The national conference on pain for frontline practitioners.

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2015

- Top 10 Reasons to Stay in the Pain Management Game
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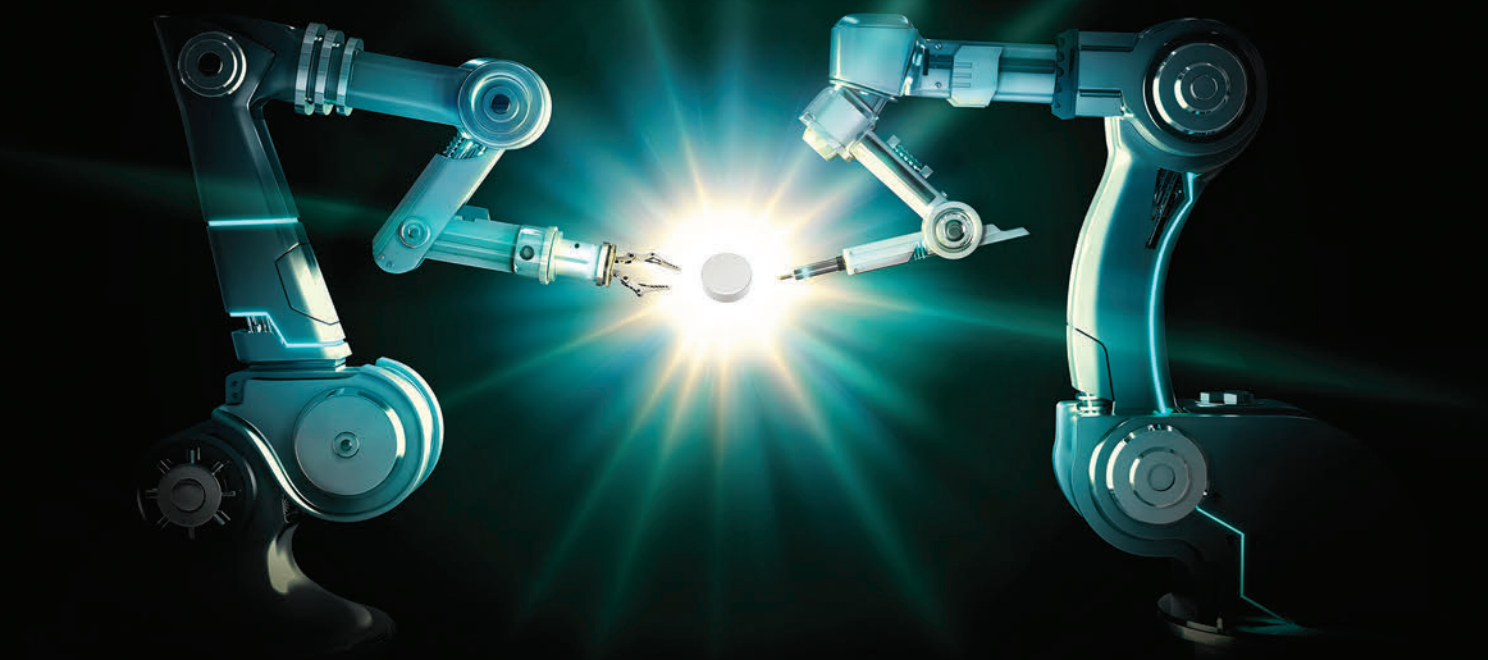
- How to Protect Your Practice From a Drug Diversion Investigation
- Safe Opioid Prescribing in the Era of Overdose
- Peripheral Neuropathies: A Primer
- Psychotherapy, Pharmacotherapy Combo Best for Late-Life Depression and Pain
- E-Prescribing to Combat Misuse and Diversion
- "Minor" Traumatic Brain Injuries Are Anything But Minor
- Treating Morton's Neuroma, an Often Misunderstood Foot Pain
- Advances in Naloxone Technologies Offer More Options for Reducing Opioid Overdoses
- Opioid Prescribing: Navigating the Ethical Battlefield

HYSINGLA™ ER:

The *first and only* once-daily hydrocodone with abuse-deterrent properties and no acetaminophen



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 3A4 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 see Additional Warnings and Precautions on the following pages.

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

Hysingla ER: *The same opioid molecule your hydrocodone patients are familiar with*

- **One tablet daily provides 24 hours of hydrocodone delivery**
- **Formulated with properties intended to make the tablet more difficult to misuse and abuse**
  - 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**
  - 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
- **Proven effective in a clinical trial**
- **Contains no acetaminophen**
- **Flexibility of 7 dosage strengths: 20, 30, 40, 60, 80, 100, and 120 mg tablets**
  - The starting dose for patients who are not opioid tolerant is Hysingla ER 20 mg orally every 24 hours. Opioid-tolerant patients are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid. Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression

INDICATIONS AND USAGE

Hysingla ER (hydrocodone bitartrate) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Hysingla ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Hysingla ER is not indicated as an as-needed analgesic.

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.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- Hysingla ER contains hydrocodone, a Schedule II controlled substance. Hysingla ER exposes users to the risks of opioid addiction, abuse, and misuse. 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. 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 during therapy for the development of these behaviors or conditions. 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.

Dosage and Administration

- Hysingla ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving Hysingla ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death.

Titration and Maintenance of Therapy

- Continually re-evaluate patients receiving Hysingla ER to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse, or misuse.

For more information, visit HysinglaER.com

HYDROCODONE REENGINEERED

Hysingla™ ER
(Hydrocodone Bitartrate) II
EXTENDED-RELEASE TABLETS

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with modified-release opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death. The risk of respiratory depression is greatest during the initiation of therapy or following a dose increase; therefore, closely monitor patients for respiratory depression. Proper dosing and titration of Hysingla ER are essential. 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.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Hysingla ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening to the neonate if not recognized and treated, and requires management according to protocols developed by neonatology experts.

Interactions with Central Nervous System Depressants

- Hypotension, profound sedation, coma, respiratory depression, or death may result if Hysingla ER is used concomitantly with other CNS depressants, including alcohol or illicit drugs that can cause CNS depression. 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.

Use in Elderly, Cachectic, and Debilitated Patients and Patients with Chronic Pulmonary Disease

- Closely monitor elderly, cachectic, and debilitated patients, and patients with chronic obstructive pulmonary disease because of the increased risk of life-threatening respiratory depression. Consider the use of alternative non-opioid analgesics in patients with chronic obstructive pulmonary disease if possible.

Use in Patients with Head Injury and Increased Intracranial Pressure

- Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or impaired consciousness). Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of Hysingla ER in patients with impaired consciousness or coma.

Hypotensive Effect

- Hysingla ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. Monitor patients during dose initiation or titration. 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.

Gastrointestinal Obstruction, Dysphagia, and Choking

- Use caution when prescribing Hysingla ER for patients who have difficulty swallowing, or have underlying gastrointestinal disorders that may predispose them to obstruction, dysphagia, or choking. Consider use of an alternative analgesic in these patients.

Decreased Bowel Motility

- Hysingla ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. 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.

Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of CYP3A4 inhibitors may prolong opioid effects. Use with CYP3A4 inducers may cause lack of efficacy or development of withdrawal symptoms. If co-administration is necessary, evaluate patients frequently and consider dose adjustments until stable drug effects are achieved.

Driving and Operating Machinery

- Hysingla ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Interaction with Mixed Agonist/Antagonist Opioid Analgesics

- Avoid the use of mixed agonist/antagonist analgesics in patients who have received or are receiving Hysingla ER, as they may reduce the analgesic effect and/or precipitate withdrawal.

QTc Interval Prolongation

- QTc prolongation has been observed following daily doses of 160 mg of Hysingla ER. Avoid use in patients with congenital QTc syndrome. 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 QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

ADVERSE REACTIONS

- Most common treatment-emergent adverse reactions (≥5%) reported by patients treated with Hysingla ER in the clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence.

Please see Additional Warnings and Precautions on the preceding pages.

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

Hysingla™ ER

(Hydrocodone Bitartrate) II

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

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 3A4 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 3A4 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
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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 303511-0C, Revised 02/2015 (A)

KEYNOTE ADDRESS

Top 10 Reasons to Stay in the Pain Management Game

"Pain medications are neither panacea nor pariah, and experienced prescribers understand the need for a nuanced approach to pain management," said Michael R. Clark, MD, MPH, MBA, of Johns Hopkins University School of Medicine and the American Society of Pain Educators.

He identified several key elements necessary for the development of a successful individualized, patient-focused pain management practice:

- Skill in risk assessment, monitoring, and documentation
- An understanding of psychosocial factors that contribute to pain
- Familiarity with alternate and adjuvant modalities of treating pain
- Sensitivity to age- and gender-related differences in pain conditions
- The ability to motivate patients to be invested in the success of their treatment

"No one said this is easy. Given the time and resource constraints of our medical practices, it clearly is a challenge. And the complexity of the task is only compounded by a changing legal/regulatory environment in which states are starting to take matters into their own hands, crafting their own responses to the epidemic of opioid and heroin addiction," explained Dr. Clark.

Dr. Clark then passed the baton to Charles Argoff, MD, CPE, professor of neurology and director of the Comprehensive Pain Center at Albany Medical College, who outlined his "Top 10 Reasons to Stay in the Pain Game," or "Why The Deli Will Have to Wait."

1. The current state of pain management. Pain is the number one reason people in the United States seek healthcare, according to a recent Institute of Medicine (IOM) report. A national pain strategy released in April 2015 proposed a new plan to improve the treatment of chronic pain both now and in the future. The strategy includes objectives and plans in key areas of pain and pain care including professional education and training, public education, communication, service delivery, reimbursement for care, preventive care, and attention to disparities in population research.

"There are new scientific discoveries reported nearly daily and new treatments—both medical and nonmedical—that are newly available or currently in development. Now is not the time to leave the field," Dr. Argoff said.

2. The public's perception of pain. There is still a lifetime of work to be done to educate the public and especially the media, healthcare providers, and payors that chronic pain is real and needs to be taken seriously.

