. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. "Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction. HYSINGLA ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants. *Risks Specific to Abuse of HYSINGLA ER* HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. Abuse Deterrence Studies *Summary* The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate. HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*. **9.3 Dependence** Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. HYSINGLA ER should be discontinued by a gradual downward titration *[see Dosage and Administration (2.6)]*. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

10 OVERDOSAGE **10.1 Symptoms** Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. **10.2 Treatment** In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

CAUTION
DEA FORM REQUIRED

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

This brief summary is based on Hysingla ER Prescribing Information 303511-0B, Revised 11/2014 (A)

Continued from page 12

(serotonin–norepinephrine reuptake inhibitors) are better analgesics than other antidepressants, Dr. Sullivan said. These are "clearly preferred for neuropathic pain and probably preferred for musculoskeletal pain," he noted.

Depression with chronic pain is frequently complicated by post-traumatic stress disorder (PTSD) or anxiety, substance abuse, and occasionally, borderline personality disorder, Dr. Sullivan said. Antidepressants with serotonin blockade, like trazodone, nefazodone, or mirtazapine, are associated with better sleep and anxiety, and are better tolerated among patients with PTSD or panic symptoms.

Patients suffering from depression and pain also frequently have trauma issues, often from childhood. "This trauma needs to be recognized and addressed before depression treatment can succeed," he emphasized.

"Emphasize that depression treatment will help other pain treatments work better." If patients report that antidepressants make them feel worse, providers should carefully explore what that means rather than dismissing—or accepting—such statements at face value, he said. "It can mean 'I felt the clinician was ignoring my pain, or ignoring me, and writing the prescription to get me out the door'," he explained. Or it might mean "the antidepressant made me more anxious, more angry, more depressed."

"Don't oversell antidepressants" to patients, he concluded. "They are imperfect medications with side effects." Instead, providers should encourage patients to "put their nickel down" by participating in the selection of a treatment from among the available options. "If they are invested in the choice of treatment, they are less likely to reject the treatment," he said.

Ameritox Thought Leaders Discuss the Resurgence of Heroin

Abuse of prescription pain medicine shifts to heroin as it becomes a readily available, cheaper alternative

Ameritox, a provider of pain medication monitoring, is focused on reversing the rampant misuse, abuse, and diversion of prescription painkillers that has proliferated in the US over the last decade. An old epidemic that many experts say grew from the abundance and abuse of prescription opioids is seeing a resurgence: Heroin abuse.

In an interview with Rick Tucker, an Ameritox compliance education consultant and former assistant special agent in charge of the DEA, and Mike DeGeorge, PharmD, Director of Medical Affairs at Ameritox, the roots of the current heroin epidemic facing the US, and how chronic pain patients prescribed opioids are affected by it, were discussed.

How has heroin abuse changed over the last few decades?

Rick Tucker: Heroin in the last decade has attained a degree of social acceptability that it didn't have before. Persons across all social and economic positions are now using heroin. The proliferation of the abuse of prescription pain medications led to abusers looking for drugs to satiate the need of an opiate. The fact that the abuser basically cannot get enough prescription meds to meet their dependence, coupled with a recent decrease in heroin prices, make heroin a viable alternative for these abusers.

How is the heroin people are abusing today different from older versions?

Rick Tucker: The heroin being used today is coming from four major sources – Southwest Asia, Mexico, Colombia, and to a lesser extent, Southeast Asia. In recent years all of these sources have worked to make a better "product," resulting in heroin being more pure now than it has ever been. In addition, the price of pure heroin recently decreased to meet the "street price" of prescription medications. The prices of both heroin and prescription pain meds on the street are now basically the same.

What does the typical heroin user look like today?

Rick Tucker: Very few heroin users today used heroin in their first experience with illicit drugs. Increasingly, in the past few years according to US Substance Abuse and Mental Health Services Administration (SAMHSA) research, opiate abusers are found to have taken prescription pain medications for their first "high." In the 2012 SAMHSA research, 1.88 million respondents age 12-25 years used prescription opiates for their first experience. Only 156,000 used heroin.[1]

How are prescription painkillers and heroin connected?

