PWJ
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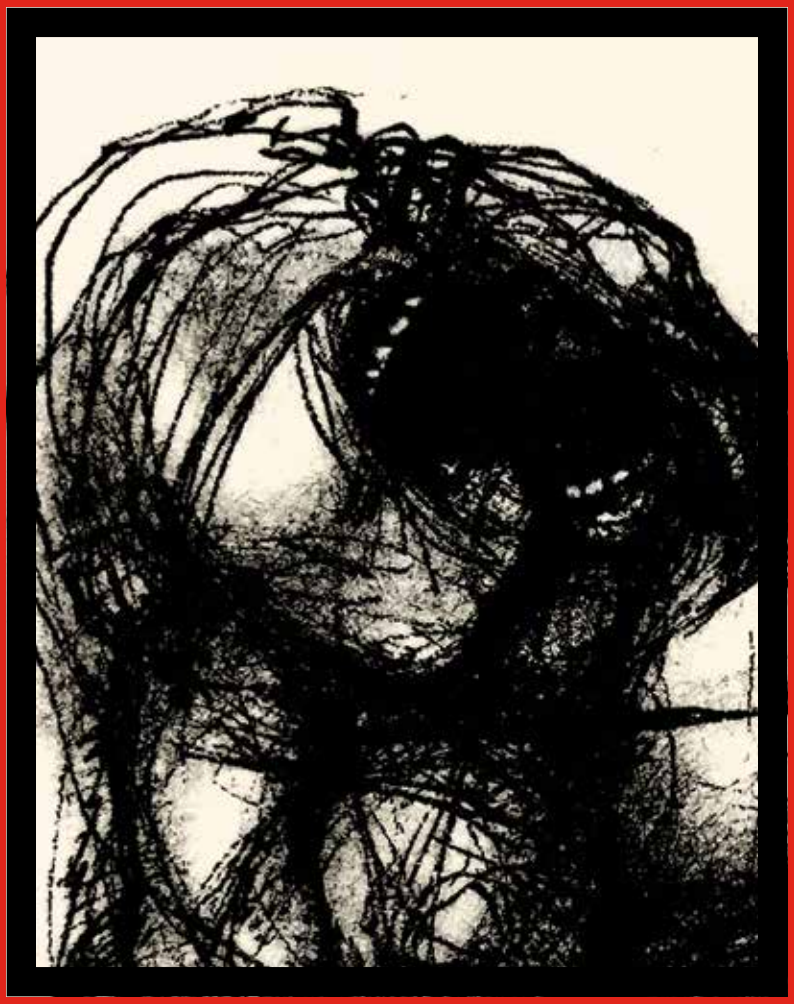

WHAT'S INSIDE:

THE PENDULUM SWINGS IN BOTH DIRECTIONS.

EDUCATION GOES FORWARD.

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PAINWEEK JOURNAL

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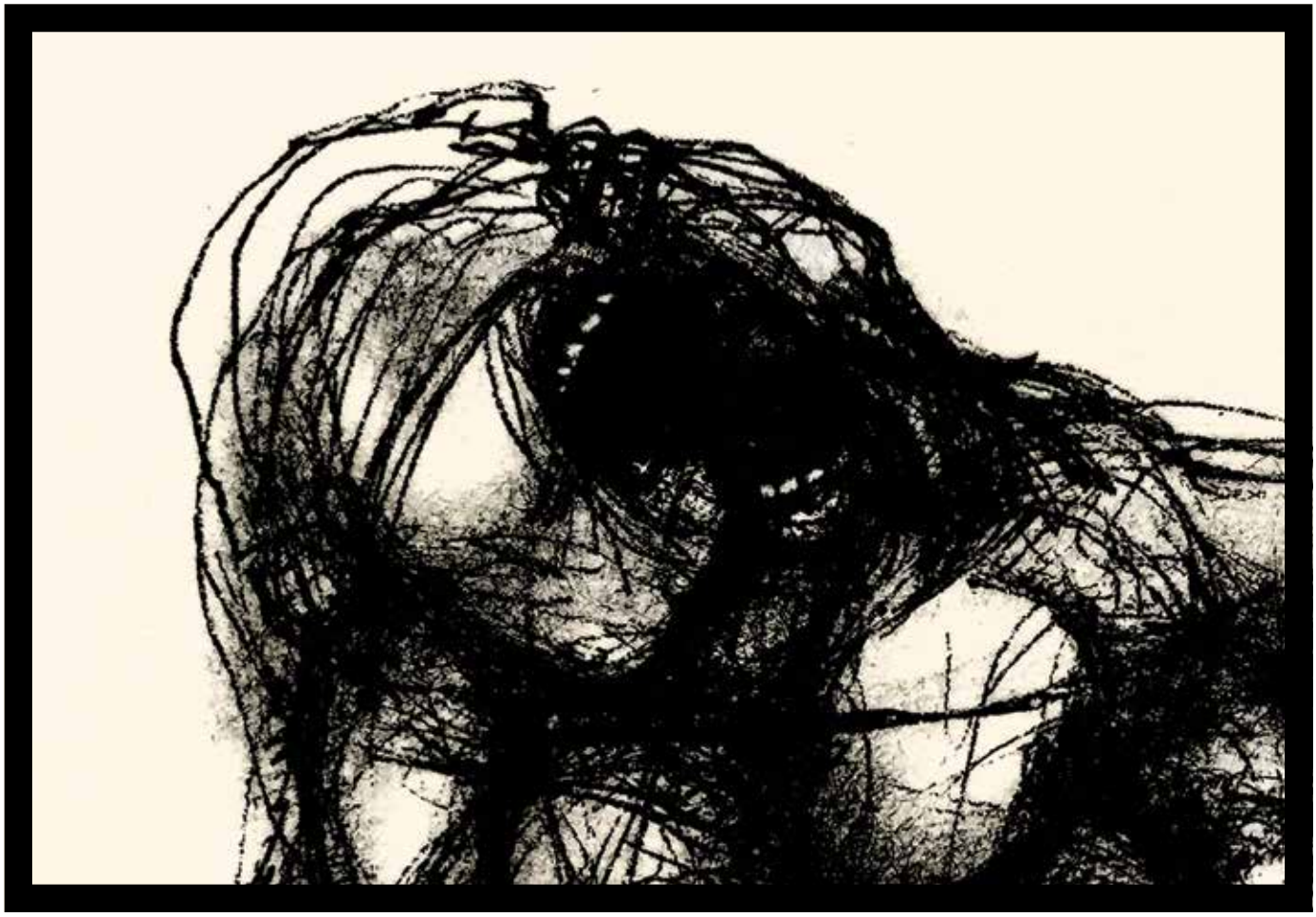
CONTENTS



FEATURES

SHORT CUTS

2018 PAINWEEK CONFERENCE PREVIEW P.61

It's like doing hard time.

If your patients are taking opioids for chronic pain, they might be experiencing **Painstipation**, the constipation caused by opioids. This is more commonly referred to as opioid-induced constipation (OIC).

Prescribe RELISTOR for OIC—the only product in its class* that is not metabolized via the CYP3A4 pathway.

*PAMORA (peripherally acting mu-opioid receptor antagonist) approved for OIC.

INDICATION

- RELISTOR® (methylnaltrexone bromide) is an opioid antagonist. RELISTOR tablets are indicated for the treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

IMPORTANT SAFETY INFORMATION – RELISTOR tablets, for oral use

- RELISTOR tablets are contraindicated in patients with known or suspected mechanical 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 tablets and consult their healthcare provider.
- Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR tablets. 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 tablets with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.
- In a clinical study, the most common adverse reactions for RELISTOR tablets (≥ 2% of RELISTOR patients and at a greater incidence than placebo) in patients with chronic non-cancer pain were: abdominal pain (14%), diarrhea (5%), headache (4%), abdominal distention (4%), vomiting (3%), hyperhidrosis (3%), anxiety (2%), muscle spasms (2%), rhinorrhea (2%), and chills (2%).
- The use of RELISTOR tablets during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier. Advise pregnant women of the potential risk to a fetus. Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR tablets.
- A dosage reduction of RELISTOR tablets is recommended in patients with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault). No dosage adjustment of RELISTOR tablets is needed in patients with mild renal impairment.
- A dosage reduction of RELISTOR tablets is recommended in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. No dosage adjustment of RELISTOR tablets is needed in patients with mild hepatic impairment (Child-Pugh Class A).

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary for RELISTOR tablets and injection on adjacent page and for more information go to www.relistor.com.

REFERENCE: RELISTOR [prescribing information]. Bridgewater, NJ: Salix Pharmaceuticals.

Salix Pharmaceuticals

RELISTOR®
methylnaltrexone bromide
Tablets

RELISTOR®
methylnaltrexone bromide
Subcutaneous Injection

RELISTOR®
methylnaltrexone bromide
Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) 150 mg tablets, for oral use.

RELISTOR (methylnaltrexone bromide) injection, for subcutaneous use.
8 mg/0.4 mL methylnaltrexone bromide in single-dose pre-filled syringe.
12 mg/0.6 mL methylnaltrexone bromide in a single-dose pre-filled syringe, or single-dose vial.

Initial U.S. Approval: 2008

INDICATIONS AND USAGE

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain
RELISTOR tablets and RELISTOR injection are indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

Opioid-Induced Constipation in Adult Patients with Advanced Illness
RELISTOR injection is indicated for the treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.

CONTRAINDICATIONS
RELISTOR tablets and injection are contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation
Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Cases of gastrointestinal perforation have been reported in adult patients with OIC 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
Discontinue if severe or persistent diarrhea occurs during treatment.

Opioid Withdrawal
Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Monitor closely for adequacy of analgesia and symptoms of opioid withdrawal.

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 clinical practice.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain
The safety of RELISTOR tablets was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 12-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR tablets 450 mg orally (200 patients) or placebo (201 patients). After 4 weeks of double-blind treatment administered once daily, patients continued 8 weeks of double-blind treatment on an as needed basis (but not more than once daily).
The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR tablets are shown in Table 4. Adverse reactions of abdominal pain, diarrhea, hyperhidrosis, anxiety, rhinorrhea, and chills may reflect symptoms of opioid withdrawal.

Table 4: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Tablets in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 1)

Adverse Reaction	RELISTOR Tablets n = 200	Placebo n = 201
Abdominal Pain**	14%	10%
Diarrhea	5%	2%
Headache	4%	3%
Abdominal Distention	4%	2%
Vomiting	3%	2%
Hyperhidrosis	3%	1%
Anxiety	2%	1%
Muscle Spasms	2%	1%
Rhinorrhea	2%	1%
Chills	2%	0%

*Adverse reactions occurring in at least 2% of patients receiving RELISTOR tablets 450 mg once daily and at an incidence greater than placebo.
**Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness.

The safety of RELISTOR injection was evaluated in a double-blind, placebo-controlled trial in adult patients with OIC and chronic non-cancer pain receiving opioid analgesia. This study (Study 2) included a 4-week, double-blind, placebo-controlled period in which adult patients were randomized to receive RELISTOR injection 12 mg subcutaneously 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 injection 12 mg subcutaneously was administered less frequently than the recommended dosage regimen of 12 mg once daily.
The most common adverse reactions in adult patients with OIC and chronic non-cancer pain receiving RELISTOR injection are shown in Table 5. The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Table 5: Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR Injection in Adult Patients with OIC and Chronic Non-Cancer Pain (Study 2)

Adverse Reaction	RELISTOR Injection n = 150	Placebo n = 162
Abdominal Pain**	21%	7%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	<1%
Chills	1%	0%

*Adverse reactions occurring in at least 1% of patients receiving RELISTOR injection 12 mg subcutaneously once daily and at an incidence greater than placebo.
**Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness.

During the 4-week double-blind period, in patients with OIC and chronic non-cancer pain that received RELISTOR 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 injection 12 mg subcutaneously 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 2) 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 injection was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with OIC and chronic non-cancer pain (Study 3). Patients were allowed to administer RELISTOR injection 12 mg subcutaneously 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 2. Additionally, in Study 3, 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 injection was evaluated in two, double-blind, placebo-controlled trials in adult patients with OIC and advanced illness receiving palliative care: Study 4 included a single-dose, double-blind, placebo-controlled period, whereas Study 5 included a 14-day multiple dose, double-blind, placebo-controlled period. The most common adverse reactions in adult patients with OIC and advanced illness receiving RELISTOR injection are shown in Table 6 below.

Table 6: Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR Injection in Adult Patients with OIC and Advanced Illness* (Studies 4 and 5)

Adverse Reaction	RELISTOR Injection 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 at least 5% of patients receiving all doses of RELISTOR injection (0.075, 0.15, and 0.3 mg/kg) and at an incidence greater than placebo.
**Includes: abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort and abdominal tenderness.
The rates of discontinuation due to adverse reactions during the double-blind, placebo-controlled clinical trials (Study 4 and Study 5) were comparable between RELISTOR (1%) and placebo (2%).

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

Gastrointestinal
Perforation, cramping, vomiting.

General Disorders and Administration 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 0.3 mg/kg of RELISTOR did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

USE IN SPECIFIC POPULATIONS

Pregnancy
The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Advise pregnant women of the potential risk to a fetus.

Lactation
Because of the potential for serious adverse reactions, including opioid withdrawal, in breastfed infants, advise women that breastfeeding is not recommended during treatment with RELISTOR. 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.

Pediatric Use
Safety and effectiveness of RELISTOR tablets and injection have not been established in pediatric patients.

Geriatric Use
In clinical studies of RELISTOR tablets, no overall differences in effectiveness were observed. Adverse reactions were similar; however, there was a higher incidence of diarrhea in elderly patients. In clinical studies of RELISTOR injection, no overall differences in safety or effectiveness were observed between elderly patients and younger patients.
Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dosage adjustment based on age is recommended. Monitor elderly patients for adverse reactions.

Renal Impairment
In a study of subjects with varying degrees of renal impairment receiving RELISTOR injection subcutaneously, there was a significant increase in the exposure to methylnaltrexone in subjects with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault) compared to healthy subjects. Therefore, a dosage reduction of RELISTOR tablets and RELISTOR injection is recommended in patients with moderate and severe renal impairment (creatinine clearance less than 60 mL/minute as estimated by Cockcroft-Gault). No dosage adjustment of RELISTOR tablets or RELISTOR injection is needed in patients with mild renal impairment (creatinine clearance greater than 60 mL/minute as estimated by Cockcroft-Gault).

Hepatic Impairment
Tablets
In a study of subjects with varying degrees of hepatic impairment receiving a 450 mg dose of RELISTOR tablets, there was a significant increase in systemic exposure of methylnaltrexone for subjects with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment compared to healthy subjects with normal hepatic function. Therefore, a dosage reduction of RELISTOR tablets is recommended in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment. No dosage adjustment of RELISTOR tablets is needed in patients with mild hepatic impairment (Child-Pugh Class A).
Injection
There was no clinically meaningful change in systemic exposure of methylnaltrexone compared to healthy subjects with normal hepatic function. No dosage adjustment of RELISTOR injection is needed for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, monitor for methylnaltrexone-related adverse reactions.

OVERDOSAGE
A study of healthy subjects 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.

NONCLINICAL TOXICOLOGY

Carcinogenesis
Oral administration of methylnaltrexone bromide at doses up to 200 mg/kg/day (about 81 times the subcutaneous maximum recommended human dose (MRHD) of 12 mg/day based on body surface area) in males and 400 mg/kg/day (about 162 times the subcutaneous MRHD of 12 mg/day) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 243 times the subcutaneous MRHD of 12 mg/day) for 104 weeks did not produce tumors in mice and rats.