"The media has had a tragic field day, focusing nearly solely on negative aspects of pain management without reporting sufficiently on the very positive and exciting progress being made in our field," Dr. Argoff said.

3. Not enough qualified pain management providers. Addressing the gap in the United States between the number of patients who are in pain and who are in need of evaluation and treatment, the number of pain specialists, and the number of primary care providers (PCPs) who are also involved in the care of persons in pain is a top priority. The IOM report estimates that 100 million adults in the United States experience chronic pain, yet there are only approximately 4000 pain specialists. At the same time, there are more than 400,000 PCPs, including internists, family practice providers, pediatricians, obstetricians/gynecologists, and geriatricians.

Data from a recent survey involving 3000 primary care providers, pain specialists, chiropractors, and acupuncturists indicated that 52% of patients with chronic pain are primarily treated by a PCP, 2% by a pain specialist, 40% by a

Michael Clark, MD, welcomes the audience to PAINWeek '15 during the keynote address.

chiropractor, and 7% by an acupuncturist. Other survey findings indicated that long-acting opioids, anticonvulsives, and antidepressants are prescribed much more frequently by pain specialists compared with PCPs, and that both PCPs and pain specialists reported prescribing opioids less often now due to concerns regarding regulatory oversight.

4. Optimal pain management requires a multidisciplinary effort. People in pain benefit most when their pain is assessed and addressed in an integrated fashion. This approach must be embraced by those creating undergraduate and graduate-level healthcare provider education, those paying for health care, those reporting about health care, and those receiving care. "Chronic pain does not exist in a vacuum, and the broader medical community needs to become engaged," Dr. Argoff said.

5. Lifelong pain management education. Fewer than 50% of 170 accredited US medical or osteopathic schools currently require students to complete a pain management course as part of undergraduate medical training. Dr. Argoff asked, "How can we possibly be prepared to optimally evaluate our patients who are experiencing chronic pain, unless we receive such training?"

Pain management training needs to be mandatory and uniform at multiple levels and across all types of healthcare providers, he argued. Although progress is being made, it is not happening quickly enough.

"One consequence of this is the demonization of the person in pain. With so many healthcare providers ill prepared to appropriately and comprehensively assess and treat peoples' chronic pain, the person in pain becomes the problem," Dr. Argoff said.

6. Where will you be treated, if you need pain management? As non-pain management providers increasingly refuse to treat pain, and as pain specialists limit their treatment modalities due to regulatory concerns, too many patients with pain will be lost without anyone to care for them. Dr. Argoff continued, "I often ask myself what would I do if I couldn't find someone to treat my pain?"

7. Changes to patient satisfaction measures. The Center for Medicare & Medicaid Services (CMS) is now using new measures of patient satisfaction that may significantly affect pain management. Historically there have been many approaches to measuring patient satisfaction. Now patients are asked to rate their satisfaction on a scale from 1 to 10. The number reported by CMS is the percentage of respondents who answer 9 or 10, which must be 80% or above for an institution or a provider to pass.

"Patients don't know this when they're given these surveys, and providers are not allowed to coach patients about this scoring system or provide them with a practice questionnaire. This scheme may have profound implications because reimbursement is tied to these scores," Dr. Argoff said.

8. The need to teach evidence-based medicine (EBM) as it was defined. In 1996, David Sackett, the father of EBM, and his international colleagues wrote an editorial outlining what EBM is:

The conscientious, judicious, and explicit use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available evidence from systemic research. By individual clinical expertise, we mean the proficiency and judgment of individual clinicians as they acquire such through clinical experience and practice."

Dr. Argoff argued that this is not the way EBM guidelines are currently derived, stating that many clinical guidelines do not include clinical experiences in any way, but are generated solely from literature review.

The patients we treat often have comorbidities that would exclude them from inclusion in many studies and disqualify them from many of the particular studies that so-called evidence-based guidelines are based on," he said.

9. The need to address inherent conflicts of interest. Ensuring that the virtues of corporations are on a level playing field with what is best for the patient is of utmost importance. "We've received notice from the largest US healthcare insurers that use of Botox for chronic migraine is considered experimental, even though it's been approved for this use since October of 2010," said Dr. Argoff.

Under current insurance guidelines, patients with chronic migraine need to demonstrate treatment failure on as many as 3 oral treatments for 60 days each before the patient is considered an appropriate candidate for Botox, even though none of these oral treatments are approved by the FDA for chronic migraine.

Many of the largest health insurers are publicly traded companies that are responsible to corporate stakeholders. "It is time for us to look at the elephant in the room and take a stand against corporations delegating how we should treat our patients," Dr. Argoff said.

10. Remember why you became a healthcare provider. "I hope you all continue to be great healthcare providers," Dr. Argoff concluded. "We are all here to listen to and learn from our colleagues, and to speak and interact with each other, all in the name of improving the care of the people with chronic pain who depend on us."

Get things moving with reliable and rapid relief.

RELISTOR helps provide chronic non-cancer pain patients relief from opioid-induced constipation—without compromising analgesia.[1,2]

- 6 out of 10 RELISTOR® (methylnaltrexone bromide) patients (n=150) had at least 3 Spontaneous Bowel Movements (SBMs) per week ($P<0.001$)[1,2]
- One-third of patients taking RELISTOR (n=150) experienced an SBM within 4 hours of their first dose ($P<0.001$)[1]

INDICATIONS

RELISTOR is indicated for the treatment of 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 advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied.

IMPORTANT SAFETY INFORMATION

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 full 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.

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RELISTOR®
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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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Education Key When Considering Prescribing Medical Marijuana

Clinicians should educate themselves and their patients if they choose to use medical marijuana in their practice, according to Michael E. Schatman, PhD, a clinical psychologist who has spent decades working in multidisciplinary chronic pain management.

Much has been published on medical marijuana within the past year, but the data on safety are not encouraging and data on clinical efficacy are limited. Generally, the quality of research from countries like Israel and Brazil has been much better than US research because the laws governing it are different in those countries, Dr. Schatman explained. However, help may be on the way in the form of the 21st Century Cares Act. The law was recently amended to facilitate medical cannabis research, rescheduling it from a 1 to a 1-R designation and calling for an additional $1.75 billion in National Institutes of Health funds.

Currently, all federally funded medical marijuana research must use low-grade marijuana grown at the University of Mississippi, which comes in 3 different dosage strengths: low at 1.29% tetrahydrocannabinol (THC), moderate potency at 3.53%, and high potency at 7%.[1]

These potencies present a challenge, because published data from Mehmedic et al showed that the average THC of government-seized marijuana varied from 3.4% to 8.8%,[2] meaning that the cannabis that is being tested for medicinal use is not the same as what many may be using recreationally.

There are new clinical efficacy data related to medical marijuana, but they are generally data from other countries. One study out of Australia concluded

Dr. Schatman discusses the challenges associated with medicinal marijuana.

medical marijuana was associated with a 70% reduction in chronic pain symptoms. However, it made no mention of the constituents of the marijuana used or the types of pain.[3]

An American study of medical marijuana for patients with diabetic neuropathic pain concluded that a 7% THC formulation worked better than a 4% or a 1% formulation, but it also resulted in more cognitive impairment.[4]

Discussing the safety of medicinal marijuana use, Dr. Schatman cited data demonstrating that smoking remains the most common route of administration,[5] and a recent review showed that pulmonary effects may be worse than previously thought.[6] These data are sometimes difficult to interpret, however, because many people who smoke marijuana also smoke tobacco.

Although research into cannabidiol is "just starting," Dr. Schatman cited several studies that show its safety has been established when coadministered with fentanyl,[7] that it enhances fracture healing,[8] and has been associated in animal models with protective effects on lesion-induced intervertebral disc degeneration.[9]

"We need to look at isolated constituents–primarily cannabidiol–in order to maximize analgesia and functionality," Dr. Schatman explained.

He expressed frustration with zealous proponents of the drug who tend to ignore the existing empirical data, seeking to guide practice based upon what they simply want to believe.

Dr. Schatman directed clinicians to an article published in the *Clinical Journal of Pain* that outlined a "medicinal cannabis treatment agreement," calling it "absolutely brilliant."

These agreements can help physicians address inappropriate utilization by the authorized patient and prompt discussion of the risk of marijuana generally and to specific populations.

Dr. Schatman noted he is on the speaker's bureau for Mallinckrodt.

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How to Protect Your Practice From a Drug Diversion Investigation

As government regulation increases to control opioid abuse, legitimate pain management practitioners and patients alike are at greater risk than ever for being unfairly stigmatized.

Healthcare providers got an insider's look at how law-enforcement officials conduct drug diversion investigations, learning how to avoid unintentional mistakes that may garner unwanted scrutiny from regulatory bodies and how to better protect their practices.

Two members of the National Association of Drug Diversion Investigators, Marc Gonzalez, PharmD, and Steven Louie, JD, hosted an interactive session detailing actual cases in which "pill mills" were busted, letting clinicians enact scenarios in which they assume the role of the drug diversion investigator.

Dr. Gonzalez and Mr. Louie identified a laundry list of factors from previously documented legal cases that could provoke probable cause for law enforcement to obtain a warrant, make an arrest, or conduct a personal or property search in the event that criminal charges are being considered for drug diversion (see *Table*).

The investigators then assigned clinicians to work in teams to develop a plan for how they would act on anonymous tips provided for several case-based scenarios, as well as for organizing an undercover investigation and obtaining a search warrant. While working through the cases, Dr. Gonzalez and Mr. Louie offered practical advice to attendees in the event that they become subjects of a drug diversion investigation.

- Observe the right to remain silent.
- Do not prescribe controlled substances to new patients without obtaining a full history and performing a comprehensive workup.
- Follow Federation of State Medical Boards Model Guidelines.
- Create a "Practice Committee" within your community.
- Establish a liaison with local law enforcement.

As government interventions are ramped up to control opioid prescription abuse, legitimate pain management healthcare providers and patients alike are at greater risk than ever for being

Safe Opioid Prescribing in the Era of Overdose

Drug screening, risk stratification, and pharmacogenetic testing should be used to guide prescribing habits.