Rick Tucker: Typical pain medications and heroin are both opiates. When abusers of pain medications cannot obtain quantities to satiate their dependence, they often turn to heroin. According to a report from the National Institute of Drug Abuse, "although heroin use in the general population is rather low, the numbers of people starting to use heroin have been steadily

rising since 2007. This may be due in part to a shift from abuse of prescription pain relievers to heroin as a readily available, cheaper alternative, and the misperception that highly pure heroin is safer than less pure forms because it does not need to be injected."

What prompted Ameritox to conduct this research?

Mike DeGeorge: As Rick mentioned, heroin use has been on the rise in the US. Recent data showed that 75% of heroin users were introduced to opioid use through prescription opioids.[2] For that reason, we sought to investigate the use of heroin in a population of individuals prescribed opioids for pain. We did this by examining over 170,000 samples from patients prescribed opioids that were received at our lab.

How is this current heroin epidemic affecting pain patients?

Mike DeGeorge: In our study, we found that 1.3% of the 170,000 samples tested positive for the heroin metabolite, 6-monoacetylmorphine. This is significantly greater than the 0.3% seen in the general population.[1]

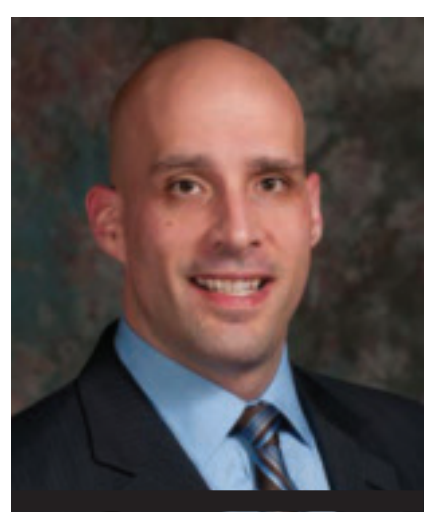
Rick Tucker

Ameritox: Does Ameritox's research show that there is a relationship between opioid and heroin abuse?

Mike DeGeorge: Based on our research, there does appear to be a relationship between heroin use and misuse of prescription opioids. We found that when patients were positive for heroin, their urine samples tested negative for their prescribed opioid 56% of the time. In 23% of those same samples we also found evidence of the use of a synthetic opioid without a prescription, including drugs such as methadone, fentanyl and buprenorphine.

What other trends are you finding among chronic pain patients who tested positive for heroin?

Mike DeGeorge: The other trend we saw was that heroin positive samples were more likely to test positive for cocaine, marijuana, a non-prescribed prescription stimulant product, or a non-prescribed sedative hypnotic, including benzodiazepines. Interestingly, heroin positive samples were more likely to test negative for those same sedative hypnotics when they were prescribed to them.



Mike DeGeorge, PharmD

The demographics of the heroin positive patients in our study matched well with those of the general population reported previously. Specifically, males and patients between the ages of 19 and 39 years were most likely to test positive. Geographically, samples from the Midwest and Northeast were the most likely to test positive for heroin. From a payer standpoint, samples from patients who have Medicaid as their primary payer were the most likely to contain evidence of heroin use.

How do "drug cocktails" affect people using heroin?

Mike DeGeorge: When heroin is used with prescription opioids and benzodiazepines, the individual is at greater risk for central nervous system and respiratory depression, which can ultimately lead to an overdose death. In our study, more than 4% of the samples tested positive for heroin, a sedative hypnotic, and a synthetic opioid. Additional, slightly more than 1% of the samples tested positive for the combination of heroin, a sedative hypnotic, a synthetic opioid, and cocaine.

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Complementary and Alternative Medicine Can Provide 'Self-Efficacy' for Patients with Chronic Low Back Pain

Complementary and alternative medicine (CAM) for chronic low back pain: "what works, how much, and for how long?" The answer: it depends on the strength of the evidence, the expertise of the clinician, the patient's values—and finding the overlap.

In his presentation, Michael S. Saenger, MD, Atlanta, Georgia, reviewed evidence-based CAM in the management of chronic low back pain that included identifying nonscientific evidence that commonly leads to CAM misuse.