Mutagenesis
Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Impairment of Fertility
Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 122 times the subcutaneous MRHD of 12 mg/day; about 3.3 times the oral MRHD of 450 mg/day) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Animal Toxicology and/or Pharmacology
In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone caused concentration-dependent inhibition of hERG current.

PATIENT COUNSELING INFORMATION
See FDA-approved Patient Labeling (Patient Information).

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Kevin L. **Zacharoff**

information

sources may influence whether a practitioner thinks chronic pain assessment and management should be based on the specific needs of the person with chronic pain, or dictated by a more scientific and mechanistic approach. In October of 2000, the 106th US Congress passed H.R. 3244, which President Clinton signed into law. Title VI, Sec. 1603 provided for the *Decade of Pain Control and Research* to begin January 1, 2001. This was only the 2nd "medically-declared decade" by Congress; the first being the preceding decade, which was the *Decade of the Brain*. I'm not sure what the fruits of these two designated decades actually are: we still don't understand much about the brain and we are still hungry for evidence based treatment for chronic pain. That being said, I believe we owe it to our patients to give them the best that medical research and data have to offer, but also not forget they are people in need. I have been hearing the call for pain treatment to be evidence based for a long time, and more than ever believe we must also listen to anecdotal evidence and other clinician's experiences, and pay attention to the raging debates about what to do and what not to do. Patients with untreated or undertreated chronic pain need to be taken care of *now*—not when the scientific evidence finally arrives, if it ever does. Let's see what this issue of PWJ does to help formulate the basis for what we do for our patients with chronic pain *now*, based on available science, clinical experience, and a humanistic approach.

This issue begins with an article about something we see every day that may become invisible to us, but shouldn't. Sometimes things we think were risky yesterday become "go-to" strategies today. So is the case when we discuss nonsteroidal anti-inflammatory drugs (NSAIDs) and their role in managing chronic pain. **Drs. Timothy J. Atkinson** and **Jeffrey Fudin** start with the mother of all NSAIDs—aspirin—and take us on a journey of the good, the bad, and the ugly. These often-obtained OTC medications carry significant benefits and risks, and we are reminded in this article that we still need to give them consideration, respect, and use them with caution. Educating patients about when *not* to use prescription and OTC formulations is critical from a safety perspective. This article is timely and its messages are necessary for us in these days of reinforcement about using opioid analgesic alternatives.

From the humanistic perspective, **Dr. Heather Tick** makes a good case that the growing number of stakeholders clamoring for a way towards a "pain care crisis" solution will only see it if they team up. Painting a very clear portrait of the intersection of inadequate pain treatment and harm from indiscriminate prescribing of opioid analgesics, the author adeptly points towards common misconceptions and complementary and alternative treatments. The need for patient engagement in a successful pain treatment plan is stressed because, let us never forget, patients are stakeholders too, and part of the "village." Enjoy this one and keep its messages in mind always.

In my opinion, complex regional pain syndrome (CRPS) is probably one of the most intriguing and challenging pain conditions. In his primer of CRPS from the perspective of the primary care clinician, **Dr. Philip Getson** gives the nonexpert reader an "everything you need to know" explanation of CRPS from assessment to diagnosis to treatment. I think one of the most important take-away messages is that there has been too little emphasis on the role of alternative therapies and the need for collaboration of healthcare providers and patient family members in treating this often debilitating pain condition. Not all of this may be supported scientific evidence, but is likely very important all the same.

Dr. Sean Li takes us on a historical voyage from the evolution of neuromodulation to the basic science behind the role it has played in managing chronic pain. Laying out a framework for the variety of different neuromodulator based approaches specifically targeted towards certain painful conditions, the author provokes thought about the future of pain management as targeted therapy becomes more commonplace.

This issue's *Pundit Profile* spotlights **Dr. Ramon L. Cuevas-Trisan**, the Chief of the Physical Medicine and Rehabilitation Service at West Palm Beach Medical Center in Florida. He is devoted to pain management *and* education, and we are given insight into what drives him, where he comes from, what his recipes for success are, including the importance of listening. He makes a difference on many levels, and it's good to know what makes him as passionate about pain management as he is.

Our *Next Generation* focuses on pharmacist **Dr. Abigail T. Brooks**. She may not know it, but I still have the winning essay she wrote in 2014 that I pegged as a winner when she was a PGY2 Pain & Palliative Care Pharmacy Resident. Back when I read that essay, I knew she was someone to watch, someone who would become part of the next generation of leaders in the field of pain management. Now she's a PAINWeek regular, and it's gratifying to read more about the person beneath the persona.

So there we have this issue of PWJ*;* some science, some feeling, and lots for us to think about. It leaves me pondering how much more we have to cover and re-cover in order to help be the "village" and navigate these turbulent times while we wait for the science to catch up and provide us with real-world and practical guidance.

Hopefully, by the time you read this issue, you will have already made plans to attend the National PAINWeek conference in September. I hope to see you there.

—Kevin L. **Zacharoff** MD, FACIP, FACPE, FAAP

Kevin L. Zacharoff is Pain Educator and Consultant and Faculty, Clinical Instructor at SUNY Stony Brook School of Medicine, Department of Preventive Medicine, in Stony Brook, New York.

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Featured Faculty

Timothy J. **Atkinson** PHARMD, BCPS, CPE **P.12**

Timothy J. Atkinson is a Clinical Pharmacy Specialist, Pain Management, and Director, PGY-2 Pain & Palliative Care Pharmacy Residency Program at the VA Tennessee Valley Healthcare System in Murfreesboro. He coauthored his article with **Jeffrey Fudin**, PharmD, DAIPM, FCCP, FASHP, Chief Executive Office / Chief Medical Officer, Remitigate LLC, in Delmar New York, and Clinical Pharmacy Specialist and Director, PGY2 Pharmacy Pain & Palliative Care Residency, Stratton VA Medical Center (WOC), in Albany, New York; Adjunct Associate Professor, Albany College of Pharmacy and Health Sciences; Adjunct Associate Professor, Western New England University College of Pharmacy and Health Sciences, Springfield, Massachusetts.

Philip **Getson** DO **P.30**

Philip Getson is an Assistant Professor of Medicine in Neurology at Drexel University College of Medicine in Philadelphia and a Family Physician in practice in New Jersey for 42 years. He is considered by his peers an expert in the evaluation and treatment of complex regional pain syndrome and has evaluated over 1400 patients with this disorder and continues to do so. He is a Board Certified Thermologist with over 30 years' experience in reviewing and interpreting thermographic images and has been utilizing ketamine infusion therapy for more than 11 years. Questions regarding his article can be directed to him at pgetson1@comcast.net.

Sean **Li** MD **P.44**

Sean Li is the Regional Medical Director and an interventional pain physician at Premier Pain Centers, an affiliate of the National Spine and Pain Centers, in Shrewsbury, New Jersey, and is an attending physician at Riverview Medical Center in Red Bank, New Jersey. He has published numerous professional articles and written text book chapters on the topic of pain and is actively involved in clinical research to help advance the field of interventional pain medicine.

Heather **Tick** MD **P.20**

Heather Tick is the Gunn-Loke Endowed Professor of Integrative Pain Medicine in the Departments of Family Medicine and Anesthesiology & Pain Medicine at the University of Washington School of Medicine in Seattle. She was the lead author of a White Paper on evidence based nonpharmacologic pain care, for the Academic Consortium for Integrative Medicine and Health: a consortium of 72 medical schools and health systems. She has written scholarly articles as well as 2 books for general audiences on nonpharmacologic strategies for team based collaborative care for painful conditions.

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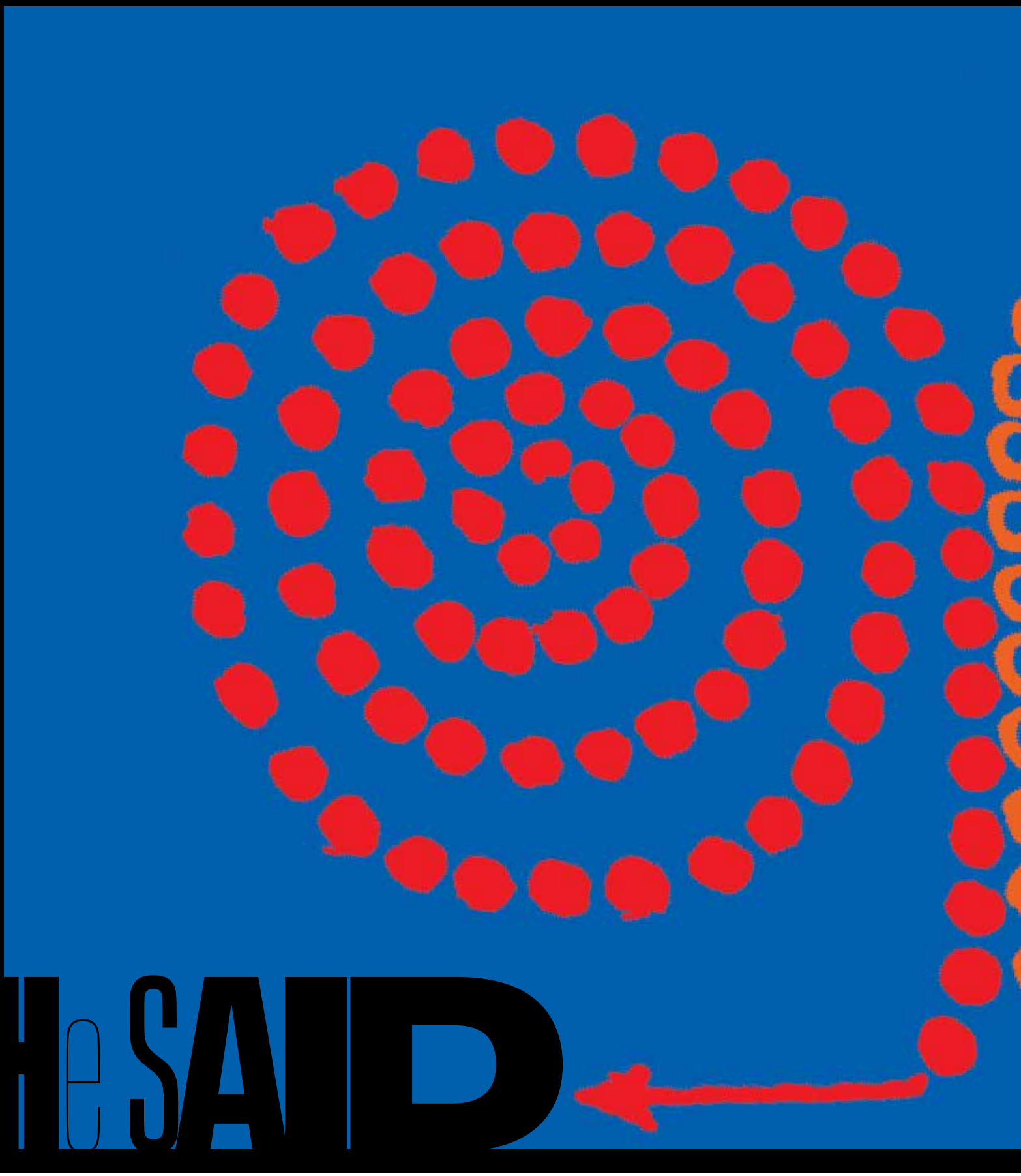

By Timothy J. **Atkinson** PHARMD, BCPS, CPE **&** Jeffrey **Fudin** PHARMD, DAIPM, FCCP, FASHP

What's the Deal with NSAIDs?

INTRODUCTION

PHARMACOTHERAPY

Nonsteroidal anti-inflammatory drugs (NSAIDs)

are ubiquitously utilized for a variety of reasons including analgesia by consumers who may purchase them over-the-counter or obtain them by prescription. Despite their routine use, they can sometimes be a dangerous analgesic selection with extended use and in general may be routinely misunderstood, as their place in therapy continues to be questioned by clinicians who struggle to reconcile controversy resulting from recent studies with an avalanche of negative press over the past couple of decades.[1] Almost every analysis or review article published on NSAIDs in the past 20 years has highlighted their significant adverse effect profile. Therefore, in order to provide safe and effective treatment for patients with chronic pain, clinicians need to familiarize themselves with the history of NSAIDs, maximize balancing their risks and benefits in treatment paradigms.

"Aspirin quickly became the most popular painkiller worldwide, used for backache, headache, and arthritis. It's notable that NSAIDs became the cornerstone of management for many pain conditions at a time when opioid formulations were widely available."

SAID History

Willow bark had been used for centuries for its antipyretic and anti-inflammatory properties, but it wasn't until 1828 that Johann Buchner, a professor of pharmacy, isolated bitter tasting crystals from willow bark and named it "salicin." About 10 years later, a more active and pure form of salicylic acid was produced by Raffaele Piria, the Italian chemist. In the decades that followed, scientists demonstrated that salicylic acid could successfully treat rheumatoid arthritis, rheumatic fever, and gout. From as early as 1853, the French chemist Francis Gerhardt was working to make salicylic acid more tolerable by buffering it with sodium and acetyl chloride into the first form of acetylsalicylic acid (ASA). However, it was not until 1899 when Felix Hoffman created a more stable form of ASA that was first marketed as Aspirin® by Bayer. Aspirin quickly became the most popular painkiller worldwide, used for backache, headache, and arthritis.[2] It's notable that NSAIDs became the cornerstone of management for many pain conditions at a time when opioid formulations were widely available. To illustrate how critical NSAIDs had become to the management of inflammatory disorders, consider a quote from the 1939 rheumatology treatment guidelines: "Because of its antipyretic action in rheumatic fever, because of its analgesic property, because of its relative harmlessness and ready accessibility, it has won a place in the armoury of the attack on rheumatism that has scarcely been challenged."[3] The efficacy of NSAIDs is well established. In patients with osteoarthritis pain for example, NSAIDs are widely considered the most effective first-line treatment option for controlling pain, improving function, and decreasing stiffness. In fact, NSAIDs are 3 times more effective than acetaminophen in these categories despite the latter being recommended more often.[4]

Due to the newer and diverse formulations of the NSAID class, it might be easy to forget how much aspirin was required to effectively treat various pain conditions. Common conditions in the early 20th century were rheumatic fever and rheumatoid arthritis, which required 12 grams (37 tablets) and 5.2 grams (16 tablets), respectively, every day. Patients were often told to increase their dose daily until their ears started ringing (tinnitus) and then decrease by 1 tablet the next day.[5] Pill burden and gastrointestinal (GI) intolerance were common concerns but there were few alternative treatment options, and aspirin use remained the preferred therapy. One trial studied the effect of therapeutic doses of aspirin on acid/base balance and found 80% of patients developed salicylism (a toxic condition, marked by nausea, vomiting, and tinnitus) and primary respiratory alkalosis (often characterized by weakness or cramps) a consequence of the ingestion of large amounts of ASA which, like all NSAIDs, is a weak acid.[5]

Mechanism of Action

The modern age of NSAIDs began in 1965 with the approval of indomethacin. Indomethacin is highly selective COX-1 inhibitor and known to cause considerable GI upset; however, it was a dramatic improvement over ASA in terms of acid load, pill burden, and GI tolerability.[2] Sir John Vane, the British pharmacologist, was the first to characterize the NSAID mechanism of action, showing it was the inhibition of prostaglandin synthesis, and winning a Nobel Prize for his work in 1982. This scientific breakthrough resulted in a kind of NSAID renaissance from 1976 to 1992, with 15 new NSAIDs in as many years. Today there are more than 25 NSAIDs available for use each belonging to distinct chemical classes with unique selectivity, efficacy, and toxicity.[6]

Pharmacology

NSAIDs reduce pain, fever, and inflammation by inhibition of prostaglandin biosynthesis at cyclo-oxygenase (COX) enzymes.[1] There are 2 known isoforms of the COX enzyme, COX-1 and COX-2, each with distinct physiological roles. COX-1 is constitutively expressed in nearly all cells and produces thromboxane (TXA_2) and prostacyclin (PGI_2) in equal amounts maintaining a balance.[7] NSAIDs and ASA bind to the same active site for COX-1, serine 529, which suppresses platelet function and increases bleeding risk. ASA's binding is unique, however, because it binds irreversibly and inhibits platelets for their entire life cycle (7 to 10 days), which is responsible for its cardioprotective utility. NSAIDs bind reversibly and increase bleeding risk for a limited period consistent with their half-life. COX-2 is expressed in the brain, kidneys, and blood vessels, the areas most susceptible to thrombotic events, and expression can be induced by cytokine release from injury or inflammation.[8-12] The COX enzyme selectivity and binding characteristics of each NSAID is strongly associated with their risk of adverse effects.