The number of opioid prescriptions filled in US pharmacies has tripled since the early 1990s, from 76 million in 1991 to 219 million in 2001.[1] During this time period, emergency department (ED) visits for opioid misuse or abuse and opioid-related drug overdose deaths also rose sharply.

Continuing the upward trajectory, ED visits attributable to opioids increased from 600,000 to more than 1.2 million from 2004 to 2010, and overdose deaths have quadrupled from 4000 to more than 12,000 annually from 1999 to 2010, according to data from the Substance Abuse and Mental Health Services Administration.[2]

"As a result many states are enacting legislation to ensure appropriate, safe opioid prescribing," said Brett Badgley Snodgrass, MSN, APRN, FNP-C.

"Safe prescribing is of utmost importance, primarily to decrease diversion and abuse, but also to make it as safe and appropriate for our patients," she said.

To ensure safe and effective chronic pain management, urine drug testing, risk stratification, and pharmacogenetic testing are also paramount.

"Drug screening is one of the elements we use in guiding our prescriptive habits when we're talking about opiates or controlled substances. It absolutely should be used in practice; how often depends on state mandates, the individual prescriber, and the patient," Ms. Snodgrass said.

Drug testing helps providers determine if patients are taking their medications as prescribed, and also if they are taking other drugs that may interfere with their medications. Such screening methods include urine analysis, blood immunoassays, and gas chromatography/mass spectrometry (GC/MS).

"Urine drug screening is one of the easiest and most reliable ways to obtain information on drug use. It can be performed quickly, so you can perform

unfairly stigmatized, said Dr. Gonzalez. An increasing number of general practice and family medicine clinicians are opting out of offering pain management services, and pain management specialists are overloaded.

It is more important than ever for pain management providers to protect themselves from unnecessary litigiousness, while at the same time avoiding the unintended adverse consequence of underprescribing pain medications to patients who need them. "Don't become complacent," cautions Dr. Gonzalez. "Have a plan in place."

The best way to do this is to establish a community standard of what it means to be an ordinary, reasonable practitioner. "Regulatory will see right away that you have gone above and beyond your standard duties," Dr. Gonzalez emphasized. "Nothing is completely bulletproof, but this is pretty close."

TABLE. Red Flags for Probable Cause in Drug Diversion Investigations

Demonstrating lack of "good faith" — defined as honesty of purpose, lack of intent to defraud, and being faithful to one's duty or obligation — when conducting a patient examination, as indicated by spending very little time with the patient
Issuing large numbers of prescriptions
Distributing an inordinate quantity of controlled substances
Directing patients to fill prescriptions at different pharmacies or to travel far distances to fill prescriptions
Issuing prescriptions to a patient known to be delivering drugs to others
Asking patients what they want and prescribing what they want
Writing prescriptions used at intervals inconsistent with legitimate treatment, or writing multiple prescriptions during the same visit
Billing patients based on the type of prescription, number of prescriptions written, or quantity of drug dispensed instead of by the office visit
Treating patients whose conditions never improve or worsen
Prescribing every patient the same amount of medication (eg, 100 hydrocodone; 100 Xanax)
Attracting long lines of patients or crowds
Writing prescriptions using multiple, sometimes fictitious names

a point-of-care test and have some working knowledge of what is in that patient's urine when he or she leaves your office," Ms. Snodgrass said.

When interpreting point-of-care test results, clinicians should assess the risk of false positives or negatives and should not make definitive decisions based on findings. If a urine drug test yields an unexpected finding, providers should limit the provision of the opioid to a 7- to 14-day period.

Clinicians should also be aware that some medication use or abuse may go undetected on a point-of-care test. Prescription drugs such as fentanyl, oxycodone, and carisoprodol are often omitted, certain opioid normetabolites may not react (typically <0.1%), and high thresholds are typically used in point-of-care tests.

Confirmation testing with more accurate methods such as GC/MS should be performed prior to making a final care decision, she advised.

Genomic testing to detect genetic predispositions—such as allelic variation in the CYP2D6 and CYP2C19 genes, which can markedly increase or decrease drug metabolism—is a new trend in opioid management that can improve diagnostic and prescribing accuracy and speed.

Weaning is another key aspect in managing patients taking opioids, either as a natural course of therapy when pain scores decrease and a patient has recovered or when a patient is displaying aberrant or divertive behavior.

The clinician's main goal during opioid weaning should be preventing withdrawal symptoms. Most patients can have their opioid treatment tapered with a 10% to 20% weekly decrease.

"Treating pain is not synonymous with opiate use. We need to consider all other alternatives." Ms. Snodgrass added that healthcare providers should not be afraid to use an opioid when it is appropriate. Some patients truly have no other options, such as elderly patients for whom other medications are contraindicated. For these patients, Ms. Snodgrass advised starting with a low dosage and titrating upward very slowly.

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Not an actual patient.

TWO SOURCES OF PAIN

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NUCYNTA® ER is the first and only FDA-approved long-acting opioid designed to control both nociceptive pain and the neuropathic pain associated with diabetic peripheral neuropathy (DPN).

NUCYNTA® ER is an opioid agonist indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve NUCYNTA® ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- NUCYNTA® ER is not indicated as an as-needed (prn) analgesic

Please see additional Important Safety Information and Brief Summary, including BOXED WARNING, on the following pages.

NUCYNTA™ ER
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TIME TO DUAL

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- Proven efficacy in chronic low back pain and DPN[1,2]
  - Based on efficacy demonstrated in a prospective, randomized, double-blind, active- and placebo-controlled, multicenter phase 3 chronic low back pain study (N=981) showing significant change in mean pain intensity from baseline in Week 15 (Week 12 of the maintenance phase) vs placebo[1]
  - Based on efficacy demonstrated in a double-blind, parallel-group, enriched-enrollment randomized phase 3 DPN study (N=977) showing significant change in mean pain intensity over the last week of the 12-week, double-blind, maintenance phase vs placebo[2]
- 5 dosage strengths: 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg[3]*
  Individualize dosing based on patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse; titrate as needed to provide adequate analgesia and minimize adverse reactions
- Administer NUCYNTA® ER ~q12h[3]

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- $0 co-pay for first prescription of NUCYNTA® ER with a $25 co-pay on each additional prescription if eligible†

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- **NUCYNTA® ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (5.2)**
- **Accidental ingestion of NUCYNTA® ER, especially in children, can result in fatal overdose of tapentadol. (5.2)**
- **Prolonged use of NUCYNTA® ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.3)**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA® ER because co-ingestion can result in fatal plasma tapentadol levels. (5.4)**

CONTRAINDICATIONS: Significant respiratory depression; acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment; known or suspected paralytic ileus; hypersensitivity (e.g., anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product; concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days.

*Please see full Prescribing Information for DOSAGE AND ADMINISTRATION.
†Some restrictions and limitations apply. See full terms and conditions available at NUCYNTA.com. Available to commercially insured and cash-paying patients only. Patients covered by Medicare, Medicaid, or any other state- or federally funded benefit program are excluded. Patients must be 18 years of age or older. This promotion cannot be combined with any other programs, offers, or discounts. Depomed reserves the right to rescind, revoke, or amend this offer without further notice.
‡Source: MMIT 2.0, May 2015.

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NUCYNTA® ER (tapentadol) IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS: Addiction, Abuse, and Misuse: NUCYNTA® ER contains tapentadol, an opioid agonist and a Schedule II controlled substance that can be abused in a manner similar to other opioid agonists, legal or illicit. There is a greater risk for overdose and death due to the larger amount of tapentadol present in NUCYNTA® ER. Assess risk for opioid abuse or addiction prior to prescribing NUCYNTA® ER. Addiction can occur in patients appropriately prescribed NUCYNTA® ER at recommended doses; in those who obtain the drug illicitly; and if the drug is misused or abused. Therefore, routinely monitor for signs of misuse, abuse, and addiction. Patients at increased risk (e.g., patients with a personal or family history of substance abuse or mental illness) may be prescribed NUCYNTA® ER, but use in such patients necessitates intensive counseling about the risks and proper use along with intensive monitoring for signs of addiction, abuse, and misuse.

Life-threatening Respiratory Depression: Can occur at any time during the use of NUCYNTA® ER even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. To reduce the risk of respiratory depression, proper dosing and titration are essential. Overestimating the dose when converting patients from another opioid product can result in fatal overdose with the first dose. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of NUCYNTA® ER during pregnancy can result in withdrawal signs in the neonate, which may be life-threatening and require management according to protocols developed by neonatology experts. Neonatal opioid withdrawal syndrome presents as poor feeding, irritability, hyperactivity and abnormal sleep pattern, high-pitched cry, tremor, rigidity, seizures, vomiting, diarrhea, and failure to gain weight.

Interactions With Central Nervous System Depressants: Hypotension, profound sedation, coma, respiratory depression, and death may result if NUCYNTA® ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, tranquilizers, general anesthetics, neuroleptics, other opioids). When considering the use of NUCYNTA® ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. If the decision to begin NUCYNTA® ER is made, start with NUCYNTA® ER 50 mg every 12 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

Use in Elderly, Cachectic, or 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. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients in the lower range of recommended doses. Closely monitor these patients, particularly when initiating and titrating NUCYNTA® ER and when given concomitantly with other drugs that depress respiration.

Use in Patients With Chronic Pulmonary Disease: Patients with significant chronic obstructive pulmonary disease or cor pulmonale and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or pre-existing respiratory depression, should be monitored for respiratory depression particularly when initiating therapy and titrating with NUCYNTA® ER. Consider the use of alternative nonopioid analgesics in these patients.

Hypotensive Effect: May cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics). Monitor for signs of hypotension during dose initiation or titration. Avoid use in patients with circulatory shock; may cause vasodilation that can further reduce cardiac output and blood pressure.

Use in Patients With Head Injury or Increased Intracranial Pressure: Monitor patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy. NUCYNTA® ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Seizures: May aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures. Monitor patients with a history of seizure disorders for worsened seizure control during therapy.