He guided attendees through the nuances of how they can determine whether clinical studies of CAM are powered to detect differences, including the definition of randomized controlled trials, numbers needed to treat, intent to treat, confidence intervals, and the Jadad score, which independently assesses a study's methodological qualities.

> CAM may be useful in transitioning patients with chronic low back pain away from therapies that are dangerous, ineffective, or passive.

The goal: to guide patients to "take advantage of therapies that have the best evidence," versus "snake oil."

Categories of CAM include whole medical systems; mind-body medicine; natural, biologically based products; manipulation and body-based practices; and energy medicine.

Whole medical systems embrace traditional Chinese medicine, Ayurvedic medicine, traditional healers, homeopathy, and naturopathy, while mind-body medicine comprises progressive relaxation, deep breathing exercises, meditation and mindfulness, prayer, music therapy, and yoga.

Dr. Saenger reviewed mindfulness, yoga/Tai Chi, dietary supplements (eg, "Devil's claw," or Harpagophytum, a plant native to southern Africa), acupuncture, spinal manipulation therapy, massage, the Alexander technique, and Reiki in depth for the treatment of chronic low pack pain, reviewing rel-

The UNDEAD DEAD Nerve: Neuropathic Pain Has Diverse Causes

Damaged nerve and residual nociceptor activity may complicate the picture

Unrecognized nerve damage and residual function can be a "spontaneous pain generator," said Gary W. Jay, MD, DAAPM, FAAPM, Medical Director of The DNA Center in Daytona Beach, Florida.

"There is substantial evidence that abnormal nerve activity is an important mechanism underlying the spontaneous pain typical of neuropathic pain states," Dr. Jay said. "It is hypothesized that sites of ectopic foci include developing on injured or regenerating nerves in the periphery, at the level of the nociceptor, neuromas, or segments of injured nerves; at the dorsal root ganglion, and in the dorsal horn laminae of the spinal cord."

These abnormal ectopic foci can be considered "spontaneous pain generators," that result in paroxysmal and spontaneous pain, he said.

Neuropathic pain is typically thought of as painful peripheral neuropathy, such as that suffered among patients with severe diabetes. In contrast, the pain caused by shingles (herpes zoster) and inflammatory involvement of the trigeminal nerves, are usually considered to be focal neuralgias.

Abnormal activity in damaged nerves is just part of the picture, however. Residual pain nerve activity in damaged tissues can create a more complex situation, he suspects.

"While neuropathic pain has become operationally defined as an abnormal pain state that arises from a damaged peripheral nervous system or central nervous system, there is supporting evidence suggesting that several disease states within this category have active residual involvement of nociceptors at the site of the original injury, creating a mixed nociceptive-neuropathic pattern," Dr. Jay said.

Low back pain is one of the most common disorders, affecting about two-thirds of the adult population in the US at some time in their lives. Degeneration of intervertebral discs has long been considered to be the primary etiology of low back

evant clinical trials, efficacy, safety, and cost for each.

After reviewing the state of evidence-based practice for CAM for chronic low back pain, he concluded that the quality of evidence is low to moderate, with short term, modest benefits possible from Devil's claw, massage, spinal manipulation, and acupuncture. Long-term modest benefits are possible using the Alexander technique, yoga, Tai Chi and, possibly, mindfulness.

Duration of therapy depends both on cost and treatment benefit and on whether the patients themselves can practice the therapy, such as yoga, in contrast, for example, to spinal manipulation, massage, and acupuncture.

When asking, "can I apply this CAM for my patient," Dr. Saenger said that if the treatment is reasonably valid and moderately effective, considerations should then include the preferences and expectations of the patient, the cost of therapies, the local availability of therapies, and possible side effects.

Ultimately, CAM may be useful in transitioning patients with chronic low back pain away from therapies that are dangerous, ineffective, or passive—high-dose opioids, benzodiazepines, chronic muscle relaxants and chronic sleep medications—towards therapies that are safe, moderately effective, and self-efficacious, which he defined as deep breathing, stretching, use of the Alexander technique, yoga/Tai Chi, and progressive relaxation, or mindfulness. Therapies that can bridge this transition include massage, spinal manipulation, and acupuncture.

He left attendees with this thought: although what is known about CAM—"not much"—long-term opioid therapy for chronic noncancer pain is also based on low-quality evidence.