Adverse Effects

Research related to NSAIDs have focused heavily on their adverse effects for the past 20 years. In the early 1990s, research focused exclusively on elucidating the risk of GI bleeding, and more recently on their cardiovascular adverse effects. The type and degree of COX inhibition and corresponding PGI_2/TXA_2 ratio is the preferred hypothesis surrounding many of the adverse effects of NSAIDs.[7,13] Research has provided important guidance on the effect of NSAID dose on adverse effects. Of note, high dose NSAID therapy vs low to medium doses presents nearly double the risk of GI events and a 50% increased risk of renal failure.[14-16] All NSAIDs lose COX selectivity at higher doses. NSAIDs can affect both COX-1 and COX-2 simultaneously increasing exposure and overall risk of additional side effects. Duration of NSAID therapy can be just as important as the dosage, with the highest risk of GI adverse events in the first 14 days of therapy. Cardiovascular risk is fairly consistent, but risk of renal failure appears to increase over time and prolonged exposure to NSAID use.[16-18]

However, inappropriate use of NSAIDs is a pervasive problem that is often underappreciated, perhaps causing adverse events to be *over*estimated compared to actual risk when taken as recommended. In 2010, 12.8% of the US population took both prescription and over-the-counter (OTC) NSAIDs regularly which, for comparison, is double the number of patients taking opioids for chronic pain.[19] In addition, 40% of prescription NSAID users report taking OTC NSAIDs in addition to their prescription NSAID, and 29% of the population believe that OTC NSAID use is safer than prescription NSAID use.[2,20] Nearly 16% of the population take NSAIDs and ASA together, which can significantly increase risk of bleeding. ASA alone results in nearly 30% of all episodes of NSAID related GI bleeding.[21]

> **Duration of NSAID therapy can be just as important as the dosage, with the highest risk of GI adverse events in the first 14 days of therapy. Cardiovascular risk is fairly consistent, but risk of renal failure appears to increase over time and prolonged exposure to NSAID use.**

Gastrointestinal Adverse Effects

The degree of COX-1 inhibition by an NSAID plays an integral part in determining a patient's bleeding risk because COX-1 inhibition directly affects platelet aggregation.[7,22] Because of the COX-1 reversible binding, it would require a consistent intake of NSAIDs to increase the risk of bleeding. Strong COX-1 inhibitors, which have >50 times the selectivity of COX-1 agents (such as indomethacin, ketorolac, piroxicam, sulindac), are associated with more GI ulcers and bleeding.[1,23,24] Nonetheless, NSAIDs currently marketed vary in their degree of COX-1/COX-2 inhibition and selectivity, and familiarity with these properties can be useful to determine bleeding risk.

In 2009, the number of deaths attributed to GI bleeding was 7,215—of which one-third were typically attributable to NSAID use.[24] Clinicians should counsel patients to avoid concomitant use of prescription and OTC NSAID/aspirin, and should provide strategies for gastric protection, if appropriate. Risk factors for NSAID related GI injury include high NSAID dose, older age, *H. pylori* infection, history of ulcer or ulcer complications, and concomitant use of OTC NSAID, low-dose ASA, anticoagulants, or corticosteroids.[1] Strategies to mitigate GI risk include utilization of gastroprotective therapy (high dose misoprostol, proton pump inhibitors) or utilizing a COX-2 selective agent.[1]

Cardiovascular Events

No anti-inflammatory, except ASA, has ever been intentionally used or indicated for its ability to inhibit COX-1 selectively. NSAIDs are primarily used for their antipyretic, analgesic, and anti-inflammatory properties, which are all mediated by COX-2. It's just as important to recognize that when we use a COX-1 selective NSAID for pain management, higher doses may be required to achieve enough COX-2 inhibition for analgesic efficacy, but also may result in significant adverse effects. Theoretically, NSAIDs with COX-2 > COX-1 inhibition will have an increased analgesic benefit while minimizing the bleeding risk. However, the Food and Drug Administration (FDA) removed the 2 most potent COX-2 selective inhibitors, rofecoxib (Vioxx®) and valdecoxib (Bextra®), from the market due to the increased risk of serious and potentially fatal CV events.[25,26]

The FDA class warnings on NSAIDs were strengthened in 2015 after a meta-analysis was published showing that high dose NSAID therapy results in increased CV risk even with agents like ibuprofen, which is COX-1 selective. The study also showed that celecoxib and diclofenac use had significant CV risk at high doses. Only naproxen did not increase CV risk, but demonstrated significant GI risk.[26] The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial studied CV risk of rofecoxib and naproxen in patients with rheumatoid arthritis (RA). Limitations of the study included: **1** the choice of a higher risk cohort with RA, including patients with high CV risk where nearly half of CV events occurred in the study originating from 4% of patients at baseline who had significant history of atherosclerotic cardiovascular disease, **2** no patients were allowed to take ASA even when indicated for prevention, and **3** selection of naproxen as comparator, which had already been established as the NSAID with lowest CV risk, and perhaps even protective effect in comparison to other NSAIDs.[27] In contrast, the CLASS (Celecoxib Long-term Arthritis Safety Study) trial studied celecoxib vs diclofenac or ibuprofen in patients with osteoarthritis (OA) and patients were allowed to continue taking ASA for prevention. Celecoxib showed no significant difference in rate of myocardial infarction and decreased risk of stroke

> **"...inappropriate use of NSAIDs is a pervasive problem that is often underappreciated, perhaps causing adverse events to be overestimated compared to actual risk when taken as recommended."**

compared to diclofenac and ibuprofen.[28] The CLASS trial was criticized for allowing ASA as a protective agent, which gave this an unfair advantage over the RIGOR trial. This "unfair advantage" was disproven in a subsequent analysis; however, we, the authors of this article (TA, JF) strongly believe studies should be designed to reflect real world practice that would routinely include cardiac prevention and GI prophylaxis.[29]

The wrong lessons may have been acquired from those early studies based on recent, albeit limited, study results. The PRECISION (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen) trial compared moderate doses of celecoxib (Celebrex®) with naproxen and ibuprofen in patients at risk for CV in a randomized, double-blind, placebo-controlled trial. This trial more accurately reflected current practice by allowing patients to continue taking medications like aspirin for CV protection. In the trial, celecoxib was noninferior to both naproxen and ibuprofen; patients had more CV events in the latter 2 treatment groups.[30] In a recent meta-analysis of all NSAID induced CV events, celecoxib decreased composite CV endpoint for all comparisons and, when rofecoxib was removed from the coxib comparison group, no coxib had significant results, indicating the rofecoxib trial results may have significantly skewed the data against COX-2 selective agents exaggerating their potential for harm in CV events.[31] While some COX-2 selectivity is preferable, we (TA, JF) recommend using the lowest effective dose and counseling patients on the strengths of NSAID therapy to avoid unrealistic expectations. Furthermore, strategies should be employed to reduce NSAID risks including avoiding oral NSAIDs in patients with history or serious risk of cardiovascular disease.

NSAID Discontinuation Prior to a Procedure

Patients are often instructed to stop their NSAIDs prior to a procedure or surgery to decrease bleeding risk. Many healthcare providers may be either not familiar with bleeding risk of individual NSAIDs or managing patients with a predetermined protocol requiring patients to stop their NSAID 7 to 10 days prior to the procedure. This would be appropriate for ASA but for those that rely on NSAID use for mobility in their daily lives, this may be an unnecessary burden. A more practical approach is discontinuing each agent according to its bleeding risk.[32] Risk of bleeding from the NSAID reverses when it is completely eliminated from the body. Each medication has an elimination half-life that is the measurement of how long it takes for 50% of the medication to be removed from the body. At 5 half-lives, each medication is considered completely removed from the body and therefore unable to exert its effects including bleeding. The half-lives for each NSAID are widely available, but in general NSAIDs are completely eliminated between 1 to 4 days making 7 to 10 day discontinuation likely unnecessary. The American Society of Regional Anesthesia concurs with this approach recommending 5 half-lives be used when the exact bleeding risk is unknown.[33]

Topical NSAIDs

Topical NSAIDs are often underutilized for pain management, which is unfortunate because their evidence for pain relief in a localized area is very strong. As with oral formulations, topical NSAIDs have been shown to improve function and stiffness for those with osteoarthritis 3 times more than acetaminophen, and may be superior to opioids in promoting mobility. They can achieve higher tissues concentrations at site of injury than oral comparators and have limited side effects reported.[34] In fact, when used topically, there is limited systemic absorption with minimal levels detectable in serum. This is partly due to high protein binding of NSAIDs in general (greater than 90%), leaving very little unbound in serum to exert an effect. This means that patients who can't take oral NSAIDs for safety reasons could consider taking topical NSAIDs to address localized pain with little risk of systemic adverse effects. Unfortunately, FDA requires the class effect warnings for GI and CV adverse effects on all NSAID products including topicals, which confuses providers and discourages appropriate prescribing.

Conclusion

NSAIDs represent a significant and important part of the analgesic armamentarium, particularly because of their anti-inflammatory properties that are devoid of well-known long-term toxicities associated with traditional steroids. Their cardiovascular, renal, and gastrointestinal risks should be carefully balanced against comorbid conditions and length of therapy. Topical NSAIDs may offer an alternative approach to using oral NSAIDs in higher risk patients, as systemic absorption is minimal or unmeasurable. Clinicians must weight benefits of chronic NSAID use against risks and should remember that continual or intermittent use could help augment analgesic response when NSAIDs are used concomitantly with other analgesics such as opioids, skeletal muscle relaxants, noradrenergic reuptake inhibitors, and/or other therapies. ◘

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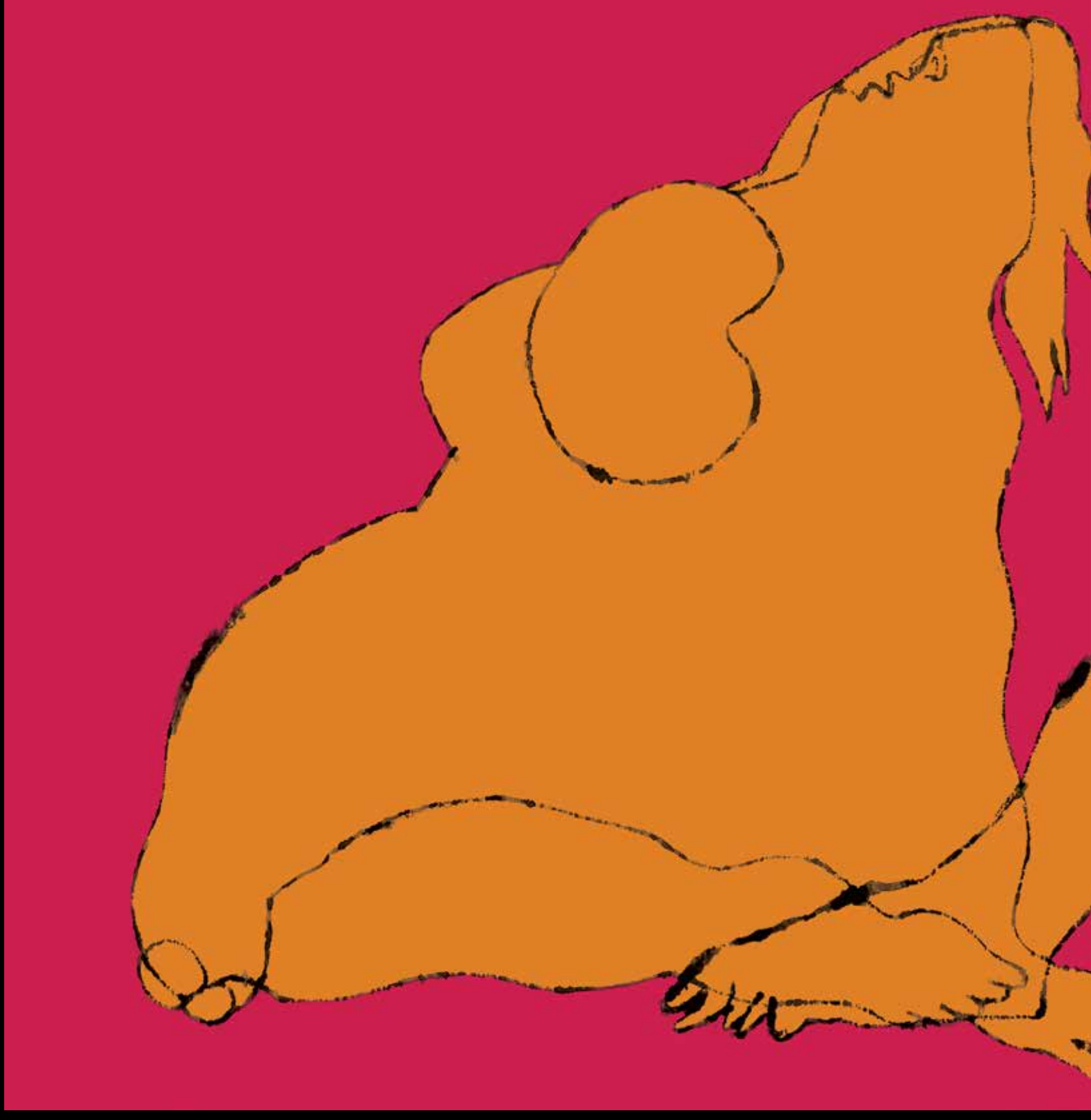
By Heather **Tick** MD