Serotonin Syndrome: Cases of life-threatening serotonin syndrome have been reported with the concurrent use of NUCYNTA® ER and serotonergic drugs. Serotonergic drugs comprise selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system, and drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose. Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g.,

tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal. If concomitant treatment with SSRIs, SNRIs, TCAs, or triptans is clinically warranted, careful observation of the patient is advised, particularly when initiating or titrating the dose.

Use in Patients With Gastrointestinal (GI) Conditions: Contraindicated in patients with GI obstruction including paralytic ileus; may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Avoidance of Withdrawal: Withdrawal symptoms (e.g., anxiety, sweating, insomnia, restlessness, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection) may occur:

- After abrupt discontinuation or a significant dose reduction of NUCYNTA® ER in physically dependent patients. When discontinuing NUCYNTA® ER, gradually taper the dose.
- If mixed agonist/antagonist (e.g., butorphanol, nalbuphine, pentazocine) and partial agonist (e.g., buprenorphine) analgesics are used in patients who have received or are receiving NUCYNTA® ER. Avoid use with mixed agonists/antagonists and partial agonists.
- If opioid antagonists (e.g., naloxone, nalmefene) are administered in physically dependent patients. Administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Driving and Operating Heavy Machinery: May impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NUCYNTA® ER and know how they will react to the medication.

Hepatic Impairment: Avoid use in patients with severe hepatic impairment (Child-Pugh Score 10 to 15). In patients with moderate hepatic impairment (Child-Pugh Score 7-9), initiate treatment with NUCYNTA® ER 50 mg no more than once every 24 hours, with a maximum dose of 100 mg per day. Monitor for respiratory and CNS depression when initiating and titrating NUCYNTA® ER.

Renal Impairment: Use in patients with severe renal impairment (CL_{CR} <30 mL/min) is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

DRUG INTERACTIONS

Alcohol: See BOXED WARNING.

Muscle Relaxants: Monitor patients receiving muscle relaxants and NUCYNTA® ER for signs of respiratory depression that may be greater than otherwise expected. Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Anticholinergics: Use with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

USE IN SPECIFIC POPULATIONS

Pregnancy/Nursing Mothers: *Pregnancy Category C.* NUCYNTA® ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonates born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms. Observe newborns for symptoms of neonatal opioid withdrawal syndrome. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of NUCYNTA® ER is stopped.

Labor and Delivery: Opioids cross the placenta and may produce respiratory depression in neonates. NUCYNTA® ER is not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate.

Use in Elderly, Renal Impairment, and Hepatic Impairment: See WARNINGS AND PRECAUTIONS.

DRUG ABUSE AND DEPENDENCE:
See BOXED WARNING

OVERDOSAGE: Institute supportive measures to manage respiratory depression, circulatory shock, and pulmonary edema as required. The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression.

ADVERSE REACTIONS: In clinical studies, the most common (≥10%) adverse reactions were nausea, constipation, vomiting, dizziness, somnolence, and headache.

Select Postmarketing Adverse Reactions: Anaphylaxis, angioedema, and anaphylactic shock have been reported very rarely with ingredients contained in NUCYNTA® ER. Advise patients how to recognize such reactions and when to seek medical attention. Panic attack has also been reported.

Please see Brief Summary, including BOXED WARNING, on the following pages.

NUCYNTA™ ER
TAPENTADOL EXTENDED-RELEASE TABLETS

Depomed®

NUCYNTA™ ER
TAPENTADOL EXTENDED-RELEASE TABLETS

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

This does not include all the information needed to use NUCYNTA® ER safely and effectively. See full Prescribing Information for NUCYNTA® ER.

INDICATIONS AND USAGE

NUCYNTA® ER is indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Usage

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve NUCYNTA® ER for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- NUCYNTA® ER is not indicated as an as-needed (prn) analgesic.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND INTERACTION WITH ALCOHOL

See full prescribing information for complete boxed warning.

- **NUCYNTA® ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (5.2)**
- **Accidental ingestion of NUCYNTA® ER, especially in children, can result in fatal overdose of tapentadol. (5.2)**
- **Prolonged use of NUCYNTA® ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. 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. (5.3)**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA® ER because co-ingestion can result in fatal plasma tapentadol levels. (5.4)**

CONTRAINDICATIONS

Significant respiratory depression; acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment; known or suspected paralytic ileus; hypersensitivity (e.g., anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product; concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: NUCYNTA® ER contains tapentadol, a Schedule II controlled substance. As an opioid, NUCYNTA® ER exposes users to the risks of addiction, abuse, and misuse. As modified-release products such as NUCYNTA® 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 tapentadol present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NUCYNTA® 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 NUCYNTA® ER, and monitor all patients receiving NUCYNTA® 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 NUCYNTA® ER for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as NUCYNTA® ER, but use in such patients necessitates intensive counseling about the risks and proper use of NUCYNTA® ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of NUCYNTA® ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of tapentadol and can result in overdose and death.

Opioid agonists such as NUCYNTA® ER are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NUCYNTA® 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. 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.

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. 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 NUCYNTA® 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 NUCYNTA® ER and following dose increases. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA® ER are essential. Overestimating the NUCYNTA® 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 NUCYNTA® ER, especially by children, can result in respiratory depression and death due to an overdose of tapentadol.

Neonatal Opioid Withdrawal Syndrome: Prolonged use of NUCYNTA® 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 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.

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.

Interactions with Central Nervous System Depressants: Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on NUCYNTA® ER therapy. The co-ingestion of alcohol with NUCYNTA® ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Hypotension, profound sedation, coma, respiratory depression, and death may result if NUCYNTA® 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 NUCYNTA® ER in a patient taking a CNS depressant, assess the duration of 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 NUCYNTA® ER is made, start with NUCYNTA® ER 50 mg every 12 hours, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

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. Therefore, closely monitor such patients, particularly when initiating and titrating NUCYNTA® ER and when NUCYNTA® ER is given concomitantly with other drugs that depress respiration.

Use in Patients with Chronic Pulmonary Disease: Monitor for respiratory depression those patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or pre-existing respiratory depression, particularly when initiating therapy and titrating with NUCYNTA® ER, as in these patients, even usual therapeutic doses of NUCYNTA® ER may decrease respiratory drive to the point of apnea. Consider the use of alternative non-opioid analgesics in these patients if possible.

Hypotensive Effect: NUCYNTA® ER may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressantdrugs (e.g., phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dose of NUCYNTA® ER. In patients with circulatory shock, NUCYNTA® ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NUCYNTA® ER in patients with circulatory shock.

Use in Patients with Head Injury or Increased Intracranial Pressure: Monitor patients taking NUCYNTA® ER who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA® ER. NUCYNTA® ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of NUCYNTA® ER in patients with impaired consciousness or coma.

Seizures: NUCYNTA® ER has not been evaluated in patients with a predisposition to a seizure disorder, and such patients were excluded from clinical studies. The active ingredient tapentadol in NUCYNTA® ER may aggravate convulsions in patients with convulsive disorders, and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA® ER therapy.

Serotonin Syndrome: Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (e.g. mirtazapine, trazodone, and tramadol), and drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose. Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal.

Use in Patients with Gastrointestinal Conditions: NUCYNTA® ER is contraindicated in patients with GI obstruction, including paralytic ileus. The tapentadol in NUCYNTA® ER may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Avoidance of Withdrawal: Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including NUCYNTA® ER. In these patients, mixed agonists/antagonists and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing NUCYNTA® ER, gradually taper the dose.

Driving and Operating Heavy Machinery: NUCYNTA® ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NUCYNTA® ER and know how they will react to the medication.

Hepatic Impairment: A study with an immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Avoid use of NUCYNTA® ER in patients with severe hepatic impairment. Reduce the dose of NUCYNTA® ER in patients with moderate hepatic impairment. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression when initiating and titrating NUCYNTA® ER.

Renal Impairment: Use of NUCYNTA® ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

ADVERSE REACTIONS

The following serious adverse reactions are discussed 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)]
- Interaction with Other CNS Depressants [see Warnings and Precautions (5.4)]
- Hypotensive Effects [see Warnings and Precautions (5.7)]
- Gastrointestinal Effects [see Warnings and Precautions (5.11)]
- Seizures [see Warnings and Precautions (5.9)]
- Serotonin Syndrome [see Warnings and Precautions (5.10)]

Clinical Trial Experience

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA® ER in Patients with Chronic Pain due to Low Back Pain or Osteoarthritis

The most common adverse reactions (reported by ≥10 % in any NUCYNTA® ER dose group) were: nausea, constipation, dizziness, headache, and somnolence.

The most common reasons for discontinuation due to adverse reactions in eight Phase 2/3 pooled studies reported by ≥1% in any NUCYNTA® ER dose group for NUCYNTA® ER- and placebo-treated patients were nausea (4 % vs. 1%), dizziness (3% vs. <1%), vomiting (3% vs. <1%), somnolence (2% vs. <1%), constipation (1% vs. <1%), headache (1% vs. <1%), and fatigue (1% vs. <1%), respectively.

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA® ER in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The most commonly reported ADRs (incidence ≥ 10% in NUCYNTA® ER-treated subjects) were: nausea, constipation, vomiting, dizziness, somnolence, and headache.

Postmarketing Experience: The following adverse reactions, not above, have been identified during post approval use of tapentadol. Because these reactions 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.

Psychiatric disorders: hallucination, suicidal ideation, panic attack.

Anaphylaxis, angioedema, and anaphylactic shock have been reported very rarely with ingredients contained in NUCYNTA® ER.

The psychiatric disorders end with panic attack. Advise patients how to recognize such reactions and when to seek medical attention.

DRUG INTERACTIONS

Alcohol: Concomitant use of alcohol with NUCYNTA® ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on NUCYNTA® ER therapy.

Monoamine Oxidase Inhibitors: NUCYNTA® ER is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOIs) or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events.

CNS Depressants: The concomitant use of NUCYNTA® 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 NUCYNTA® 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.