> Several neuropathic disease states have active residual involvement of nociceptors at the site of the original injury.

pain, but there is reason to suspect it is more complicated than that, he said.

"Degeneration or deterioration of a disc can influence the central nervous system by nociceptor stimulation in the annulus fibrosus, which can induce nociceptive pain which is considered to be discogenic pain," explained Dr. Jay. "This stimulation may be secondary to mechanical or inflammatory factors."

"In the normal intervertebral disc, only the outer aspect of the annulus fibrosus receives sensory innervation," he said. But when discs degenerate, extensive nerve fiber growth is found in the middle and inner third of the diseased annulus.

The degenerating disc releases inflammatory neuropeptides that, when combined with mechanical pressure, "can induce chemical and mechanical sensitization and stimulation of the nociceptive nerve fibers," he surmised.

"In theory, almost any of the pathological processes known to create damage or dysfunction to neural tissue can be considered as potential causes for neuropathic pain," Dr. Jay said. "Viral, bacterial, aseptic inflammation, pressure due to neoplasm or other structural lesions, degenerative, ischemic, autoimmune, toxic, traumatic, and endocrine/metabolic mechanisms have all been implicated in the production of pain."

Migrainous Auras: Artistic Inspiration and Risk for Stroke, Cardiovascular Disease

An estimated 18% of Americans suffer migraines, 20% of whom experience visual and neurologically-complex perceptual disturbances known as auras. Paradoxically, those often-frightening distortions may have enriched our world by influencing the art of famous painters and authors, according to Gary W. Jay, MD, DAAPM, FAAPM, Medical Director of The DNA Center in Daytona Beach, Florida.

"Famous people who might've experienced auras include Lewis Carol who wrote *Alice's Adventures in Wonderland* and a rather well-known painter named Vincent van Gogh," Dr. Jay said.

Some people believe the visual distortions at the center of these men's art, came from migraine auras. The list of other suspected and known famous migraineurs includes Frederich Nietzsche, Sigmund Freud, Claude Monet, Pablo Picasso, and Georges Pierre-Seurat.

"There are different types of migraines," Dr. Jay explained. "You can have an aura without headache, visual aura with no headache associated. I wouldn't say it's common, nor quite rare – perhaps 5% to 6%. It may only happen once or twice."

Aura itself is therefore an indication for a full neurological workup, he said. Although migraine is not associated with loss of consciousness, aura symptoms sometimes lead to misdiagnosis as seizure.

Continued on page 21

PDMPs: 'One Tool in the Toolbox' for Tracking Controlled Substance Prescriptions

Prescription drug monitoring programs impact opioid prescribing and clinical decision making

Drug-induced deaths are now the leading cause of injury death in 17 states and the District of Columbia. In response to this crisis, 49 states and one territory had passed legislation authorizing Prescription Drug Monitoring Programs (PDMPs) as of January 2013, and 43 states had an operating PDMP.

What does this mean for the practicing clinician?

"PDMPs are tools that can potentially help track how medications are being prescribed and dispensed," said Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP, a clinical instructor at the State University of New York Stony Brook School of Medicine, Stony Brook, New York, and Vice President of Medical Affairs at Inflexxion, Inc., Newton, Massachusetts. "They are, at best, one tool in the toolbox."

In essence, "a PDMP is a state-wide electronic database that gathers information from pharmacies on dispensed prescriptions for controlled substances," he said, adding that states that permit practitioners to dispense also require them to submit prescription information to the PDMP. Although prescription data are made available upon request from end users and are sometimes distributed via unsolicited reports, "states vary widely in which categories of users are permitted to request and receive prescription history reports and under what conditions."

Additional recipients of data may also include licensing boards, law enforcement and drug control agents, medical examiners, drug courts, criminal diversion programs, addiction treatment programs, public and private third-party payers, and other public health and safety agencies.

On August 27, 2013, the State of New York mandated use of its free program, I-STOP (Internet System for Tracking Over-Prescribing), requiring most prescribers to consult the Prescription Monitoring Program (PMP) Registry when writing prescriptions for Schedule II, III, and IV controlled substances, he said.