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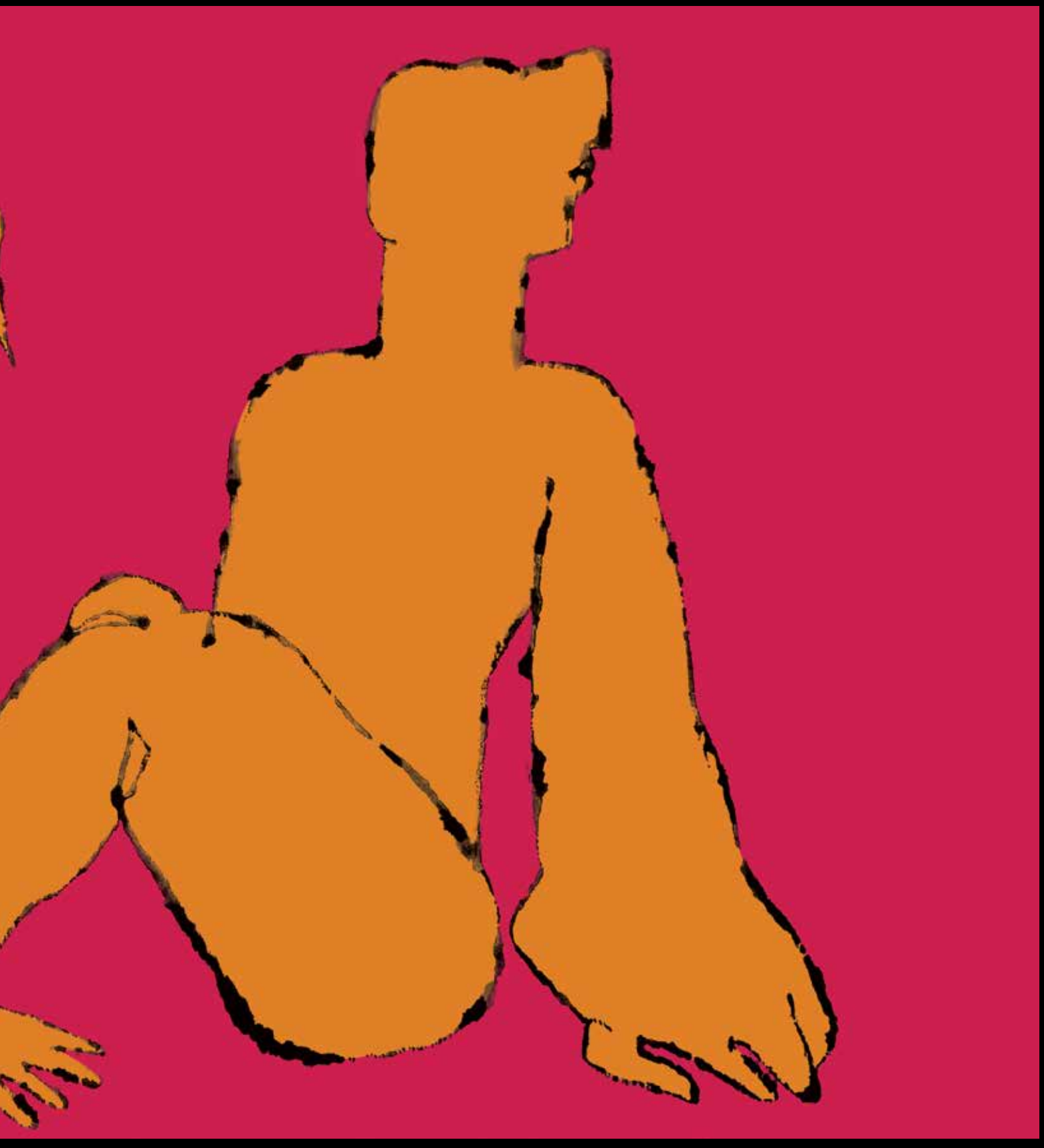

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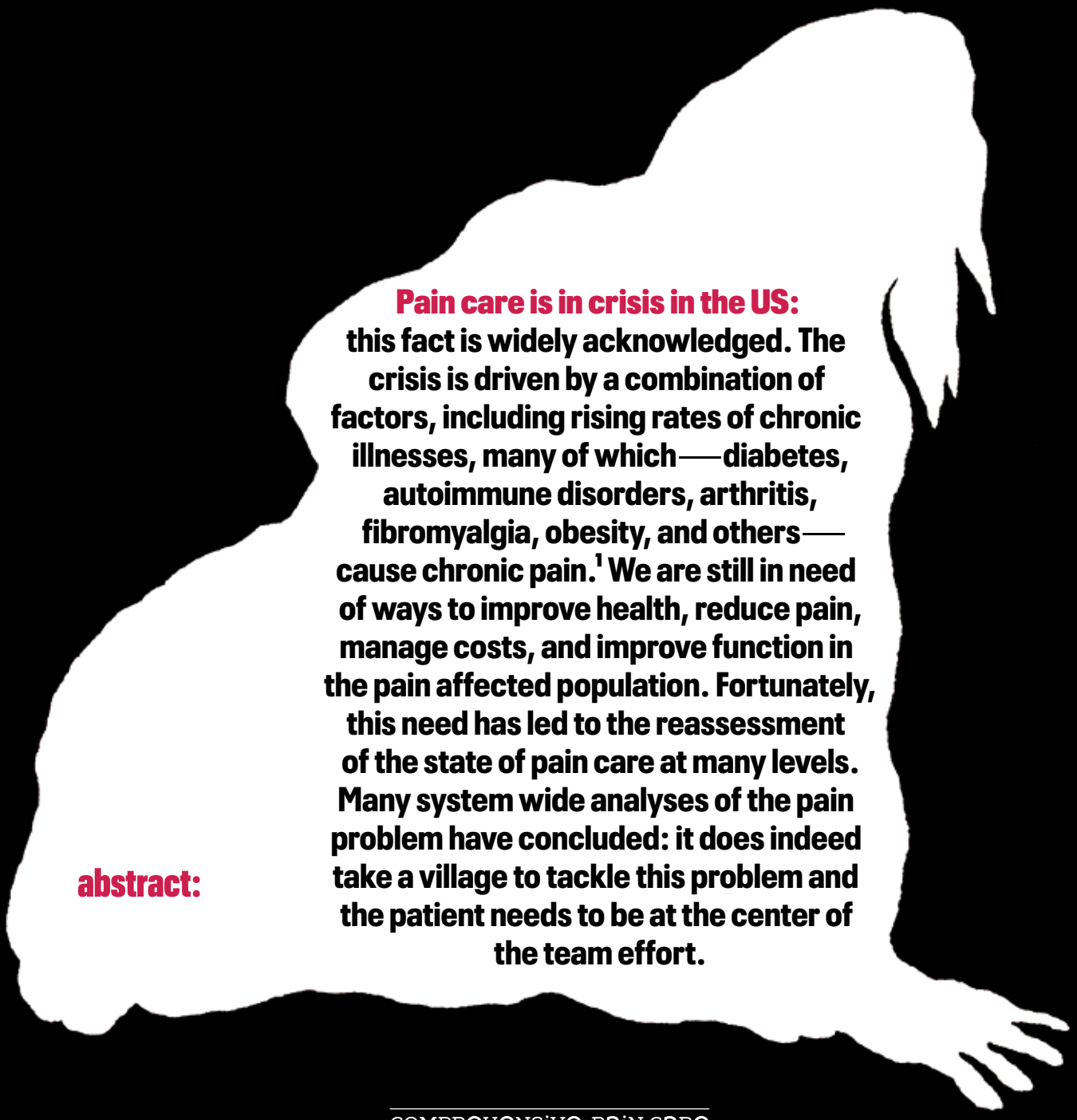

abstract:

Pain care is in crisis in the US: this fact is widely acknowledged. The crisis is driven by a combination of factors, including rising rates of chronic illnesses, many of which—diabetes, autoimmune disorders, arthritis, fibromyalgia, obesity, and others—cause chronic pain.[1] We are still in need of ways to improve health, reduce pain, manage costs, and improve function in the pain affected population. Fortunately, this need has led to the reassessment of the state of pain care at many levels. Many system wide analyses of the pain problem have concluded: it does indeed take a village to tackle this problem and the patient needs to be at the center of the team effort.

The Past/The Problem

Our main strategy for treating chronic pain since the late 1980s depended on the use of opioids, based on their track record of effectiveness for the treatment of acute and cancer pain. The medical community had previously avoided using chronic opioid therapy in noncancer pain because patients developed tolerance to the medications and would generally need steadily increasing doses. But in 1986, Portenoy and Foley wrote a paper reporting on 38 noncancer pain patients using chronic opioids at low doses and they concluded from this small study that opioids were safe and the risk of harm was low.[2] These conclusions were premature because chronic pain treatment with long-term opioids had not yet been adequately studied. Influenced by extensive marketing and despite the lack of long-term studies on chronic noncancer pain, standard pain practice shifted to long-term treatment with opioids. Predictably the doses used were escalated as patients became tolerant and, for a while, doctors were led to believe that this was not a serious concern. The goal of treatment was to reduce pain scores (usually on a 0 to 10 scale) and it was assumed that less patient reported pain would reflect improved patient function even though the 1986 Portenoy and Foley paper indicated that functional improvement rarely occurred. Subsequent studies revealed that pain scores are unrelated to function and that higher opioid doses are associated not with better but with poorer function.[3] Tragically, long-term and high dose opioids are often associated with increased levels of pain due to altered brain and endocrine physiology and opioid induced hyperalgesia.[4] Using opioids as the main pillar of pain care has resulted in the current problems of poorly treated pain, iatrogenic addiction, and overdose deaths.

Comprehensive treatment is needed and each iteration of recommendations advocates the inclusion of non-pharmacologic strategies as part of comprehensive pain care. Most of the stakeholders are realizing that low risk, low cost, evidence based nonpharmacologic strategies should be used first before the pharmacology, procedures, and surgeries.

The Search for a Better Way Forward

The first of the reassessment analyses of the twinned crises of inadequate pain treatment and harm from escalating doses of opioids came from military medicine in 2010 and the Surgeon General's Pain Task Force Report.[5] It was followed by the National Academy of Medicine report in 2011, which led to a new National Pain Strategy.[6,7] Reassessments by the FDA, CDC, and the American College of Physicians have led to new regulations and recommendations. The Joint Commission has developed new standards that took effect on January 1, 2018.[8-11] These standards are scorable and require the availability of nonpharmacologic therapies.

Pain societies, Workers Compensation boards, insurers, and other stakeholders are also re-evaluating their own strategies and fortunately most of these groups have come to very similar conclusions: it takes a village to treat pain. Comprehensive treatment is needed and each iteration of recommendations advocates the inclusion of nonpharmacologic strategies as part of comprehensive pain care.[12] Most of the stakeholders are realizing that low risk, low cost, evidence based nonpharmacologic strategies should be used first before the pharmacology, procedures, and surgeries.[5-11]

This recognition has led practitioners to expand the scope of their assessment and treatment of pain patients. Assessment tools for mood, anxiety, sleep, and outcome measures of function are becoming the standard in pain care. This has been a very positive step forward. The mainstay of treatment is shifting towards the use of nonopioid medications, sometimes many drugs concurrently. Polypharmacy is having some positive and some negative effects. These drugs can help alleviate depression and anxiety, and improve sleep while reducing and sometimes eliminating the use of opioids. However, drug side effects and the interactions between multiple drugs and their metabolites limit the benefits of this strategy. Far too often, the importance of incorporating evidence based nonpharmacologic approaches to pain are overlooked and team based interdisciplinary care is not being made available.

Nonpharmacologic Care by Others… and of Oneself

The scope of nonpharmacologic care is broad and includes self-care practices as well as practitioner dependent practices such as acupuncture, massage, chiropractic, psychology, mind-body practices, physical therapy, and other movement

TERMINOLOGY: Words Matter

The terminology used for nonpharmacologic practices has gone through an evolution of nomenclature and can be confusing. Some of the terms imply a stratification of usefulness that is not based on evidence. The term...

Complementary suggests that the practices are added on to standard care

Alternative implies that the practices are instead of standard care

Integrative is used to imply that there can be a coordination of different types of care without an inherent bias to one or other type of treatment

Given the growing body of literature on nonconventional care practices, as well as the need to use a uniform standard for assessing the usefulness of treatments, the term ***evidence based nonpharmacologic pain care*** is most reflective of the goals.

The scope of nonpharmacologic care is broad and includes self-care practices as well as practitioner dependent practices such as acupuncture, massage, chiropractic, psychology, mind-body practices, physical therapy, and other[s]...

based practices. Increasing numbers of patients have already been using these types of care strategies independently and often without notifying their conventional medical practitioners.[13,14] A few conventionally accepted, and insured nonpharmacologic treatments, such as physical therapy, cognitive behavioral therapy, and sleep hygiene, are included in the standard treatment protocols available at most university pain centers and other nonacademic clinics as well.

Improving Patient Engagement

Scientific studies have shown that healthy lifestyle factors such as proper nutrition; adequate sleep; frequent movement and exercise; attention to mood, depression, and anxiety; and the avoidance of environmental toxics such as smoking and harmful chemicals, promote better health outcomes as well as improved pain related conditions.[15-17] These self-care practices are often called *lifestyle medicine* and they can profoundly influence our health. Genetics only account for a small proportion of our health outcomes—20% to 30% by most estimates. The other 70% to 80% of health outcomes are caused by changes in gene expression, or epigenetics. Epigenetics is the turning on and off of genes—affecting gene expression not the genetic code—and is influenced by the environment including lifestyle: what we eat, drink, think, feel, and do.[18,19]

When patients believe that their health and their pain are controlled by healthcare practitioners, drug availability, or other external factors over which they as patients have no control, they are displaying an external locus of control. Healthy lifestyle choices affecting gene expression require patient engagement in the process of self-care. This fosters the development of an internal locus of control and is associated with healthier outcomes. Patient engagement is increasingly seen as a key to successful pain care outcomes.

Many of the practitioner directed nonpharmacologic pain care strategies also improve patient engagement because there is often more direct patient-practitioner contact time that enables more discussion, coaching, and reinforcement around healthy lifestyle choices.

Key Evidence Based Strategies

Nutrition

A prime example of encouraging a patient's internal locus of control is reminding them that "You change your body chemistry every time you eat."[20] Nutritional status impacts overall health and bodywide inflammation. Inflammation is linked to increased pain through swelling, pain generating cytokines and communication molecules, and the sensitization of tissues. The standard American diet is high in animal protein, sugar and processed grain based foods, and low in unprocessed plant derived nutrients. Factory produced foods are usually stripped of many of their native nutrients and instead contain numerous chemical preservatives, artificial flavorings, colorings, as well as pesticide and antibiotic residues. With the growing recognition of the risks of taking pharmaceutical NSAIDs,[21] there can be an

expanded role for the prevention of inflammation through diet.[22] An anti-inflammatory diet consists of:

- ***Unrefined plant based foods—vegetables, beans, nuts, seeds, legumes, fruits, and whole grains***
- ***Low animal protein consumption***
- ***Healthy oils***
- ***Herbs and spices***
- ***Low sugar intake***
- ***Tea, coffee, and moderate wine and dark chocolate***

There are many studies on the impact of an anti-inflammatory diet on obesity, metabolic syndrome, diabetes, arthritis, vascular disease, depression, and cancer, all of which can cause pain or have an influence on existing pain states.[23,24]

Micronutrient deficiencies are common in North America despite calorie excess and widespread obesity. In pain populations there is a high likelihood of deficiencies of fiber, vitamin D, magnesium, and omega 3 fatty acids. Each of these nutritional components has evidence for positively impacting overall health and reducing inflammation. There is basic science and clinical data suggesting that supplementation with these nutrients can be beneficial for pain patients.[25-28]

Other Evidence Based Modalities

In a review of literature using systematic reviews, the Pain Task Force of the Academic Consortium for Integrative Medicine and Health has cited evidence of benefit for "acupuncture therapy, chiropractic and osteopathic care, massage therapy, physical therapy, mind/body therapies such as mindfulness based stress reduction and cognitive behavioral therapies and movement therapies in addition to exercise and physical therapy such as yoga and tai chi."[28]

These therapies, used as standalone interventions or in combination with medications, procedures, or surgery, have been shown to[29]

- ***Reduce the need*** *for opioids to manage postsurgical and acute pain, reducing the risk of progression to chronic opioid use*
- ***Reduce pain*** *while also reducing anxiety and depression, nausea and vomiting, facilitating restful sleep, and increasing a sense of well-being and desire to participate in one's own recovery*
- ***Not only reduce*** *chronic pain but to improve function with benefits lasting well beyond intervention periods*
- ***Provide economic benefits*** *based on evidence of cost effectiveness, cost savings through avoided high tech conventional care, lower future healthcare utilization, and through a reduction of productive loss for employers as a result of engaging healthier lifestyle choices, benefiting the whole person in addition to a targeted disease or condition*