Serotonergic Drugs: There have been post-marketing reports of serotonin syndrome with the concomitant use of tapentadol and serotonergic drugs (e.g., SSRIs and SNRIs). Caution is advised when NUCYNTA® ER is coadministered with other drugs that may affect serotonergic neurotransmitter systems such as SSRIs, SNRIs, MAOIs, and triptans. If concomitant treatment of NUCYNTA® ER with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Muscle Relaxants: Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression. Monitor patients receiving muscle relaxants and NUCYNTA® ER for signs of respiratory depression that may be greater than otherwise expected.

Mixed Agonist/Antagonist Opioid Analgesics: Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonists (e.g., buprenorphine) may reduce the analgesic effect of NUCYNTA® ER or precipitate withdrawal symptoms. Avoid the use of mixed agonist/antagonist analgesics in patients receiving NUCYNTA® ER.

Anticholinergics: The use of NUCYNTA® ER with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

USE IN SPECIFIC POPULATIONS

Pregnancy

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.

Teratogenic Effects - ***Pregnancy Category C***

There are no adequate and well-controlled studies in pregnant women. NUCYNTA® ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: Opioids cross the placenta and may produce respiratory depression in neonates. NUCYNTA® ER is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that 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.

Nursing Mothers: There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the breastfeeding child cannot be excluded.

Because of the potential for adverse reactions in nursing infants from NUCYNTA® ER, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Withdrawal symptoms can occur in breast-feeding infants when maternal administration of NUCYNTA® ER is stopped.

Pediatric Use: The safety and efficacy of NUCYNTA® ER in pediatric patients less than 18 years of age have not been established.

Geriatric Use: Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA® ER, 28% (1023/3613) were 65 years and over, while 7% (245/3613) were 75 years and over. No overall differences in effectiveness or tolerability were observed between these patients and younger patients.

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.

Renal Impairment: The safety and effectiveness of NUCYNTA® ER have not been established in patients with severe renal impairment (CL_{CR} <30 mL/min). Use of NUCYNTA® ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

Hepatic Impairment: Administration of tapentadol resulted in higher exposures and serum levels of tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The dose of NUCYNTA® ER should be reduced in patients with moderate hepatic impairment (Child-Pugh Score 7 to 9).

Use of NUCYNTA® ER is not recommended in severe hepatic impairment (Child-Pugh Score 10 to 15).

DRUG ABUSE AND DEPENDENCE

Controlled Substance: NUCYNTA® ER contains tapentadol, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. NUCYNTA® ER can be abused and is subject to misuse, addiction, and criminal diversion. The high drug content in the extended release formulation adds to the risk of adverse outcomes from abuse and misuse.

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 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, and people suffering from untreated addiction. Preoccupation with achieving 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.

NUCYNTA® ER, like other opioids, 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.

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, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

NUCYNTA® ER should not be abruptly discontinued. If NUCYNTA® 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.

OVERDOSAGE

Clinical Presentation: Acute overdosage with opioids can be manifested 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.

Treatment of Overdose: In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

Rx Only

Depomed®

Peripheral Neuropathies: A Primer

Treatment options should focus on slowing progression, relieving pain, and restoring function.

Understanding the anatomy of the body's nervous systems not only assists clinicians with diagnosing a patient with peripheral neuropathy, it also allows patients to understand how treatments and approaches can assist them in alleviating pain.

Speaking at PAINWeek 2015, Natalie H. Strand, MD, a physician at Freedom Pain Hospital, in Scottsdale, Arizona, described the pathophysiology and the clinical presentation of painful peripheral neuropathies; reviewed the anatomy of the nervous system and available diagnostic testing for peripheral neuropathy; and reviewed treatment for painful peripheral neuropathy.

Peripheral neuropathy is a condition that encompasses a group of disorders that may involve a single nerve root (mononeuropathy), multiple individual nerves (mononeuropathy multiplex), or small fibers that do not conform to dermatomes (peripheral polyneuropathies).

Dr. Strand noted that there are more than 100 types of peripheral neuropathy. Several of the mostly commonly encountered types include motor neuropathy, sensory neuropathy, sensorimotor neuropathy, autonomic neuropathy, as well as combinations.

There is a range of clinical features of peripheral neuropathy for clinicians to consider. These include sensory neuropathy, numbness, loss of sensation or feeling in body parts, loss of balance, emotional disturbances, and sleep disruptions, among others.

When assessing a patient for symptoms of motor neuropathies, clinicians should pay attention to any signs of muscle weakness; painful cramps; fasciculations in the muscle (something that can observed in the clinic); muscle atrophy; and changes in skin (waxy or thickened), hair (shorter or longer), or nails.

When conducting an assessment for autonomic neuropathy, symptoms to be alert to include the inability to sweat properly, loss of bladder control, dizziness or lightheadedness, difficulty eating, and life-threatening symptoms such as difficulty breathing or an irregular heartbeat.

"The medical diagnosis underlying the neuropathy must first be established and managed, when possible," Dr. Strand advised.

Psychotherapy, Pharmacotherapy Combo Best for Late-Life Depression and Pain

Treating these chronic conditions together may minimize the stigma of depression treatment.

Late-life depression affects adults aged 60 years and older and is associated with increased healthcare utilization and costs, reduced quality of life, poorer prognosis for comorbid conditions, lower survival rates, and suicide.

Chronic pain warrants attention in older adults due to its high prevalence. and the condition is independently associated with anxiety and depression.

"Chronic low back pain (CLBP) is one of the most disabling and therapeutically challenging pain conditions afflicting older adults," explained Jordan F. Karp, MD, of the University of Pittsburgh Medical Center in Pennsylvania.

In a study comparing patients with CLBP to those with knee arthritis, Dr. Karp and colleagues found that patients with CLBP had higher rates of mood disorders, slower gait (0.88 m/s vs 0.96 m/s; $P = .002$), and more comorbid conditions (mean 3.36 vs 1.97; $P < .001$). Furthermore, patients with CLBP performed significantly worse on psychological measures than those with knee arthritis.

"Treating these chronic conditions together may minimize the stigma of depression treatment and improve treatment acceptability," Dr. Karp said.

A 2002 study by Brown et al that involved 121 community-dwelling rheumatoid arthritis patients aged 34 to 84 years sought to examine the effects of pain and depression on cognitive function.[4]

Higher levels of pain and depression and older age were associated with poor performance on cognitive tasks, the researchers found. Similarly, higher levels of pain were associated with depression, and analyses revealed that depression mediated the relationship between pain and cognition.

As with any comprehensive clinical evaluation, Dr. Strand noted that a complete history should be obtained, as well as physical and laboratory examination, electrodiagnostic studies (which are commonly used), quantitative sensory testing, and any additional testing as indicated (imaging, rheumatologic screen, thyroid function tests, chest radiographs, HIV testing, Lyme titers, skeletal survey).

The etiology of peripheral neuropathy is varied and includes alcoholism, autoimmune diseases, diabetes, exposure to poisons, medications, infections, inherited disorders, trauma or pressure on a nerve, tumors, and vitamin deficiencies. Other disease states include kidney disease, liver disease, connective tissue disorders, and amyloidosis.

Diabetic peripheral neuropathy is the most common form of diabetic neuropathy. Patients may describe such symptoms as numbness; a reduced ability to feel pain or changes in temperature; a sharp, jabbing pain that may be worse at night; and a tingling or burning feeling. Causes of diabetic peripheral neuropathy include damage to nerves and blood vessels, inflammation in the nerves, smoking, and alcohol abuse. Poor blood sugar control, kidney disease, smoking, and pressure points are risk factors for diabetic peripheral neuropathy.

Dr. Strand provides an overview on the pathophysiology of neuropathy.

Complications of peripheral neuropathy include loss of a limb (the worst case scenario), neurogenic arthropathy (Charcot joint), and social isolation (often undertreated), Dr. Strand said.

Clinicians should consider conducting a filament test, nerve conduction studies, and quantitative sensory testing to confirm a diagnosis.

Treatment options for a patient with the condition should revolve around the following: slowing progression, relieving pain and restoring function.

Dr. Strand's take-home message about diabetic peripheral neuropathy is to stress the need to understand and recognize the early signs of the condition, to communicate to patients that there are many modifiable risk factors, and to maintain glycemic control.

"When depression was entered into the analyses, the previously significant effects of pain on cognition were no longer found," Dr. Karp reported. "Interestingly, depression still mediated the pain-cognition relationship even after controlling for age."

Because the effects of pain and depression are interrelated, Dr. Karp advises the use of a unified approach.

The ADAPT trial assessed the utility of a stepped-care approach for older patients presenting in primary care settings with depression and CLBP for whom previous treatment failed. The primary aim of the study was to compare combined high-dose venlafaxine with problem-solving therapy for depression and pain (PST-DP) with high-dose venlafaxine with supportive management (SM) to determine outcomes on depression, pain, and disability scales.

The study involved 250 patients assigned to 6-week treatment with lower-dose venlafaxine (up to 150 mg/d) with SM. Those who responded to treatment as defined as a score less than 5 on the 9-item Patient Health Questionnaire (PHQ-9) and a greater than 30% improvement on the Numeric Rating Scale for Pain (NRS) left the study.

In phase 2, patients whose depression did not respond to treatment were assigned to either 14-week treatment with higher-dose venlafaxine (up to 300 mg/d) and SM (n = 71) or 14-week treatment with higher-dose venlafaxine (up to 300 mg/d) and PST-DP (n = 68). The median venlafaxine dosage was 244 mg/d. On average patients in the PST-DP group received 8.4 sessions and those in the SM group received 9.2 sessions.

Remission was defined as a positive response as demonstrated by a PHQ-9 score less than 5 and a greater than 30% reduction on the NRS on two sequential visits.

Comparing the PST-DP group vs the SM group, final remission rates were 31% vs 18% on both pain and depression outcomes ($P = .11$); 44% vs 33% on depression outcomes ($P = .17$); and 43% vs 47% on pain ($P = .73$), respectively.