Consider Less Immunosuppressant Opioids in Elderly

Opioids have direct effects on immunity that may compromise optimal immune function

Interaction between opioids and the immune system is complex in that both trauma and pain can cause immunosuppression, with relief of pain, in part, alleviating this condition. Although definitive human data are lacking, animal studies show strong evidence of opioid immunosuppression, said Joseph V. Pergolizzi, MD, adjunct Assistant Professor of Pharmacology in the Department of Pharmacology at Temple University School of Medicine, Philadelphia, Pennsylvania.

"Treatment strategies in special populations like the elderly might benefit from the avoidance of drugs that have intrinsic immunosuppressive properties," said Dr. Pergolizzi.

Not all opioids share the same immunosuppressive properties. This distinction may help guide providers treating elderly patients with characteristic "immunosenescence," or decline in immune system responsiveness.

In both animals and humans undergoing surgery, surgical stress has been shown to activate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, leading to suppressed immune function, including natural killer (NK) cell activity, cytokine production, and lymphoproliferation.

Pain is also a stressor that can impair immune functions; notably, NK activity. Decreases in NK activity in the perioperative period and their association with greater rates of cancer recurrence and mortality have been described for cancers of the breast, head and neck, colon and rectum, and lung.

"Opioids, however, have additional direct effects on many aspects of immune function," Dr. Pergolizzi said. "These effects depend on multiple factors, including structure of the individual opioid agent and dose range used." Potential mechanisms include modulation of the hypothalamic pituitary axis, stimulation of the sympathetic nervous system, and direct action via mu receptors on immune cells.

"The registry provides practitioners with direct, secure access to view dispensed controlled substance prescription histories for their patients," he said, adding the PMP is available "24/7" (https://commerce.health.state.ny.us). The reports include all controlled substances dispensed in New York State and reported by the pharmacy/dispenser for the past 6 months, allowing practitioners to evaluate their patient's treatment with controlled substances "and determine whether there may be abuse or nonmedical use."

Studies of PDMP use, for example, in an emergency department, found that 41% of cases had altered prescribing after the clinician reviewed the PDMP data: 61% of patients received fewer or no opioid pain medications than originally planned, with "39% receiving more opioid medication than previously planned because the physician was able to confirm the patient did not have a recent history of controlled substance use," Dr. Zacharoff said.

A survey in Oregon found typical PDMP users to be emergency medicine and primary care clinicians and pain/addiction specialists. Among users, 95% reported accessing the PDMP "when they suspected a patient of abuse or diversion." Fewer than half checked it for every new patient or every time they prescribed.

"Nearly all users reported that they discuss worrisome PDMP data with patients," Dr. Zacharoff said, with 54% reporting making mental health/substance abuse referrals and 36% reporting sometimes discharging patients from the practice. Those surveyed reported "frequent patient denial or anger."

He concluded that more research on PMDPs is needed, including how they are incorporated into workflow and clinical decision making, what barriers exist, and how clinicians share results with patients

Opioids that are immunosuppressive include codeine, methadone, morphine, remifentanil, and fentanyl, he said. Less immunosuppressive agents are buprenorphine, hydromorphone, oxycodone, and tramadol. One study of the effect of the continuous infusion of fentanyl or buprenorphine on immune responses found that for fentanyl, a significant reduction of the immune function was present for all parameters studied, whereas buprenorphine did not affect the immune responses evaluated, he said.

In summarizing the key take-home messages from his presentation, Dr. Pergolizzi said that "both therapeutic and chronic uses of opioids compromise the optimal functioning of the immune system, and overwhelming evidence suggests that opioid use affects both innate immunity and adaptive immunity."

For that reason, "chronic administration of opioids decreases the proliferative capacity of macrophage progenitor cells and lymphocytes; additionally, the differentiated function of immune cells is significantly affected by opioids. These effects are mediated by either a direct action of opioids on the target cells or by indirect centrally mediated pathways."

Furthermore, "molecular biological and biochemical characterization suggest that immune cells differentially express classical opioid receptors," meaning that "not all opioids have the same effect on the immune system."

Although the clinical relevance of these finding remains to be determined, "special populations like the elderly maybe be more susceptible to the immunosuppressive effects of opioids," he concluded.