Conclusion

As outlined by the Surgeon General's Pain Task Force Report and the National Pain Strategy, the current health system requires transformational change in order to provide coordinated, collaborative, integrative care using all available evidence based therapeutic strategies for the benefit of our patients' well-being. Military medicine is actively moving to such a model as are many civilian centers. Insurers and health systems are striving to change decades old systems of care provision, to develop coordinated service teams and to restructure reimbursement to meet the challenges of system transformation. The goal is a worthy one with the potential for improved pain care and patient outcomes, significant cost savings, and the overall health benefits of positive lifestyle choices. ◘

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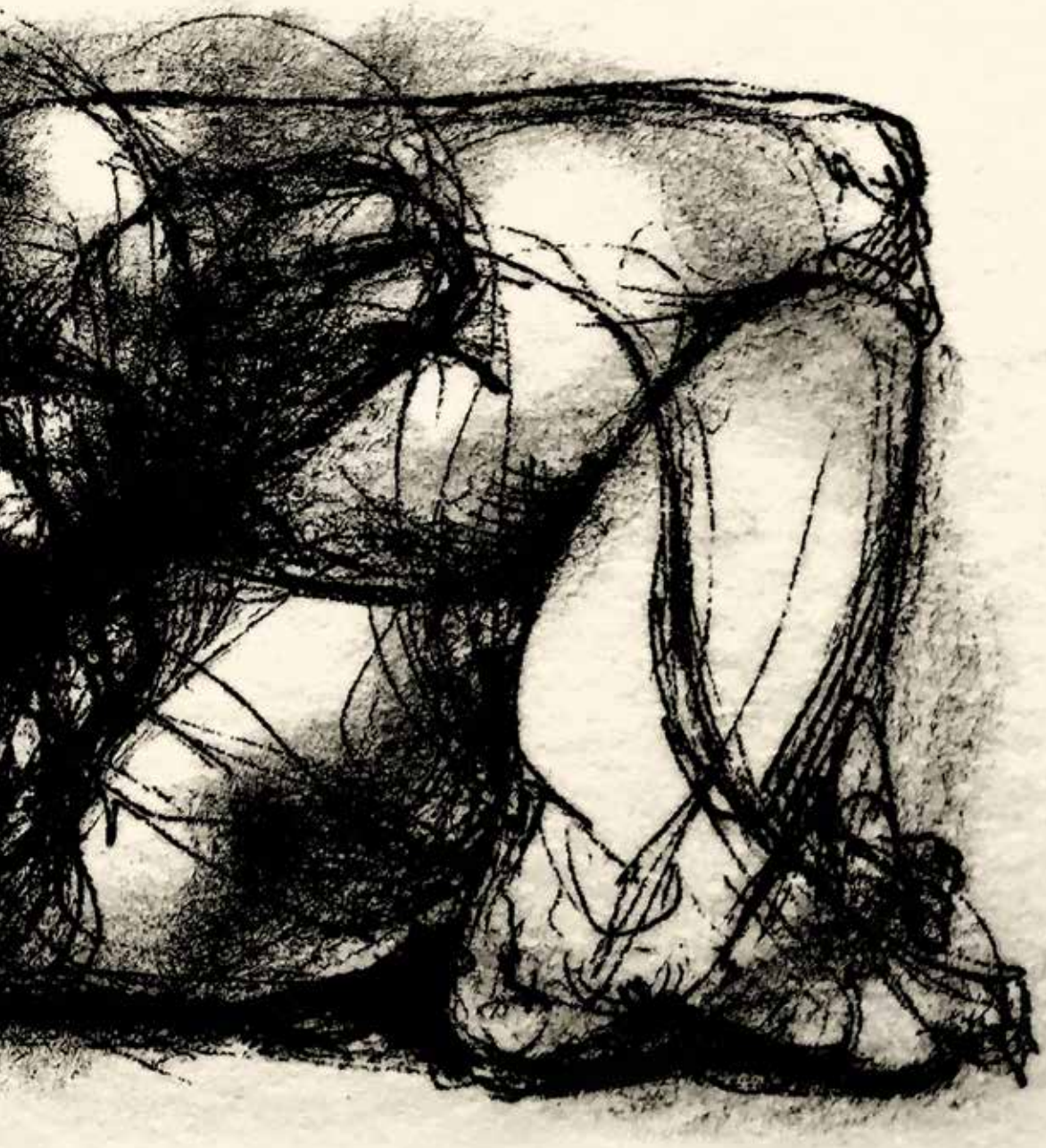
By Philip **Getson** DO



COMPLEX regional pain SYNDROME

a primer from the perspective of the primary care physician

abstract:

I am a fan of Sherlock Holmes. I have been since my teenage years. As I progressed through my medical education, I realized that using logic and deductive reasoning would help me in my medical practice. So, when in 1987, before the Internet, I was presented with a medical mystery and, thinking "The game's afoot," I headed to a local medical library where, after 2 days of research, I was able to make a diagnosis of reflex sympathetic dystrophy. This began a journey which, over 30 years, has led me to evaluate more than 1400 patients with this disorder, now called complex regional pain syndrome. It still remains a medical mystery despite the fact that up to 10 million Americans are afflicted with this "unknown and poorly understood" disorder.

Holmes once said,

"Life is infinitely stranger than anything that the mind of man can invent."

So begins my discussion, with assistance from Holmes, Watson, and Sir Arthur Conan Doyle, on complex regional pain syndrome.

The word complex **is defined in Webster's Dictionary as "a whole made up of complicated or interrelated parts."** Perhaps this is what the International Association for the Study of Pain had in mind in 1993 when they renamed reflex sympathetic dystrophy *complex regional pain syndrome*. This disorder, historically dating back to the 17th Century, has been known as causalgia, Sudeck's atrophy, posttraumatic pain syndrome, shoulder hand syndrome, algodystrophy, sympathalgia, reflex neurovascular dystrophy, and reflex sympathetic dystrophy before being renamed complex regional pain syndrome and then later subdivided into CRPS types I and II. Essentially, type I represents the "old" causalgia and type II the "old" reflex sympathetic dystrophy, primarily differentiated by the presence or absence of an initiating event to a major nerve.[1]

The Diagnosis of CRPS

In 2007, because of confusion in identifying and definitively classifying an individual with CRPS, the Budapest Criteria were finalized. The following criteria must be met for a diagnosis of CRPS:

1 **Continuing pain, which is disproportionate to any inciting event.**

2 **Must report at least one symptom in 3 of the 4 following categories:**

a. Sensory reports of hyperalgesia and/or allodynia **b.** Vasomotor reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry **c.** Sudomotor/edema reports of edema and/or sweating changes and/or sweating asymmetry **d.** Motor/trophic reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3 **Must display at least one sign** (a sign is counted **only** if observed at the time of the diagnosis) **at the time of evaluation in 2 or more of the following categories:**

a. Sensory evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement) **b.** Vasomotor evidence of temperature asymmetry and/or skin color changes and/or asymmetry **c.** Sudomotor/edema evidence of edema and/or sweating changes and/or sweating asymmetry **d.** Motor/trophic evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4 **There is no other diagnosis that better explains the symptoms.**[2]

"Most people, if you describe a chain of events to them, will tell you what the result would be. There are few people, however, that if you told them the result would be able to evolve from their own inner consciousness what the steps were that led up to that result. This power is what I mean when I talk of reasoning backwards or analytically."

Signs and symptoms of CRPS can be summarized as follows:

- **Pain that is described as deep, aching, cold, burning, and/or increased skin sensitivity**
- **An initiating injury or traumatic event such as a sprain, fracture, minor surgery, etc, that should not cause as severe a pain as being experienced or where the pain does not subside with healing**
- **Moderate to severe pain associated with allodynia (pain responses from stimuli that do not normally evoke pain)**
- **Continuing pain with hyperalgesia (heightened sensitivity to painful stimuli)**
- **Abnormal swelling in the affected area**
- **Abnormal hair or nail growth**
- **Abnormal skin color changes**
- **Abnormal sweating of the affected area**
- **Limited range of motion, weakness, or other motor disorders such as paralysis or dystonia**
- **Symptoms and signs can wax and wane**
- **Can affect anyone, but is more common in women, with a recent increase in the number of children and adolescents who are diagnosed**

Many believe that CRPS is a diagnosis of exclusion. As such, and understanding the criteria that "no other diagnosis best explains the cause of the symptoms," below is a list of some disorders that should be included in the differential diagnosis:

- **Radicular pain from an anatomic lesion such as disc herniations**
- **Diabetic and small-fiber peripheral neuropathies**
- **Entrapment type neuropathies**
- **Thoracic outlet syndrome**
- **Deep vein thrombosis**
- **Cellulitis**
- **Vascular insufficiency**
- **Brachial plexopathies**
- **Heavy metal exposure**
- **Alcohol related disorders**
- **Nutritional abnormalities**
- **Autoimmune and rheumatologic disorders**
- **Fibromyalgia**

Diagnosis

Diagnostic testing in CRPS is generally performed to exclude concurrent disorders. Tests include X-rays, CAT scans, MRIs, discograms, myelograms, arthrograms, and laboratory testing. Electrodiagnostic testing (EMGs) is frowned upon by many because of the invasive nature of the procedure. Additionally, one must recognize that CRPS is a disease of the sensory nerve fibers primarily, and electrodiagnostic testing is a test of motor fibers. Therefore, yield of a positive outcome is minimal. Additionally, there is some confusion in the interpretations of EMGs, especially with entrapment type neuropathies, as to whether the entrapment neuralgia or the CRPS represent the etiology of the symptoms thereby producing a false positive finding electrodiagnostically. Somatosensory evoked potential testing and quantitative sensory testing have been utilized with some positive result. Triple phase bone scans, once thought to be the "gold standard" for the evaluation of complex regional pain syndrome, have fallen into disfavor because of the huge numbers of false negatives.

It is my opinion, however, that infrared imaging—thermography—is the best diagnostic test for the diagnosis of CRPS. A great benefit of thermography is its ability to noninvasively image the function of the nervous system, especially with chronic pain conditions. The nervous system along with blood vessels creates most of the heat patterns we see using thermal imaging. A hallmark of CRPS is an excessive vasoconstriction of blood vessels that can cause cold hands and feet. Thermography provides images of the sympathetic nervous system and, given that CRPS is considered to be a disease of sympathetic origin, it is a perfect tool for corroboration of a clinical diagnosis.[3,4]

Exacerbating factors of complex regional pain syndrome include stress, cold, changing barometric pressure, infections (especially dental), humidity, poor diet, vaccinations, toxins (aluminum and fluoride), certain prescription medications, candida, and Lyme disease.

Constitutional symptoms associated with CRPS

Many clinicians believe that CRPS is solely limited to the upper and lower extremities. This is simply not the case. Many patients have atypical chest pain.[5] Most of these patients have neuropathic intercostobrachial nerve traction injuries. Additional cardiac symptomatology include tachycardia and bradycardia unexplained by underlying primary cardiac disease. 15% of patients complain of shortness of breath.[5] 90% of patients with longstanding disease manifest some component of neurogenic edema.[5] Approximately one-third of moderate to severe CRPS patients suffer hypothyroidism.[6] Dermatologic manifestations of CRPS, which occur in up to 81% of patients after 15 years, include erythema, mottling, livedo reticularis, Dercum's disease, and cyanosis.[6] Neurodermatitis is a common finding. Urologic manifestations occur in 25% of patients.[6] In many instances, these manifestations parallel interstitial cystitis but are more often the result of neurogenic bladder. Gastroenterologic symptomatology is extremely common.[6] Most often one sees constipation, nausea, vomiting, intermittent diarrhea, indigestion, gastroparesis and irritable bowel syndrome, and dysphagia and GERD both being noted at a rate of 73%. Other symptoms include diplopia, photophobia, otophobia, and greater occipital neuralgia. Frequently noted is deterioration of dental hygiene because the nerve roots of the mouth leading to the teeth are affected and medication contributes to the rapid deterioration and disrepair of teeth.

"It is a capital mistake to theorize before you have all the evidence. It biases the judgment."

Treatment

The treatment of CRPS must be multifaceted and requires individualized and multidisciplinary approach. First and foremost is mobility. Movement of the affected limb (as the initial presentation almost always presents in a limb) can prevent secondary complications such as frozen shoulders. Physical and/or occupational therapy should be initiated when the benefits do not outweigh the risks of worsening the condition.

Medication

The use of analgesic medication has come under great scrutiny especially in light of the "opioid epidemic." Additionally, research has shown that opioid induced hyperalgesia is a major issue that must be addressed and understood when dealing with patients with chronic pain. The risks and benefits of pain medication must be considered.

Other medications include antispasmodics, muscle relaxants, anti-inflammatory agents, agents for the treatment of neuropathic pain, and medications for problems such as headaches. Literature reports anecdotal benefits from medications

including calcium channel blockers, tricyclic antidepressants, amantadine, dextromethorphan, and SNRIs.

Sympathetic nerve blocks are still being utilized by some, both as an initial form of treatment and adjunctively with other medication. Spinal cord stimulators are utilized by many interventional pain management specialists. (I have found in my experience that these work best in individuals with one-limb disorder and without constitutional symptoms. Once the disease spreads to other areas of the body, whether it be another limb or internally, the benefit of such stimulators diminishes precipitously.)

Ketamine remains, in my opinion, the best treatment for refractory CRPS. The onset of the use of subanesthetic ketamine for the treatment of CRPS[7] began around 2002 and the escalation in the use of ketamine has been rapid. There are dozens of individuals across the country utilizing ketamine in various dosages and formats. A 2018 *Pain Medicine* article summarizes dosages and treatment schedules of ketamine.[8]

A study published some years ago detailed the use of intraoperative ketamine in the attempt to prevent extending CRPS as a result of surgical intervention. Many surgeons have been hesitant to operate on patients for fear of extending the CRPS. The article clearly stated that the use of intraoperative ketamine was beneficial in preventing the spread.[9] While the database was small in number, the use of ketamine intraoperatively has proven to be effective following the study's publication.

Most recently, there has been a great deal of emphasis on the use of bisphosphonates for the treatment of CRPS. Currently a worldwide study using neridronate is ongoing to determine its effectiveness. Data has not yet been published and formalized.

Far too little emphasis has been placed on "alternative" therapies. The importance of a healthy diet cannot be stressed enough. We have learned that eliminating gluten causes an almost immediate reduction in pain. Similarly, reduction or elimination of sugar, dairy, and caffeine has helped as well. We encourage patients in smoking cessation and diminished alcohol intake. Other alternative therapies such as acupuncture and Reiki have been beneficial in providing an improvement in the patient's overall well-being.

Conclusion

CRPS is certainly that… "complex." It involves a great deal of time on the part of the treating physician to assess the patient and work in collaboration with other physicians, healthcare professionals, and family members to deal with this extremely complicated problem. More awareness is the key to early intervention and better results. By educating physicians, we can perhaps arrive at an earlier accurate diagnosis and facilitate referral for intervention at a time when it has proven to be most beneficial. Or as Holmes would say…

"When you eliminate the impossible, whatever remains, however improbable, must be the answer."