"In older adults, no significant difference in depression was seen when comparing medication and psychotherapy, but combined treatment is significantly better than medication alone," Dr. Karp said.

Disclosure: Pfizer and Reckitt Benckiser provided medication for the trials reported.

E-Prescribing to Combat Misuse and Diversion

Legislation mandating electronic prescribing of controlled substances in New York is driving innovations in health technology.

Prescription drug overdoses are responsible for more deaths in the United States than gun, knife, and motor vehicle injuries combined, with those involving opioid analgesics increasing 300% since 1999.

Approximately 260 million opioid prescriptions were written in 2012 alone, Surescripts data indicate. "That's about one bottle of prescription-strength painkilling medication out there for every American, which is a staggering amount when you think about it," said Sean P. Kelly, MD, an emergency medicine specialist at Beth Israel Deaconess Medical Center and an assistant clinical professor of emergency medicine at Harvard Medical School, both in Boston.

Curbing the ongoing opioid epidemic, which Dr. Kelly called "unprecedented in scope," will require a multifaceted attack. "One approach is to catch the problem upstream, at the moment of prescribing," he said.

As the Chief Medical Officer of Imprivata, a software company involved in developing prescriber authentication technology to comply with Drug Enforcement Administration (DEA) standards for electronic prescribing of controlled substances (EPCS), Dr. Kelly works regularly with electronic health record (EHR) vendors to identify workflow solutions to inefficiencies in the prescribing process that make controlled substance misuse and diversion more likely.

"Getting better at understanding who we are prescribing to and how much we are prescribing is part of that," Dr Kelly said. "We need a more transparent, easier to use, and safer system that leverages good technology."

Paper-based prescription systems are susceptible to fraud. Approximately one in 10 prescribers will have their DEA number forged and will need to go through the process of getting a new one at some point in their career, according to Dr. Kelly.

In addition to security concerns, paper-based systems pose challenges for gathering metrics for meaningful use e-prescribing requirements. In the current environment, many prescribers of controlled substances are creating dual workflows—one for paper prescriptions and one for electronic—which introduces greater potential for errors, delays, and decreased provider and patient satisfaction.

"As many as 60% of patients being discharged from the hospital or emergency department have at least one prescription for a controlled substance.

Dr. Kelly provides tips on implementing e-prescribing technology.

If a patient leaves with multiple prescriptions, and one is for a controlled substance, many providers will convert the whole batch of prescriptions to the print prescription workflow," explained Dr. Kelly. "This goes against meaningful use guidelines, and the provider is losing credit for the 4 prescriptions that could have been done electronically."

In response to the need for more secure and efficient prescribing processes, the DEA first set forth regulations for EPCS in 2010, requiring all EPCS to be approved by the State Board of Pharmacies. The pharmacies used must be certified to accept controlled-substance prescriptions, and the EHR or third-party vendor that handles processing electronic prescriptions must also be certified for controlled substances.

In addition to these regulations, participating subscribers must undergo identity proofing for supervised enrollment in an EPCS program at either an institutional or individual level and must use a system called two-way authentication, which Dr. Kelly has been instrumental in developing, to ensure that the correct provider is authorizing the controlled-substance prescription.

Two-way authentication requires prescribers to meet two of the following requirements at the point of writing the electronic prescription: something you know (ie, a password or token), something you are (Federal Information Processing Standard [FIPS]-compliant fingerprint biometrics), or something you have (FIPS-compliant token or hands-free authentication via a password-protected software application).

"The DEA requires a witness at the

hospital level who signs off that the fingerprint is authentic and specific to the prescriber, and one other person in the hospital who has a DEA number who testifies that our process is complete," explained Dr. Kelly. "Two-signature verification is required for supervised enrollment, which allows the fingerprint to be logged into the software system or a token to be assigned. This confirms, 'I am who I am, and I'm logged into the system correctly.'"

He said the same procedure can be mimicked in smaller private practices, with a practice manager or lead physician serving as the witness or via a third-party credentialing service provider.

As of August 27, 2013, most prescribers in the state of New York are required by law to consult the Internet System for Tracking Overprescribing-Prescription Monitoring Program (I-STOP/PMP) Registry when writing prescriptions for schedule II, III, and IV controlled substances. Legislators there have also made it mandatory to use EPCS by March 27, 2016.

EPCS offers substantial benefit to health systems, physicians, and patients. Health systems have an opportunity to improve patient satisfaction, lower fraud risk, enforce state and federal regulations, and better meet meaningful use e-prescribing requirements.

EPCS offers physicians the potential to eliminate dual workflows, reduce errors and fraud, and limit exposure of their DEA number. For patients, EPCS has the potential to improve overall satisfaction, increase medication adherence, reduce trips to the physician's office, and reduce wait times at the pharmacy.

"We've reach a critical mass. Technology is getting better and we are now getting to the point where there is a strong push toward adopting EPCS," Dr. Kelly concluded.

"Minor" Traumatic Brain Injuries Are Anything But Minor

Evaluating for concussions, other sports-related injuries is imperative as student athletes head back to school and on to the playing field.

An reported 1.6 to 3.8 million sports- and recreation-related traumatic brain injuries occur each year in the United States,[1] many of which result in long-lasting brain damage and in some cases death.

Fortunately, best practices for traumatic brain injury have evolved as new data emerge. Gary W. Jay, MD, who has worked in pain medicine and neurorehabilitation for more than 3 decades, discussed some of these practices in a master class session at PAINWeek.

Discussing minor or mild traumatic brain injury (mTBI), "or the clinical entity in which the brain has sustained a pathologic injury," Dr. Jay said these injuries have various physiologic aspects that must be considered when treating them, such as elements of rotation at the time of the injury.

He noted that although they may be characterized as "minor," not infrequently these types of "brain injuries are substantial and the only things missing when the diagnosis is made in the emergency department may be blood and skull fracture."

Particularly as the back-to-school season is just getting started and football season is now in full swing, Dr. Jay cautions that it is important for clinicians to recognize a sports-related concussion. He discussed how best to evaluate concussions and offered some pearls about sending a student athlete back out on the field.

The Centers for Disease Control and Prevention (CDC) defines a "concussion as a type of traumatic brain injury—or TBI—caused by a bump, blow, or jolt to the head or by a hit to the body that causes the head and brain to move rapidly back and forth. This sudden movement can cause the brain to bounce around or twist in the skull, stretching and damaging the brain cells and creating chemical changes in the brain."

The CDC advocates a multistep approach to a return to play after a sports-related concussion, starting first with the athlete heading back to school, then light aerobic activity, then moderate activity, followed by heavier noncontact activity, then practice with full contact, and finally competition.

> Nearly 4 million sports- and recreation-related TBIs occur each year in the United States.

Adding to this, Dr. Jay said he recommends an interdisciplinary mTBI approach that includes medical management, neuropsychological evaluation and treatment, occupational therapy, physical therapy, and speech therapy, all used on an as-needed basis.

Beyond the patient, Dr. Jay noted that it is important for clinicians to glean information regarding traumatic brain injuries from patients' families, spouses, and significant others.

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Treating Morton's Neuroma, an Often Misunderstood Foot Pain

Treatment should be geared toward nerve decompression.

According to the American Podiatric Medical Association, people in the United States log approximately 75,000 miles on their feet by age 50 years,[1] making foot pain a common complaint heard in healthcare clinics across the nation.

"Abnormalities in gait, ill-fitting shoes, repetitive motion, and trauma can all result in foot pain," said Andrew Rader, DPM, founder of Indiana Foot & Ankle in Newburgh. "One common cause is neuralgia in the intermetatarsal region of the forefoot, known as Morton's neuroma."

Morton's neuroma is the formation of a mass of nerve fibers and cells, the cause of which may be trauma, malformation, infection, or an overgrowth of vasculature/axons, Dr. Rader explained. When found in the intermetatarsal spaces, the neuroma is actually a compression neuropathy of the common digital nerve.

"Women are up to 10 times more likely to be affected, and average age of onset is about 50 years," Dr. Rader said.

Patients commonly described the pain as cramping, stabbing, burning, aching, gnawing, radiating, and/or throbbing and may describe the sensation as having a "rolled-up sock" feeling. It is often exacerbated by tight-fitting shoe gear and physical activity.

Clinical examination is often adequate for diagnosing the pathology. Physical findings on examination may include splaying of the toes, impaired sensation on adjacent aspects of the plantar digits, and a positive Mulder's sign. Dr. Rader emphasized that magnetic resonance imaging and diagnostic ultrasound can be used for cases in which the diagnosis is ambiguous. Imaging modalities can also be used for cases in which multiple lesions or multiple web space involvement is suspected.

Once a diagnosis of Morton's neuroma is made, treatment options are wide ranging but largely anecdotal, according to Dr. Rader.

Advances in Naloxone Technologies Offer More Options for Reducing Opioid Overdoses

The pros and cons of intranasal, intramuscular, and autoinjector routes of administration.

Drug poisoning deaths involving opioids nearly quadrupled between 2010 and 2013, correlating with a 4-fold increase in sales of opioids, and heroin deaths increased nearly 40% between 2012 and 2013.[1]

The opioid receptor antagonist naloxone can reverse overdose from both prescription opioids and heroin by canceling out the respiratory and central nervous system-depressant effects of these drugs.

Advances in the way naloxone is administered offer more options for emergency medicine clinicians who see these patients, as well as the family members of people who use these drugs, according to a speaker at PAINWeek.

"Naloxone offers an important safety net for saving lives in cases of accidental or purposeful opioid overdose," said Jeffrey Fudin, PharmD, FCCP, founder and chair of Professionals for Rational Opioid Monitoring and Pharmacotherapy (PROMPT).

"Clinicians must realize that naloxone reversal kits, regardless of administration route, are not just for substance abusers. They are for any at-risk patient receiving chronic opioid therapy."

Patients at highest risk for overdose include those taking extended-release opioids, those taking more than one opioid, those taking concomitant sedative hypnotics such as benzodiazepines, those with comorbid respiratory disease and/or recent hospital admission for an opioid-related respiratory problem, and those taking antidepressants.