Continued from page 19

Migraine with aura involves periods of local neurological symptoms preceding headache, which include visual, sensory, or speech symptoms, or visual symptoms including scotoma or seeing zig-zag lines.

"Sensory auras may be numbness or tingling of the face or fingers," he added. "There may also be speech difficulties."

> The artwork that may have been inspired by migraine auras, has come to serve as a description of those symptoms.

Lewis Carol's *Alice's Adventures in Wonderland* and *Through the Looking-Glass* drew on sensations of bodily distortion and light sensitivity reported among some people who suffer from migraine, he noted.

In some cases, the artwork that Dr. Jay believes may have been inspired by migraine auras, has come to serve as a description of those symptoms.

"Some Alice in Wonderland Syndrome (AIWS) symptoms include feeling as if your body is too big or too small (and) time may feel like it slows down or speeds up," Dr. Jay said.

"[The artist] Georges-Pierre Seurat experienced migraine with visual auras," he added. "The pointillistic effect he developed was thought to be secondary to a visual aura. Other scotoma suggestive images include gliding and idle boats, smoking factories, chimneys, and more, with slightly inaccurate colors and contrasts. In some neurological writing, the 'Seurat effect' represents scintillating scotomas. … 'Picasso-like' and 'cubist' are possibly more understood as meaning migraine than the 'Seurat Effect,' though."

MOVANTIK™ (naloxegol) tablets, for oral use, C-II

BRIEF SUMMARY OF PRESCRIBING INFORMATION

For Full Prescribing Information, see package insert.

INDICATIONS AND USAGE

MOVANTIK (naloxegol) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

DOSAGE AND ADMINISTRATION

Administration

- Discontinue all maintenance laxative therapy prior to initiation of MOVANTIK. Laxative(s) can be used as needed if there is a suboptimal response to MOVANTIK after three days.
- Alteration in analgesic dosing regimen prior to initiating MOVANTIK is not required.
- MOVANTIK has been shown to be efficacious in patients who have taken opioids for at least 4 weeks. Sustained exposure to opioids prior to starting MOVANTIK may increase the patient's sensitivity to the effects of MOVANTIK *[see Clinical Studies (14) in Full Prescribing Information].*
- Take MOVANTIK on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal.
- Swallow tablets whole, do not crush or chew.
- Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK.
- Discontinue MOVANTIK if treatment with the opioid pain medication is also discontinued.

Adult Dosage

The recommended MOVANTIK dosage is 25 mg once daily in the morning.

If patients are not able to tolerate MOVANTIK, reduce the dosage to 12.5 mg once daily *[see Clinical Pharmacology (12.2) in Full Prescribing Information].*

Dosage in Adult Patients with Renal Impairment

The starting dosage for patients with creatinine clearance (CLcr) < 60 mL/min (i.e., patients with moderate, severe or end-stage renal impairment) is 12.5 mg once daily. If this dosage is well tolerated but OIC symptoms continue, the dosage may be increased to 25 mg once daily taking into consideration the potential for markedly increased exposures in some patients with renal impairment and the increased risk of adverse reactions with higher exposures *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

Dosage Recommendations due to Drug Interactions

Avoid concomitant use of MOVANTIK with moderate CYP3A4 inhibitor drugs (e.g., diltiazem, erythromycin, verapamil). If concurrent use is unavoidable, reduce the MOVANTIK dosage to 12.5 mg once daily and monitor for adverse reactions *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in Full Prescribing Information].*

CONTRAINDICATIONS

MOVANTIK is contraindicated in:

- Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation *[see Warnings and Precautions (5.1) in Full Prescribing Information].*
- Patients concomitantly using strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning *[see Drug Interactions (7.1) and Pharmacokinetics (12.3) in Full Prescribing Information].*
- Patients who have had a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients.

WARNING AND PRECAUTIONS

Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using MOVANTIK in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent or worsening abdominal pain; discontinue MOVANTIK in patients who develop this symptom *[see Contraindications (4) in Full Prescribing Information].*

Opioid Withdrawal

Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning have occurred in patients treated with MOVANTIK *[see Adverse Reactions (6.1) in Full Prescribing Information].* In addition, patients receiving methadone as therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids *[see Adverse Reactions (6.1) in Full Prescribing Information].* Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Take into account the overall risk-benefit profile when using MOVANTIK in such patients. Monitor for symptoms of opioid withdrawal in such patients.