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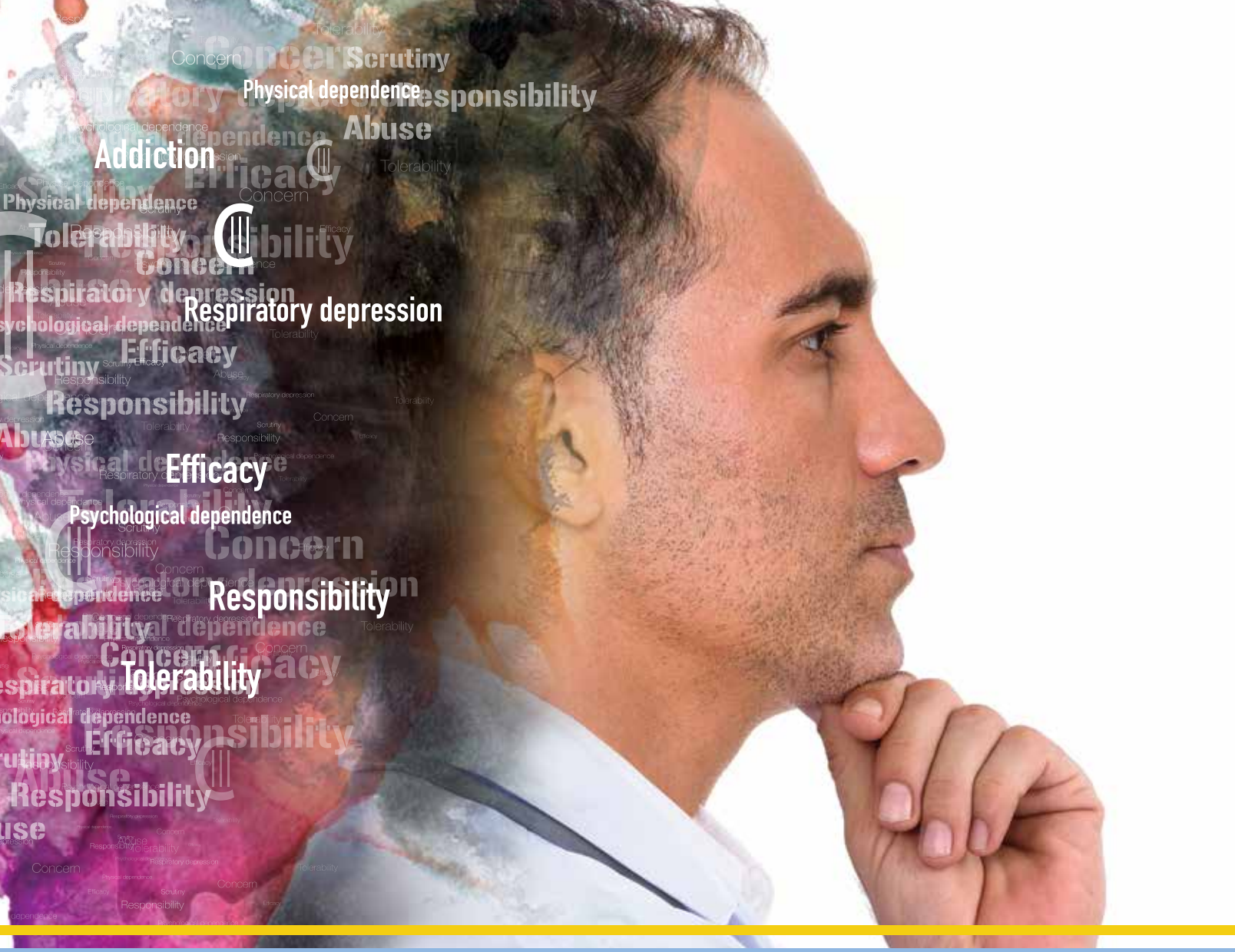

INDICATION

*BELBUCA® (buprenorphine) buccal film 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 long-acting opioid formulations, reserve BELBUCA® 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.
- BELBUCA® is not indicated as an as-needed (prn) analgesic.

IMPORTANT SAFETY INFORMATION about BELBUCA®

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; AND NEONATAL OPIOID WITHDRAWAL SYNDROME; AND RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

BELBUCA® 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 BELBUCA® and monitor patients regularly for the development of these behaviors and conditions.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of BELBUCA®. Monitor for respiratory depression, especially during initiation of BELBUCA® or following a dose increase. Misuse or abuse of BELBUCA® by chewing, swallowing, snorting, or injecting buprenorphine extracted from the buccal film will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death.

Accidental Exposure

Accidental exposure to even one dose of BELBUCA®, especially by children, can result in a fatal overdose of buprenorphine.

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- **Established tolerability with side effects comparable to placebo[1]**
- **Flexible dosing with a broad range of 7 dosage strengths, 75 mcg to 900 mcg[1]**

Neonatal Opioid Withdrawal Syndrome

Prolonged use of BELBUCA® 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.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate, limit dosages and durations to the minimum required, and follow patients for signs and symptoms of respiratory depression and sedation.

Please see full Important Safety Information at BELBUCA.com, as well as the brief summary of full Prescribing Information for BELBUCA on the following pages.

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or the FDA at 1-800-FDA-1088 or www.fda.gov/safety/medwatch.

Intended for healthcare professionals of the United States of America only.

Reference: 1. BELBUCA® (Prescribing Information). Raleigh, NC: BioDelivery Sciences International, Inc; December 2016.

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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details please see the Full Prescribing Information and Medication Guide.

BELBUCA® (buprenorphine) buccal film, CIII
Initial U.S. Approval: 1981

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; and NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **BELBUCA exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing, and monitor regularly for these behaviors and conditions. (5.1, 10)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients on proper administration of BELBUCA to reduce the risk. (5.2)**
- **Accidental exposure to BELBUCA, especially in children, can result in fatal overdose of buprenorphine. (5.2)**
- **Prolonged use of BELBUCA during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required 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)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**

INDICATIONS AND USAGE

BELBUCA 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 long-acting opioid formulations *[see Warnings and Precautions]*, reserve BELBUCA 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.
- BELBUCA is not indicated as an as-needed (prn) analgesic.

CONTRAINDICATIONS

BELBUCA is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions]*
- Hypersensitivity (e.g., anaphylaxis) to buprenorphine *[see Warnings and Precautions, and Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse BELBUCA contains buprenorphine, a Schedule III controlled substance. As an opioid, BELBUCA exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence]*. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed BELBUCA. Addiction can occur at recommended dosages and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing BELBUCA and monitor all patients receiving BELBUCA for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as BELBUCA, but use in such patients necessitates intensive counseling about the risks and proper use of BELBUCA, along with intensive monitoring for signs of addiction, abuse, or misuse. Abuse or misuse of BELBUCA by swallowing may cause choking, overdose, and death *[see Overdosage]*. Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing BELBUCA. Strategies to reduce the risk include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information]*. 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 opioids, even when used as recommended. Respiratory depression, 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]*. 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 BELBUCA, the risk is greatest during initiation of therapy or following za dosage increase. Monitor patients closely for respiratory depression when initiating therapy with BELBUCA and following a dosage increases. To reduce the risk of respiratory depression, proper dosing and titration of BELBUCA are essential *[see Dosage and Administration]*. Overestimating the dose of BELBUCA when converting patients from another opioid product may result in fatal overdose with the first dose. Accidental exposure to BELBUCA, especially in children, can result in respiratory depression and death due to an overdose of buprenorphine.

Neonatal Opioid Withdrawal Syndrome Prolonged use of BELBUCA during pregnancy can result in withdrawal 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations, Patient Counseling Information]*.

Risks due to Interactions with Benzodiazepines or Other Central Nervous System Depressants Profound sedation, respiratory depression, coma, and death may result from the concomitant use of BELBUCA with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions]*. If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when BELBUCA is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions, Patient Counseling Information]*.

Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients The use of BELBUCA in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated. Patients with Chronic Pulmonary Disease: BELBUCA-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of BELBUCA *[see Warnings and Precautions]*. 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 compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating BELBUCA and when BELBUCA is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions]*. Alternatively, consider the use of non-opioid analgesics in these patients.

Adrenal Insufficiency Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

QTc Prolongation BELBUCA has been observed to prolong the QTc interval in some subjects participating in clinical trials. Consider these observations in clinical decisions when prescribing BELBUCA to patients with hypokalemia, hypomagnesemia, or clinically unstable

cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of BELBUCA in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval *[see Dosage and Administration, Adverse Reactions, and Clinical Pharmacology]*.

Severe Hypotension BELBUCA may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. 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) *[see Drug Interactions]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of BELBUCA. In patients with circulatory shock, BELBUCA may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of BELBUCA in patients with circulatory shock.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness In 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), BELBUCA may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with BELBUCA. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of BELBUCA in patients with impaired consciousness or coma.

Hepatotoxicity Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual formulations of buprenorphine for the treatment of opioid dependence, both in clinical trials and in post-marketing adverse events reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. For patients at increased risk of hepatotoxicity (e.g., patients with a history of excessive alcohol intake, intravenous drug abuse or liver disease), obtain baseline liver enzyme levels and monitor periodically during treatment with BELBUCA.

Risk of Overdose in Patients With Moderate to Severe Hepatic Impairment In a pharmacokinetic study in subjects dosed with buprenorphine sublingual tablets, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. For patients with severe hepatic impairment, a dose adjustment is recommended, and patients with moderate or severe hepatic impairment should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine *[see Dosage and Administration, Use in Specific Populations]*.

Anaphylactic/Allergic Reactions Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. BELBUCA is contraindicated in patients with a history of hypersensitivity to buprenorphine.

Risk of Use in Patients with Gastrointestinal Conditions BELBUCA is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. BELBUCA may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders The buprenorphine in BELBUCA may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during BELBUCA therapy.

Risks of Use in Cancer Patients with Oral Mucositis Cancer patients with oral mucositis may absorb buprenorphine more rapidly than intended and are likely to experience higher plasma levels of the opioid. For patients with known or suspected mucositis, a dose reduction is recommended. Monitor these patients carefully for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine *[see Dosage and Administration, Clinical Pharmacology]*.

Risks of Driving and Operating Machinery BELBUCA may impair the mental and 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 side effects of BELBUCA and know how they will react to the medication.

ADVERSE REACTIONS

The following serious adverse reactions described elsewhere in the labeling include:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions]*
- Adrenal Insufficiency *[see Warnings and Precautions]*
- QTc Prolongation *[see Warnings and Precautions]*
- Severe Hypotension *[see Warnings and Precautions]*
- Hepatotoxicity *[see Warnings and Precautions]*
- Anaphylactic/Allergic Reactions *[see Warnings and Precautions]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*

The most common adverse reactions (≥ 5%) by patients taking BELBUCA in the controlled and open-label clinical studies: nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth, and upper respiratory tract infection.

Postmarketing Experience: The following adverse reactions have been identified during post approval use of buprenorphine. 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. Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs. Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Anaphylaxis: Anaphylaxis has been reported with ingredients contained in BELBUCA. Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology]*.

DRUG INTERACTIONS

Benzodiazepines

Clinical Impact: There have been a number of reports regarding coma and death associated with the misuse and abuse of the combination of buprenorphine and benzodiazepines. In many, but not all of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists.

Intervention: Closely monitor patients with concurrent use of BELBUCA and benzodiazepines. Warn patients that it is extremely dangerous to self-administer benzodiazepines while taking BELBUCA, and warn patients to use benzodiazepines concurrently with BELBUCA only as directed by their physician.

Benzodiazepines and Other Central Nervous System (CNS) Depressants

Clinical Impact: Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Intervention: Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions]*.

Examples: Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids, alcohol.

Inhibitors of CYP3A4

Clinical Impact: The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of BELBUCA is achieved. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease *[see Clinical Pharmacology]*, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.

Intervention: If concomitant use is necessary, consider dosage reduction of BELBUCA until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the BELBUCA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

Examples: Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)

CYP3A4 Inducers

Clinical Impact: The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine *[see Clinical Pharmacology]*, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase *[see Clinical Pharmacology]*, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.

Intervention: If concomitant use is necessary, consider increasing the BELBUCA dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider BELBUCA dosage reduction and monitor for signs of respiratory depression.

Examples: Rifampin, carbamazepine, phenytoin

Serotonergic Drugs

Clinical Impact: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

Intervention: If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue BELBUCA if serotonin syndrome is suspected.

Examples: Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Monoamine Oxidase Inhibitors (MAOIs)

Clinical Impact: MAOI interactions with opioids may manifest as serotonin syndrome opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions]*.

Intervention: The use of BELBUCA is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

Examples: phenelzine, tranylcypromine, linezolid

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Clinical Impact: May reduce the analgesic effect of BELBUCA and/or precipitate withdrawal symptoms.

Intervention: Avoid concomitant use.

Examples: butorphanol, nalbuphine, pentazocine

Muscle Relaxants

Clinical Impact: Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Intervention: Monitor patients receiving muscle relaxants and BELBUCA for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of BELBUCA and/or the muscle relaxant as necessary.

Diuretics

Clinical Impact: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs

Clinical Impact: The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Intervention: Monitor patients for signs of urinary retention or reduced gastric motility when BELBUCA is used concomitantly with anticholinergic drugs.

Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)

Clinical Impact: Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.

Intervention: None

Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Clinical Impact: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delaviridine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.

Intervention: Patients who are on chronic BELBUCA treatment should have their dose monitored if NNRTIs are added to their treatment regimen.

Examples: efavirenz, nevirapine, etravirine, delavirdine

Antiretrovirals: Protease inhibitors (PIs)

Clinical Impact: Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly.

Intervention: Monitor patients taking BELBUCA and atazanavir with and without ritonavir, and dose reduction of BELBUCA may be warranted.

Examples: atazanavir, ritonavir

USE IN SPECIFIC POPULATIONS

Pregnancy Risk Summary Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions]*. There are no adequate and well-controlled studies of BELBUCA or buprenorphine in pregnant women. Limited published data on use of buprenorphine, the active ingredient in BELBUCA, in pregnancy, have not shown an increased risk of major malformations. Reproductive and developmental studies in rats and rabbits identified adverse events at approximately 2 times the maximum recommended human dose (MRHD) of 1.8 mg/day of BELBUCA. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 54 and 2.2 times, respectively, the MRHD of 1.8 mg/day of buprenorphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths at 2.7 times and above and dystocia at approximately 27 times the MRHD of 1.8 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during organogenesis with a range of doses 5 times or greater than the MRHD of 1.8 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 5.4 and 10.8 times the MRHD of 1.8 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related [see Data]. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. 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. 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. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions]*. *Labor or Delivery* Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist such as naloxone must be available for reversal of opioid-induced respiratory depression in the neonate. BELBUCA is not recommended for use in women immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including BELBUCA, can 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 dilation, which tends to shorten labor. Data *Animal Data* The exposure margins listed below are based on body surface area comparisons (mg/m^2) to MRHD of 1.8 mg buprenorphine via BELBUCA. Following oral administration to rats no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 1351 times the MRHD of 1.8 mg). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 432 times the MRHD of 1.8 mg). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 161 times and 324 times, respectively, the MRHD of 1.8 mg). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 54 times the MRHD of 1.8 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day. Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 27 and 54 times, respectively, the MRHD of 1.8 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 4.3 and 8.7 times, respectively, the MRHD of 1.8 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 865 times the MRHD of 1.8 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 270 times the MRHD of 1.8 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 5.4 times the MRHD of 1.8 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 54 times the MRHD of 1.8 mg) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately 10.8 times the MRHD of 1.8 mg) were not statistically significant. In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 2.2 times the MRHD of 1.8 mg). Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine during gestation and lactation at 5 mg/kg/day (approximately 27 times the MRHD of 1.8 mg). Fertility, pre-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 4.3 times the MRHD of 1.8 mg), after IM doses of 0.5 mg/kg/day and up (approximately 2.7 times the MRHD of 1.8 mg), and after SC doses of 0.1 mg/kg/day and up (approximately 0.5 times the MRHD of 1.8 mg). An apparent lack of milk production during these studies occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 432 times the MRHD of 1.8 mg).