"Also consider the possibility of unanticipated drug interactions with newly prescribed medications that might increase serum levels of the parent opioid or its active metabolites," Dr. Fudin cautioned.

Naloxone is available in 3 formulations: intramuscular and intravenous injection, intranasal (off-label), and as an autoinjector (Evzio, Kaléo, Inc.). Dr. Fudin gave a comprehensive discussion of the pros and cons of each available route of administration.

Conservative treatment with accommodative shoe-gear changes improved symptoms in as many as 41% of patients evaluated in a 1995 study by Bennett and coworkers.[2] A study by Saygi and colleagues in 2005 reported improvement in symptoms in 63% of individuals with Morton's neuroma using footwear modification with orthoses alone.[3] However, prescription padding and orthoses to control pronatory and supinatory motion forces are typically ineffectual for pain relief.

Steroid injections and local anesthetics may provide temporary, but not long-term, symptom relief. In addition, evidence does not support the use of alcohol sclerosing injections for long-term relief.[4]

Although surgical nerve excision may provide pain relief for Morton's neuroma, long-term subsequent paresthesiae and shoe limitations are common. In a 2008 study by Womack et al that involved 120 patients, 50% had good or excellent outcomes, 10% had fair outcomes, and 40% reported poor outcomes.[5]

As an alternative treatment, nerve decompression via endoscopy offers a minimally invasive option to address the pathology, while preserving nerve function. In a study by Barrett et al, 95% of procedures performed in the third intermetatarsal space and 85% of those performed in the second intermetatarsal space had good-to-excellent outcomes for a 92% success rate.[6]

Disclosure: Andrew Rader received honoraria from and is a member of the speakers' bureau for Organogenesis, D.N.E. SEAL External Fixation, and CE Lasers. He also received consulting fees from D.N.E SEAL External Fixation and is a stock shareholder in Fuse Medical.

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INTRANASAL FORMULATION

Although not yet approved by the US Food and Drug Administration (FDA), intranasal naloxone offers the advantages of being inexpensive and easily accessible, without risk for needle-stick exposure.

"Intranasal naloxone is used ubiquitously. It is far less expensive compared with the FDA-approved auto-injector formulation," Dr. Fudin explained.

In a 2009 study by Kerr et al in *Addiction*, intranasal naloxone was as effective as the intramuscular formulation in reversing heroin overdose within 10 minutes of administration (72.3% vs 77.5%).[3] Despite this positive finding, more comprehensive and rigorous studies are needed regarding naloxone absorption with this route of administration.

"Although there are exciting reports of opiate overdose reversals, we do not know how many failures there were when considering attempts at reversal. It is less likely that this route will achieve comparable maximum blood concentrations within the same timeframe compared with any intramuscular formulation," Dr. Fudin said. "It therefore may not readily and quickly reverse the more fat-soluble drugs such as fentanyl compared with its effect on heroin. In a situation where time is critical, this concerns me."

As many substance abusers snort one or more drugs, the vasculature in their nasal mucosa could be compromised, and they may have a higher likelihood of a deviated septum, which could also affect intranasal absorption, he pointed out.

Another disadvantage of the intranasal formulation is that it may not be as easy as other options for caregivers and families because it requires users to manually assemble a syringe, plunger, and atomizer and inject half of the formulation in each nostril. Because these component pieces are not sold together as a kit, assembly requires more work on the part of the pharmacist.

Despite these disadvantages, intranasal naloxone may be well suited for use in emergency situations that involve well-trained responders such as police officers and emergency medical technicians (EMTs), specifically in states where EMTs are not permitted to administer injections, Dr. Fudin explained.

INTRAMUSCULAR AND INTRAVENOUS INJECTIONS

Naloxone administered via traditional intramuscular injection is another inexpensive and effective option for emergency responders who are well trained; however, it may be difficult to administer in an emergency situation in the home setting by someone who is unfamiliar with manipulating a syringe and vial.

Intravenous injections are more compli-

cated and therefore must be administered exclusively by medical professionals. If a patient who has overdosed has not been breathing for a while, venous access may be compromised; this situation may also occur with substance abusers.

Downsides to intravenous administration include the risk for needle stick and regulations in certain municipalities that restrict EMTs from injecting any drugs, whether intramuscularly or intravenously.

AUTO-INJECTOR FORMULATION

The naloxone auto-injector is the only FDA-approved formulation for in-home use in cases where there is known or suspected opioid overdose.

A 2015 study by Edwards et al validated that all persons who received training from healthcare practitioners on naloxone use were able to give the auto-injector correctly, and 90% of those who received no training were also able to give it correctly.[3] The retracting needle offers the added advantage of reducing needle-stick risk.

"The greatest and perhaps only disadvantage of the auto-injector is the cost," Dr. Fudin said.

Although it is normal for insurance providers to reject claims for off-label uses of medications, they seem to support approval of intranasal naloxone kits. State regulations regarding naloxone are changing each week, but in general many are lightening up "Good Samaritan" laws to protect first responders from liability, according to Dr. Fudin.

Some allow pharmacists to dispense it without a prescription, whereas others are formulating plans for pharmacists to do this, but only after many hours of special certificate training," Dr. Fudin said.

Disclosure: Jeffrey Fudin has worked as a consultant and is a member of speakers' bureaus for AstraZeneca, Millennium Health, Zogenix, and Kaléo. He is also a stock shareholder for Remitigate.

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Opioid Prescribing: Navigating the Ethical Battlefield

As concerns continue to mount regarding opioid overdose, misuse, and abuse, laws and guidelines regulating the prescribing of painkillers to patients have become stricter.

"Whether we are speaking in clinical, moral, ethical, or legal terms, the fundamental question remains: What is best for my patient?" said Stephen J. Ziegler, PhD, JD, associate professor in the Department of Public Policy at Indiana State University.

Jennifer Bolen, JD, a former US District Attorney and expert on medicolegal issues related to pain management, joined Dr. Ziegler in a panel discussion that centered around how physicians should handle situations in which they believe a patient is diverting or abusing pain medications, or both.

Being able to make an educated decision to do what is best for the patient is not always easy.

"In many ways it comes down to how well equipped the physician is to perform patient assessment and screening for abuse; how well the physician understands and how easily the physician can access integrated care, including behavioral health support; and how much of the physician's focus is money oriented vs patient centered," Ms. Bolen said.

However, too much caution when considering medication for patients with pain can be harmful, as well.

Although it might save time, a strategy that avoids opioids entirely could essentially result in negative consequences for prescribers. Blatantly ignoring potential treatment options for a patient with pain could have both ethical and legal ramifications.

"For some clinicians, a blanket policy of withholding opioids may seem to be the safest route," Dr. Ziegler explained.

"But such policies are not only unethical because they subordinate the patient's needs, they can also expose the clinician to accusations of medical malpractice," Dr. Ziegler cautioned.

The strategy behind prescribing opioids isn't necessarily a clear one. There are numerous patient- and pharmacologic-related issues for a physician to consider before deciding whether or not to treat an individual with prescription painkillers.

"Ensuring access while preventing the abuse of opioids is not a zero-sum game and will remain an ongoing challenge for clinicians," he said. "Patient assessment, screening for abuse, and integrated care all have a part in good patient care. Clinicians are not expected to be perfect, just reasonable."

GRALISE® (gabapentin) tablets

BRIEF SUMMARY: For full prescribing information, see package insert.

INDICATIONS AND USAGE

GRALISE is indicated for the management of Postherpetic Neuralgia (PHN). **GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.**

DOSAGE AND ADMINISTRATION

Postherpetic neuralgia

- GRALISE should be titrated to an 1800 mg dose taken orally once daily with the evening meal. GRALISE tablets should be swallowed whole. Do not split, crush, or chew the tablets.
- If GRALISE dose is reduced, discontinued, or substituted with an alternative medication, this should be done gradually over a minimum of one week or longer (at the discretion of the prescriber).
- Renal impairment: Dose should be adjusted in patients with reduced renal function. GRALISE should not be used in patients with CrCl less than 30 or in patients on hemodialysis.
- In adults with postherpetic neuralgia, GRALISE therapy should be initiated and titrated as follows:

Table 1 GRALISE Recommended Titration Schedule

	Day 1	Day 2	Days 3-6	Days 7-10	Days 11-14	Day 15
Daily dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

CONTRAINDICATIONS

GRALISE is contraindicated in patients with demonstrated hypersensitivity to the drug or its ingredients.

Table 2 GRALISE Dosage Based on Renal Function

Once-daily dosing	
Creatinine clearance (mL/min)	GRALISE dose (once daily with evening meal)
≥ 60	1800 mg
30-60	600 mg to 1800 mg
< 30	GRALISE should not be administered
Patients receiving hemodialysis	GRALISE should not be administered

WARNINGS AND PRECAUTIONS

GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration. The safety and effectiveness of GRALISE in patients with epilepsy has not been studied. **Suicidal Behavior and Ideation** Antiepileptic drugs (AEDs), including gabapentin, the active ingredient in GRALISE, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Table 3 Risk by Indication for Antiepileptic Drugs (including gabapentin, the active ingredient in Gralise) in the Pooled Analysis

Indication	Epilepsy	Psychiatric	Other	Total
Placebo patients with events per 1000 patients	1.0	5.7	1.0	2.4
Drug patients with events per 1000 patients	3.4	8.5	1.8	4.3
Relative risk: incidence of events in drug patients/incidence in placebo patients	3.5	1.5	1.9	1.8
Risk difference: additional drug patients with events per 1000 patients	2.4	2.9	0.9	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing GRALISE must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which products containing active components that are AEDs (such as gabapentin, the active component in GRALISE) are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that GRALISE contains gabapentin which is also used to treat epilepsy and that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers. **Withdrawal of Gabapentin** Gabapentin should be withdrawn gradually. If GRALISE is discontinued, this should be done gradually over a minimum of 1 week or longer (at the discretion of the prescriber). **Tumorigenic Potential** In standard preclinical *in vivo* lifetime carcinogenicity studies, an unexpectedly high incidence of pancreatic acinar adenocarcinomas was identified in male, but not female, rats. The clinical significance of this finding is unknown. In clinical trials of gabapentin therapy in epilepsy comprising 2,085 patient-years of exposure in patients over 12 years of age, new tumors were reported in 10 patients, and preexisting tumors worsened in 11 patients, during or within 2 years after discontinuing the drug. However, no similar patient population untreated with gabapentin was available to provide background tumor incidence and recurrence information for comparison. Therefore, the effect of gabapentin therapy on the incidence of new tumors in humans or on the worsening or recurrence of previously diagnosed tumors is unknown. **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking antiepileptic drugs, including GRALISE. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. GRALISE should be discontinued if an alternative etiology for the signs or symptoms cannot be established. **Laboratory Tests** Clinical trial data do not indicate that routine monitoring of clinical laboratory procedures is necessary for the safe use of GRALISE. The value of monitoring gabapentin blood concentrations has not been established.