ADVERSE REACTIONS

Clinical Trials 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.

The data described below reflect exposure to MOVANTIK in 1497 patients in clinical trials, including 537 patients exposed for greater than six months, and 320 patients exposed for 12 months.

The safety data described in Table 1 are derived from two double-blind, placebo-controlled trials (Studies 1 and 2) in patients with OIC and non-cancer related pain *[see Clinical Studies (14) in Full Prescribing Information].*

Study 3 (n=302) was a safety extension study that allowed patients from Study 1 to continue the same blinded treatment for an additional 12 weeks. Safety data for patients in Study 3 are similar to those listed in Table 1.

Study 4 (n=844) was a Phase 3, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of naloxegol versus usual care treatment for OIC (as determined by the investigator and excluding peripheral opioid antagonists) in patients with non-cancer related pain. The population enrolled in Study 4 was similar to that of the other studies. Eligible patients were randomized in a 2:1 ratio to receive either naloxegol 25 mg once daily or usual care treatment for OIC. The most commonly used laxatives in the usual care group were rectal stimulants (e.g., bisacodyl), oral stimulants (e.g., senna), and oral osmotics (e.g., macrogol, magnesium). Safety data for patients in Study 4 are similar to those listed in Table 1.

Table 1 lists adverse reactions in pooled Studies 1 and 2 occurring in ≥ 3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

Table 1. Adverse Reactions* in Patients with OIC and Non-Cancer Pain (Studies 1 and 2)

Adverse Reaction	MOVANTIK 25 mg (n=446)	MOVANTIK 12.5 mg (n=441)	Placebo (n=444)
Abdominal Pain	21%	12%	7%
Diarrhea	9%	6%	5%
Nausea	8%	7%	5%
Flatulence	6%	3%	3%
Vomiting	5%	3%	4%
Headache	4%	4%	3%
Hyperhidrosis	3%	<1%	<1%

*Adverse reactions occurring in ≥ 3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

Opioid Withdrawal

Possible opioid withdrawal, defined as at least three adverse reactions potentially related to opioid withdrawal that occurred on the same day and were not all related to the gastrointestinal system, occurred in less than 1% (1/444) of placebo subjects, 1% (5/441) receiving MOVANTIK 12.5 mg, and 3% (14/446) receiving MOVANTIK 25 mg in Studies 1 and 2 regardless of maintenance opioid treatment. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Patients receiving methadone as therapy for their pain condition were observed in Studies 1 and 2 to have a higher frequency of gastrointestinal adverse reactions than patients receiving other opioids [39% (7/18) vs. 26% (110/423) in the 12.5 mg group; 75% (24/32) vs. 34% (142/414) in the 25 mg group].

DRUG INTERACTIONS

Effects of Other Drugs on MOVANTIK

Table 2 displays the effects of other drugs on MOVANTIK.

Table 2. Effects of Other Drugs on MOVANTIK

Concomitant Agents	Mechanism of Action	Clinical Recommendation
CYP3A4 Inhibitors		
Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)	Increase plasma naloxegol concentrations and may increase the risk of adverse reactions *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.	Use with strong CYP3A4 inhibitors is contraindicated *[see Contraindications (4) in Full Prescribing Information]*.
Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil)		Avoid use with moderate CYP3A4 inhibitors; if unavoidable, decrease dosage of MOVANTIK to 12.5 mg once daily and monitor for adverse reactions *[see Dosage and Administration (2.4) in Full Prescribing Information]*.
Weak CYP3A4 inhibitors (e.g., quinidine, cimetidine)	Clinically significant increases in naloxegol concentrations are not expected.	No dosage adjustments are necessary.
Grapefruit or grapefruit juice*	Can increase plasma naloxegol concentrations.	Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK *[see Dosage and Administration (2.1) in Full Prescribing Information]*.
CYP3A4 Inducers		
Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's wort)	Significantly decrease plasma naloxegol concentrations and may decrease the efficacy of MOVANTIK *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.	Use with strong CYP3A4 inducers is not recommended.
Other Drug Interactions		
Other opioid antagonists	Potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal.	Avoid use of MOVANTIK with another opioid antagonist.