Lactation Risk Summary Based on two studies in 13 lactating women being treated for opioid dependence and their breastfed infants, buprenorphine and its metabolite norbuprenorphine are present in low levels in human milk and infant urine, and available data have

not shown adverse reactions in breastfed infants *[see Data]*. There are no data on the effects of BELBUCA on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with BELBUCA. Clinical Considerations Monitor infants exposed to BELBUCA through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of buprenorphine is stopped or when breast-feeding is stopped. Data Based on limited data from a study of six lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 0.29 mg/kg/day 5-8 days after delivery, breast milk contained a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, which are equal to 0.2% and 0.12% of the maternal weight-adjusted dose. The median concentrations of buprenorphine and norbuprenorphine in infant urine were 1.0 nmol/L and 2.3 nmol/L, respectively. Based on limited data from a study of seven lactating women being treated for opioid dependence who were taking a median oral dose of buprenorphine of 7 mg/day an average of 1.12 months after delivery, the mean milk concentrations of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L, respectively. Based on the limited data from this study, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, which are 0.38% and 0.18% of the maternal weight-adjusted dose. No adverse reactions were observed in the infants in these two studies.

Females and Males of Reproductive Potential
Infertility Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Clinical Pharmacology, Nonclinical Toxicology]*.

Pediatric Use The safety and efficacy of BELBUCA have not been established in pediatric patients.

Geriatric Use Of the total number of patients that were treated with BELBUCA in controlled and open-label chronic pain trials (2,127), 340 patients were 65 years and older. Of those, 49 patients were aged 75 years and older. The incidences of selected BELBUCA-related adverse effects were higher in older subjects. No notable differences in pharmacokinetics were observed from population pharmacokinetic analysis in subjects aged 65 compared to younger subjects. Other reported clinical experience with buprenorphine has not identified differences in responses between the elderly and younger patients. Although specific dose adjustments on the basis of advanced age are not required for pharmacokinetic reasons, use caution in the elderly population to ensure safe use. Titrate the dosage of BELBUCA slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions, and Clinical Pharmacology]*. Buprenorphine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Impairment BELBUCA has not been evaluated in patients with severe hepatic impairment. The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a pharmacokinetic study. Buprenorphine is extensively metabolized in the liver and buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. Given that increased buprenorphine plasma levels are associated with a greater risk of toxicity and overdose, a dosage reduction in patients with severe hepatic impairment (i.e., Child-Pugh C) is recommended *[see Dosage and Administration]*. Monitor patients with severe hepatic impairment for signs and symptoms of overdose. A dosage reduction in patients with moderate hepatic impairment (Child-Pugh B) is not needed, however, monitor these patients for signs and symptoms of toxicity or overdose. A dosage reduction in patients with mild hepatic impairment (Child-Pugh A) is not needed *[see Dosage and Administration, Warnings and Precautions and Clinical Pharmacology]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance BELBUCA contains buprenorphine hydrochloride, a Schedule III controlled substance.

Abuse BELBUCA contains buprenorphine, a substance with a potential for abuse similar to other Schedule III opioids. BELBUCA can be abused and is subject to misuse, abuse, addiction, and criminal diversion *[see Warnings and Precautions]*. All patients treated with opioids, including BELBUCA, require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carry the risk of addiction, even under appropriate medical use. Prescription drug abuse is the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes 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 in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating healthcare providers(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. 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. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all persons with substance use disorders. In addition, abuse of opioids can occur in the absence of true addiction. BELBUCA, 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 state and federal 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. Risks Specific to Abuse of BELBUCA BELBUCA is intended for buccal use only. Abuse of BELBUCA poses a risk of overdose and death. This risk is increased with concurrent abuse of BELBUCA with alcohol and other substances, including other opioids and benzodiazepines *[see Warnings and Precautions, Drug Interactions]*. Intentional compromise of the buccal film might result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions]*. Abuse may occur by applying the buccal film in the absence of legitimate purpose, or by swallowing, snorting, or injecting buprenorphine extracted from the buccal film. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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 (e.g., pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. BELBUCA should not be abruptly discontinued *[see Dosage and Administration]*. If BELBUCA is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, or diarrhea or 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 Use in Specific Populations]*.

OVERDOSAGE

Clinical Presentation Acute overdosage with BELBUCA is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology]*. 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. Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used. Because the duration of reversal would be expected to be less than the duration of action of buprenorphine from BELBUCA, carefully monitor the patient until spontaneous respiration is reliably re-established. Even in the face of improvement, continued medical monitoring is required for at least 24 hours because of the possibility of extended effects of buprenorphine. In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal symptoms experienced 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 begun with care and by titration with smaller than usual doses of the antagonist.

Healthcare professionals can telephone BioDelivery Sciences International, Inc. (1-800-469-0261) for information on this product.

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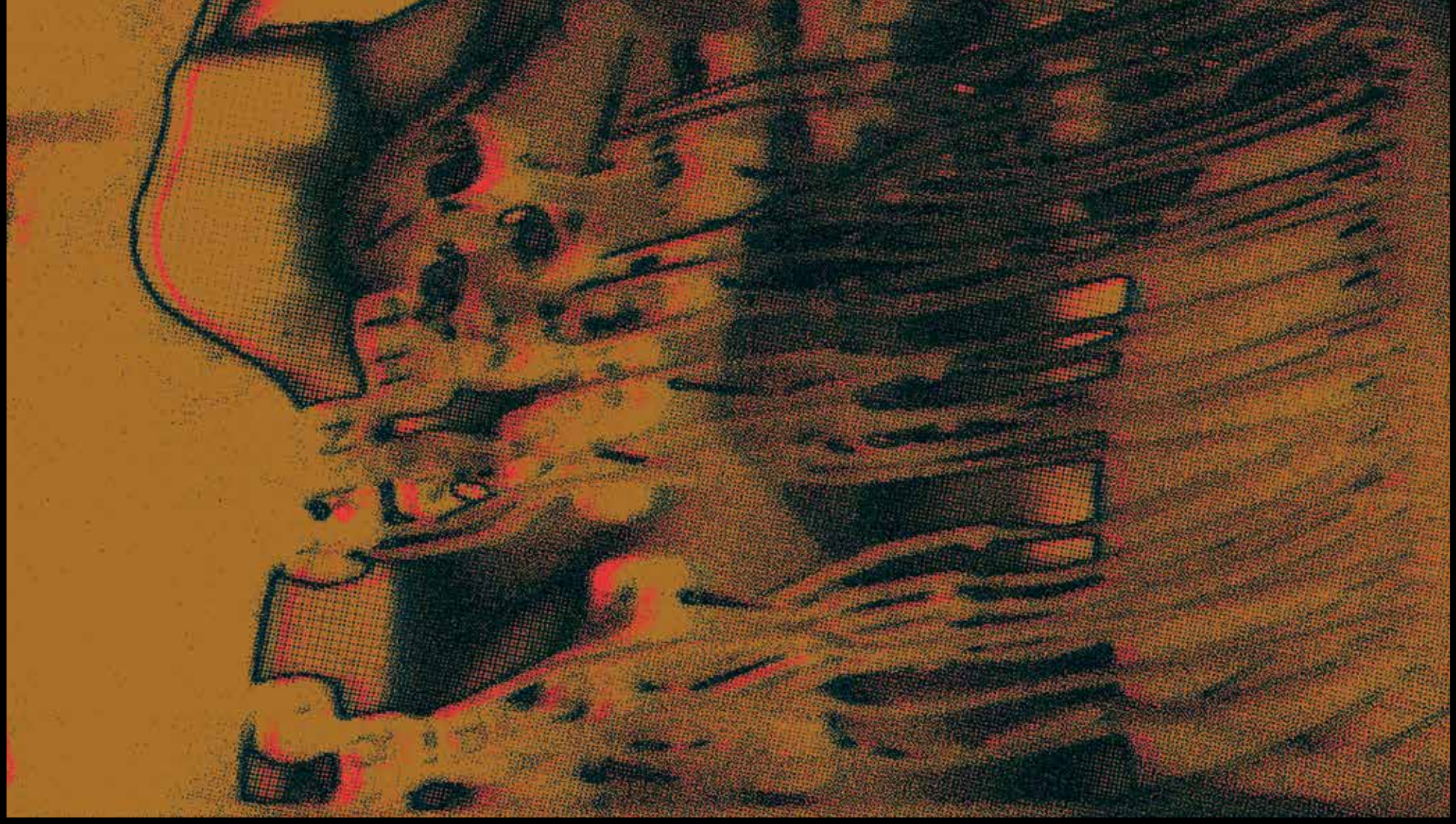


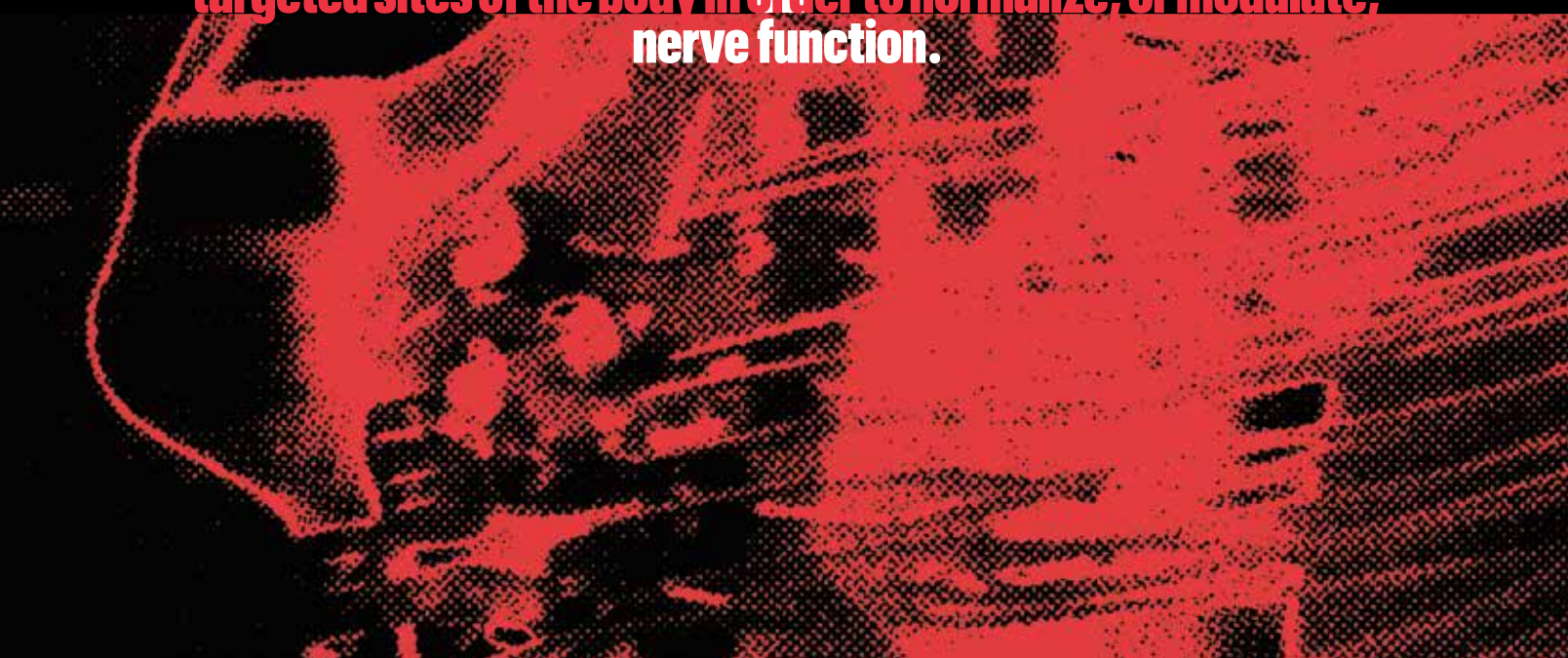
From Torpedo fiSh to HF10

the evolution of neuromodulation

By Sean **Li** MD

abstract:

The International Association on the Study of Pain describes pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1] Pain that does not resolve 3 to 6 months after the initial onset is considered chronic. In the 1600s, the human nervous system was theorized by René Descartes as a series of delicate threads in which a bell is activated by an external stimulus.[2] The gate theory of pain describes a mechanism in which activation of larger Aβ sensory fibers may close off the gate that prevents pain signals transmitted on smaller Aδ and C fibers. This theory laid the foundation for modern neuromodulation, which alters nerve activity through the delivery of electrical stimulation or chemical agents to targeted sites of the body in order to normalize, or modulate, nerve function.



F10

Ancient Neuromodulation

The use of electricity in medicine dates to 250 BC during the Parthian period in the Middle East. Used for treating pain, a Baghdad Battery was made of a copper lined clay jar filled with vinegar with an iron rod placed through the asphalt stopper, and carried a charge. In 46 AD, Scribonius Largus, a court physician to the Roman Emperor Claudius, was known to treat chronic pain conditions such as headache with electric torpedo fish, which overpowered its prey by shocking it.

Pioneers of Contemporary Neuromodulation

In March of 1967, Dr. C. Norman Shealy forever changed the landscape of pain medicine by implanting the first dorsal column stimulator in a 70-year-old man suffering from severe pain due to inoperable bronchogenic carcinoma.[3] Following this groundbreaking event, the use of electricity in treating chronic pain blossomed into an entirely new field which we know now as neuromodulation. Early pioneers in this field include Dr. Marius Kemler who described the use of spinal cord stimulation for the treatment of reflex sympathetic dystrophy (RSD) now known as complex regional pain syndrome (CRPS).[4] The work of Dr. Richard North (much of his landmark contributions were done while at Johns Hopkins), indicates that spinal cord stimulation (SCS) therapy may provide better outcomes compared to repeat spine surgery. In that study, 9 out of 19 patients in the SCS group had significant pain relief vs 3 out of 26 patients who underwent repeat surgery.[5] The work of Dr. Krishna Kumar, a Canadian pioneer in functional neurosurgery and a writer of innovative papers assessing the cost effectiveness of spinal cord stimulation, showed significant improvement in pain relief and quality of life from SCS therapy compared to conventional medical management for the treatment of chronic back and leg pain in failed back surgery patients.[6] Due to these landmark studies, SCS therapy is used to treat chronic pain conditions such as failed back surgery syndrome and complex regional pain syndrome.

Renaissance of Neuromodulation

For much of the last 50 years, after the implantation of that first spinal cord stimulator, advancement of this science can be described as evolutionary, with improvement of battery technology and development of new materials for constructing the generators and stimulator leads. Within the last 5 years, the field of neuromodulation has undergone a significant renaissance. This period of rapid growth and paradigm shifts can be attributed to the introduction of novel stimulation frequencies, wave forms, and stimulation targets fueled by powerful level one clinical trials. Concurrently, the prescription opioid epidemic became a national health crisis forcing the medical community to adopt effective alternatives to opioids in treating chronic pain. The introduction of 10 kHz high frequency (HF10) stimulation has triggered several major advancements in neuromodulation. The concept of paresthesia dependent pain relief was challenged. A new series of landmark randomized controlled trials surfaced with level one evidence for novel HF10 frequency, burst waveforms, and the dorsal root ganglion as a new target of stimulation. These contemporary concepts in neuromodulation have rejuvenated our pursuit of clinical evidence and deciphering the mechanism of action(s).

Within the last 5 years, we have witnessed a substantial paradigm shift. The notion of "paradigm shift" was first introduced by the American physicist and philosopher Thomas Kuhn in 1962, and essentially refers to when there is a fundamental

> ...the prescription opioid epidemic became a national health crisis forcing the medical community to adopt effective alternatives to opioids in treating chronic pain.

change in the concepts and customary practices of a scientific discipline.[7] Thanks to this paradigm shift, current practices include paresthesia independent stimulation that is based on anatomical targets, as opposed to paresthesia based stimulation based on intra-operative paresthesia mapping. The target of stimulation at the dorsal column has expanded to dorsal horn interneurons, and cell bodies of the dorsal root ganglion. The current paradigm shift included not only the adoption of new clinical practices and treatment algorithms but also brought practitioners a closer step to understanding the mechanism of action of neuromodulation.