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. A total of 359 patients with neuropathic pain associated with postherpetic neuralgia have received GRALISE at doses up to 1800 mg daily during placebo-controlled clinical studies. In clinical trials in patients with postherpetic neuralgia, 9.7% of the 359 patients treated with GRALISE and 6.9% of 364 patients treated with placebo discontinued prematurely due to adverse reactions. In the GRALISE treatment group, the most common reason for discontinuation due to adverse reactions was dizziness. Of GRALISE-treated patients who experienced adverse reactions in clinical studies, the majority of those adverse reactions were either "mild" or "moderate". Table 4 lists all adverse reactions, regardless of causality, occurring in at least 1% of patients with neuropathic pain associated with postherpetic neuralgia in the GRALISE group for which the incidence was greater than in the placebo group.

Table 4 Treatment-Emergent Adverse Reaction Incidence in Controlled Trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 1% of all GRALISE-Treated Patients and More Frequent Than in the Placebo Group)

Body system—preferred term	GRALISE N = 359, %	Placebo N = 364, %
Ear and Labyrinth Disorders		
Vertigo	1.4	0.5
Gastrointestinal Disorders		
Diarrhea	3.3	2.7
Dry mouth	2.8	1.4
Constipation	1.4	0.3
Dyspepsia	1.4	0.8
General Disorders		
Peripheral edema	3.9	0.3
Pain	1.1	0.5
Infections and Infestations		
Nasopharyngitis	2.5	2.2
Urinary tract infection	1.7	0.5
Investigations		
Weight increased	1.9	0.5
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	1.9	0.5
Back pain	1.7	1.1
Nervous System Disorders		
Dizziness	10.9	2.2
Somnolence	4.5	2.7
Headache	4.2	4.1
Lethargy	1.1	0.3

In addition to the adverse reactions reported in Table 4 above, the following adverse reactions with an uncertain relationship to GRALISE were reported during the clinical development for the treatment of postherpetic neuralgia. Events in more than 1% of patients but equally or more frequently in the GRALISE-treated patients than in the placebo group included blood pressure increase, confusional state, gastroenteritis viral, herpes zoster, hypertension, joint swelling, memory impairment, nausea, pneumonia, pyrexia, rash, seasonal allergy, and upper respiratory infection. **Postmarketing and Other Experience with other Formulations of Gabapentin** In addition to the adverse experiences reported during clinical testing of gabapentin, the following adverse experiences have been reported in patients receiving other formulations of marketed gabapentin. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: angioedema, blood glucose fluctuation, breast hypertrophy, erythema multiforme, elevated liver function tests, fever, hyponatremia, jaundice, movement disorder, Stevens-Johnson syndrome. Adverse events following the abrupt discontinuation of gabapentin immediate release have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain and sweating.

DRUG INTERACTIONS

Coadministration of gabapentin immediate release (125 mg and 500 mg) and hydrocodone (10 mg) reduced hydrocodone C_{max} by 3% and 21%, respectively, and AUC by 4% and 22%, respectively. The mechanism of this interaction is unknown. Gabapentin AUC values were increased by 14%; the magnitude of this interaction at other doses is not known. When a single dose (60 mg) of controlled-release morphine capsule was administered 2 hours prior to a single dose (600 mg) of gabapentin immediate release in 12 volunteers, mean gabapentin AUC values increased by 44% compared to gabapentin immediate release administered without morphine. The pharmacokinetics of morphine were not affected by administration of gabapentin immediate release 2 hours after morphine. The magnitude of this interaction at other doses is not known. An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin was taken 2 hours after antacids. It is recommended that GRALISE be taken at least 2 hours following antacid administration. There are no pharmacokinetic interactions between gabapentin and the following antiepileptic drugs: phenytoin, carbamazepine, valproic acid, phenobarbital, and naproxen. Cimetidine 300 mg decreased the apparent oral clearance of gabapentin by 14% and creatinine clearance by 10%. The effect of gabapentin immediate release on cimetidine was not evaluated. This decrease is not expected to be clinically significant. Gabapentin immediate release (400 mg three times daily) had no effect on the pharmacokinetics of norethindrone (2.5 mg) or ethinyl estradiol (50 mcg) administered as a single tablet, except that the C_{max} of norethindrone was increased by 13%. This interaction is not considered to be clinically significant. Gabapentin immediate release pharmacokinetic parameters were comparable with and without probenecid, indicating that gabapentin does not undergo renal tubular secretion by the pathway that is blocked by probenecid.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of *in utero* exposure to GRALISE, physicians are advised to recommend that pregnant patients taking GRALISE enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/. **Nursing Mothers** Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, GRALISE should be used in women who are nursing only if the benefits clearly outweigh the risks. **Pediatric Use** The safety and effectiveness of GRALISE in the management of postherpetic neuralgia in patients less than 18 years of age has not been studied. **Geriatric Use** The total number of patients treated with GRALISE in controlled clinical trials in patients with postherpetic neuralgia was 359, of which 63% were 65 years of age or older. The types and incidence of adverse events were similar across age groups except for peripheral edema, which tended to increase in incidence with age. GRALISE is known to be substantially excreted by the kidney. Reductions in GRALISE dose should be made in patients with age-related compromised renal function. [see Dosage and Administration]. **Hepatic Impairment** Because gabapentin is not metabolized, studies have not been conducted in patients with hepatic impairment. **Renal Impairment** GRALISE is known to be substantially excreted by the kidney. Dosage adjustment is necessary in patients with impaired renal function. GRALISE should not be administered in patients with CrCL between 15 and 30 or in patients undergoing hemodialysis [see Dosage and Administration].

DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of GRALISE has not been evaluated in human studies.

OVERDOSAGE

A lethal dose of gabapentin was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, labored breathing, ptosis, sedation, hypoactivity, or excitation. Acute oral overdoses of gabapentin immediate release in humans up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy and diarrhea were observed. All patients recovered with supportive care. Gabapentin can be removed by hemodialysis. Although hemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

CLINICAL PHARMACOLOGY

Pharmacokinetics *Absorption and Bioavailability* Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases. When GRALISE (1800 mg once daily) and gabapentin immediate release (600 mg three times a day) were administered with high fat meals (50% of calories from fat), GRALISE has a higher C_{max} and lower AUC at steady state compared to gabapentin immediate release. Time to reach maximum plasma concentration (T_{max}) for GRALISE is 8 hours, which is about 4-6 hours longer compared to gabapentin immediate release.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day were more than 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats receiving 1000 mg/kg/day peak plasma concentrations were more than 6.5 times higher than in humans receiving 1800 mg/day. The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic acinar cells *in vitro* and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans. Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 *in vitro* and 4 *in vivo* assays. No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately 11 times the maximum recommended human dose on an mg/m^2 basis).

Depomed®

Gralise® once-daily (gabapentin) tablets

GRALISE is indicated for the management of postherpetic neuralgia (PHN).

When your PHN patients face challenges by Night and Day

GRALISE THE NIGHT & RELEASE THE DAY

NIGHTTIME

DAYTIME

TAKE WITH EVENING MEAL

Once-daily GRALISE delivers 24-hour pain control, Night and Day[1]

- **At night, when pain is at its worst**[1]
- GRALISE is taken with the evening meal

- **Side effects that are transient**[1]
- Dizziness (10.9%) and somnolence (4.5%) were the most common side effects, and declined during the 2-week titration period to reach sustained low levels thereafter
- In clinical trials, 9.7% of GRALISE patients discontinued prematurely due to adverse reactions versus 6.9% for placebo[4]

Elderly patients experienced consistent results by Night and Day - even those over 75[3]

- Dosage adjustment of GRALISE is necessary in patients with impaired renal function. GRALISE should not be administered in patients with creatinine clearance <30 mL/min or in patients undergoing hemodialysis. Reductions in GRALISE dose should be made in patients with age-related compromised renal function.

Indication and Usage GRALISE is indicated for the management of postherpetic neuralgia (PHN). GRALISE is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

Important Safety Information Antiepileptic drugs, including gabapentin, the active ingredient of GRALISE, increase the risk of suicidal thoughts or behavior. Increased seizure frequency may occur in patients with seizure disorders if GRALISE is rapidly discontinued. Withdraw GRALISE gradually over a minimum of 1 week. The most common adverse reaction to GRALISE (≥5% and twice placebo) is dizziness.

Please see adjacent page for Brief Summary of Prescribing Information. Full Prescribing Information and Medication Guide are available at GRALISE.com.

References: 1. Argoff CE, Chen C, Cowles VE. Clinical development of a once-daily gastroretentive formulation of gabapentin for treatment of postherpetic neuralgia: an overview. *Expert Opin Drug Deliv.* 2012;9:1147-1160. **2.** Data on file, 2013. Depomed Inc. **3.** Gupta A, Li S. Safety and efficacy of once-daily gastroretentive gabapentin in patients with postherpetic neuralgia aged 75 years and over. *Drugs Aging.* 2013;30:999-1008. **4.** GRALISE [prescribing information]. Newark, CA: Depomed Inc.; December 2012.

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FOR NIGHT & DAY