*The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength)

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with MOVANTIK in pregnant women. The use of MOVANTIK during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC (area under the plasma concentration-time curve) at the maximum recommended human dose. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rabbits during the period of organogenesis at doses up to 409 times the human AUC at the maximum recommended human dose. MOVANTIK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

Oral administration of up to 750 mg/kg/day naloxegol in rats (1452 times the human AUC at the maximum recommended human dose) and 450 mg/kg/day naloxegol in rabbits (409 times the human AUC at the maximum recommended human dose) during the period of organogenesis produced no adverse effects on embryo-fetal development. Oral administration of up to 500 mg/kg/day in rats (195 times the maximum recommended human dose based on body surface area) during the period of organogenesis through lactation produced no adverse effects on parturition or the offspring.

Nursing Mothers

It is unknown whether MOVANTIK is present in human milk; however, naloxegol is present in rat milk and is absorbed in nursing rat pups. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of MOVANTIK have not been established in pediatric patients.

Geriatric Use

Of the total number of subjects in clinical studies of MOVANTIK, 11 percent were 65 and over, while 2 percent 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.

MOVANTIK exposure was higher in elderly healthy Japanese subjects compared to young subjects *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. No dosage adjustment is needed in elderly patients.

Renal Impairment

Some subjects with creatinine clearance (CLcr) values < 60 mL/minute (i.e., moderate, severe or end-stage renal disease) were shown to exhibit markedly higher systemic exposure of naloxegol compared to subjects with normal renal function. The reason for these high exposures is not understood. However, as the risk of adverse reactions increases with systemic exposure, a lower starting dosage of 12.5 mg once daily is recommended. No dosage adjustment is needed in patients with mild renal impairment *[see Dosage and Administration (2.3), and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Hepatic Impairment

The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol has not been evaluated. Avoid use of MOVANTIK in patients with severe hepatic impairment, as the dosage in these patients has not been determined. No dosage adjustment is required for patients with mild or moderate hepatic impairment *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Naloxegol is a C-II controlled substance.

Abuse

MOVANTIK is a peripherally acting opioid antagonist with no risk of abuse.

Dependence

MOVANTIK is a peripherally acting opioid antagonist with no risk of dependency.

OVERDOSAGE

In a clinical study of patients with OIC a daily dose of 50 mg (twice the recommended dosage), administered over 4 weeks, was associated with an increased incidence of GI adverse reactions, such as abdominal pain, diarrhea and nausea. These adverse reactions frequently occurred within 1-2 days after dosing.

No antidote is known for naloxegol. Dialysis was noted to be ineffective as a means of elimination in a clinical study in patients with renal failure.

If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

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AstraZeneca

IN ADULT PATIENTS WITH CHRONIC NON-CANCER PAIN

HOW DO YOU TREAT OPIOID-INDUCED CONSTIPATION?

MOVANTIK™ (naloxegol) tablets C-II: NOW FDA APPROVED. ANTICIPATED ARRIVAL IS IN THE FIRST HALF OF 2015.

MOVANTIK, a once-daily oral tablet, is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain[1]

IMPORTANT SAFETY INFORMATION ABOUT MOVANTIK

- MOVANTIK is contraindicated in:
  - Patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction due to the potential for GI perforation
  - Patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms
  - Patients with a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients
- Cases of GI perforation have been reported with the use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for severe, persistent, or worsening abdominal pain; discontinue if this symptom develops
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning, occurred in patients treated with MOVANTIK. Patients receiving methadone in the clinical trials were observed to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids. Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Monitor for symptoms of opioid withdrawal when using MOVANTIK in such patients
- The most common adverse reactions with MOVANTIK in clinical trials were abdominal pain (21%), diarrhea (9%), nausea (8%), flatulence (6%), vomiting (5%), headache (4%), and hyperhidrosis (3%)

Please see the Brief Summary of full Prescribing Information on the adjacent pages.

Reference: 1. Prescribing Information for MOVANTIK. AstraZeneca Pharmaceuticals LP, Wilmington, DE.

AstraZeneca