A Brief Look at Mechanism of Action

Prior to 1965, there had been 2 opposing theories describing the mechanism of pain signaling: the specificity theory and the pattern theory.[2] The specificity theory introduced pain as a unique sensory modality, such as taste, vision, or hearing, with its own receptor apparatus. The pattern theory describes pain based on the summation of nerve impulse intensities and patterns gathered by nonspecific receptors in the periphery. In 1965, the gate control theory of pain by Melzack and Wall described a potential mechanism by which non-noxious stimulus activation of the Aβ fibers in the dorsal column may compete with pain fiber signals in the Aδ and C fibers in closing a physiologic gate. This theory serves as the potential mechanism of action for the original spinal cord stimulator. It was later discovered that there are additional mechanisms which involve inhibitory neurotransmitters, sympathetic outflow, and wide dynamic range neurons.[8] The recent launch of high frequency stimulation has challenged this mechanism with the concept of paresthesia independent stimulation.[9] In animal models, the best assumed mechanism of action for 10 kHz high frequency spinal cord stimulation suggests direct conduction blockade of the dorsal horn interneurons responsible for pain signal propagation.[10] The exact mechanism of SCS is yet to be determined. Our current theories indicate that there may be more than one mechanism involved depending of the type of stimulation.

Future of Neuromodulation

The evolution of neuromodulation has just witnessed a revolution. From the recent explosion of new waveforms, frequencies, and stimulation targets we have developed a new set of

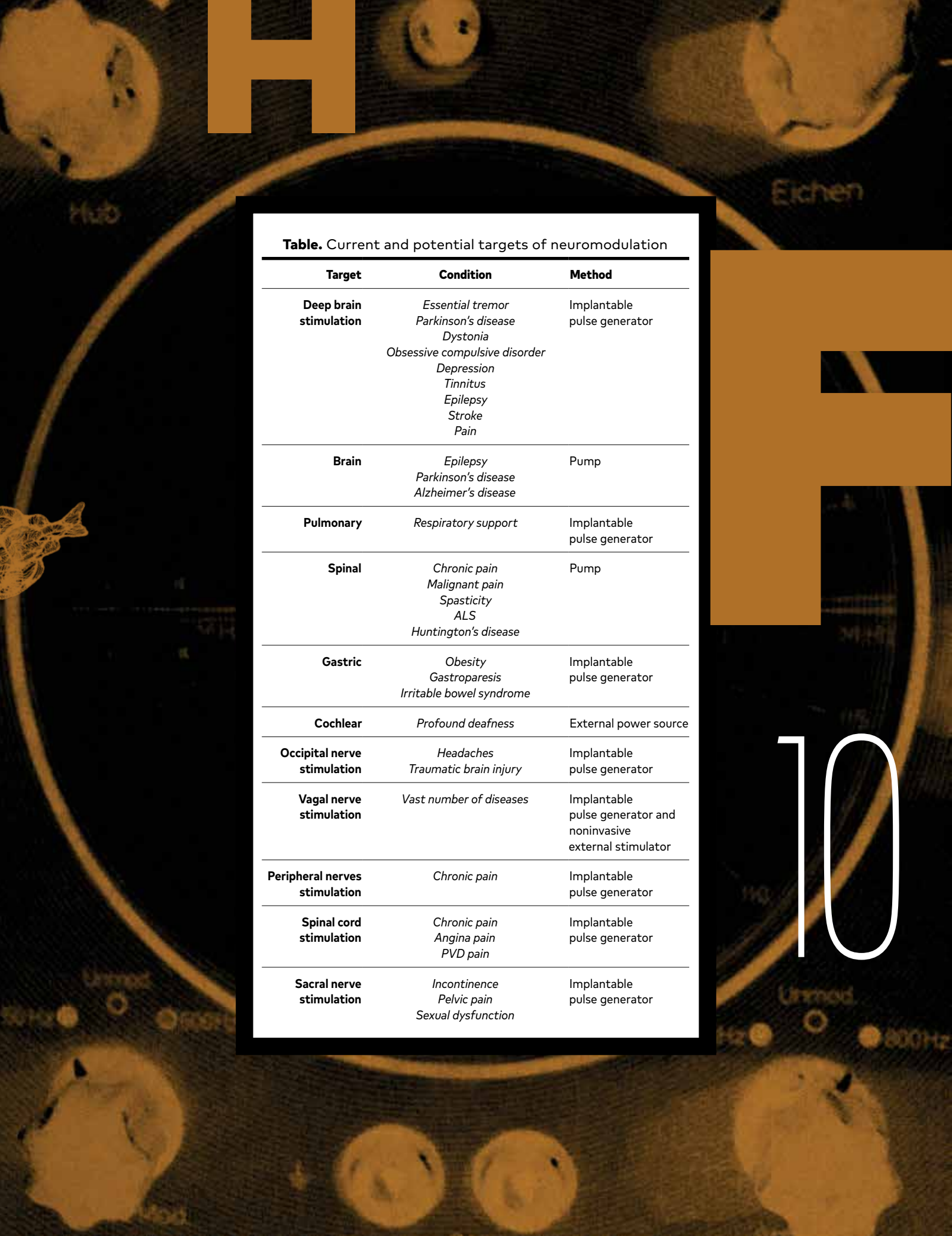


Table. Current and potential targets of neuromodulation

Target	Condition	Method
Deep brain stimulation	*Essential tremor* *Parkinson's disease* *Dystonia* *Obsessive compulsive disorder* *Depression* *Tinnitus* *Epilepsy* *Stroke* *Pain*	Implantable pulse generator
Brain	*Epilepsy* *Parkinson's disease* *Alzheimer's disease*	Pump
Pulmonary	*Respiratory support*	Implantable pulse generator
Spinal	*Chronic pain* *Malignant pain* *Spasticity* *ALS* *Huntington's disease*	Pump
Gastric	*Obesity* *Gastroparesis* *Irritable bowel syndrome*	Implantable pulse generator
Cochlear	*Profound deafness*	External power source
Occipital nerve stimulation	*Headaches* *Traumatic brain injury*	Implantable pulse generator
Vagal nerve stimulation	*Vast number of diseases*	Implantable pulse generator and noninvasive external stimulator
Peripheral nerves stimulation	*Chronic pain*	Implantable pulse generator
Spinal cord stimulation	*Chronic pain* *Angina pain* *PVD pain*	Implantable pulse generator
Sacral nerve stimulation	*Incontinence* *Pelvic pain* *Sexual dysfunction*	Implantable pulse generator

theories towards possible mechanisms of action and treatment modalities. The emerging concept of closed loop spinal cord stimulation has been introduced to provide real-time electrophysiologic feedback from the spinal cord in response to stimulation as an objective metric that may provide improved accuracy and pain relief.[11] By recording and measuring a continuous set of electrical signals called evoked compound action potentials (ECAP), we are now able to create closed loop stimulation system that allows for real-time feedback adaptation. Randomized controlled trial utilizing closed loop spinal cord stimulation is currently in progress.[12] The use of noninvasive or less-invasive neurostimulation modalities has also generated significant interest in the field of pain medicine. The introduction of noninvasive vagal nerve stimulation has raised tremendous interest in the treatment of chronic pain states such as migraine headaches and other potential inflammatory chronic pain conditions. Noninvasive transcutaneous vagal nerve stimulation recently obtained FDA approval for the treatment of both cluster and migraine headache.[13,14]

Conclusion

The future of neuromodulation in pain medicine is bright. Electricity in medicine will experience many paradigm shifts as it expands beyond treating pain. Emerging concepts and technologies will allow us to target beyond just pain conditions but specific organ systems and disease processes **(see Table)**. ◘

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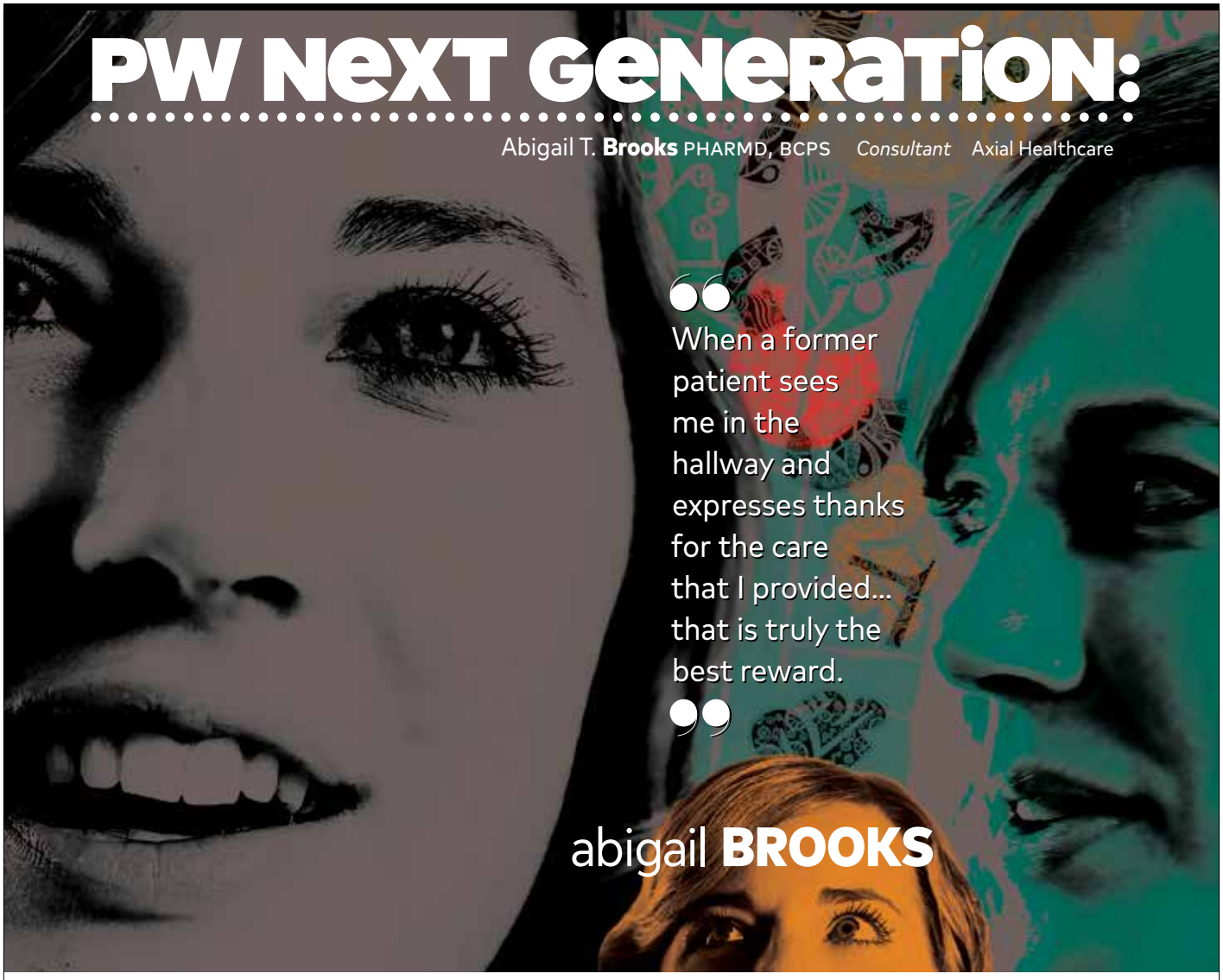
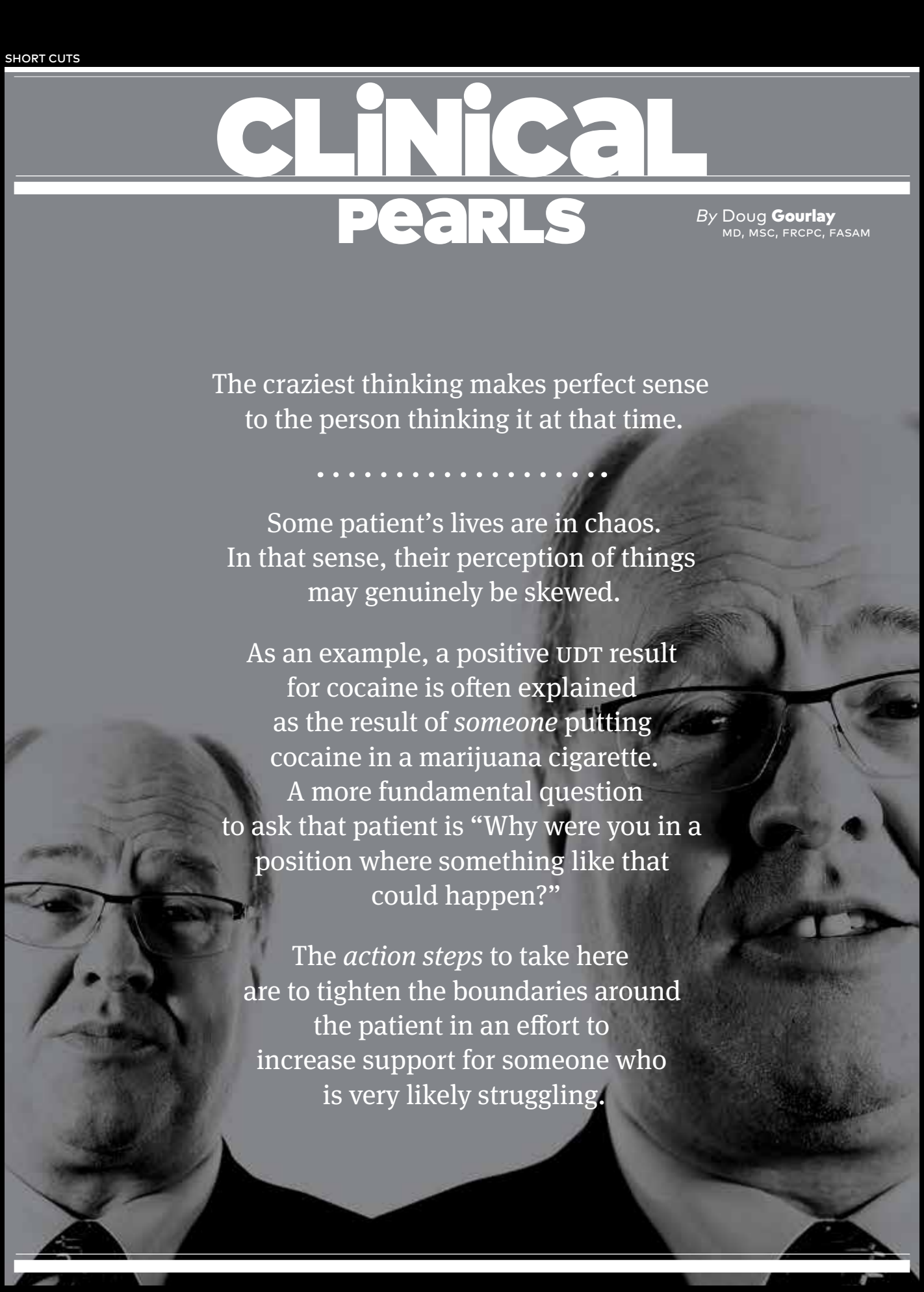


GPS Nashville, TN **Typical Day** "My typical work day is spent seeing patients to optimize their pain medication regimen as part of a multidisciplinary chronic pain clinic. I also educate patients and their family members, reinforcing positive approaches to manage chronic pain. When not seeing patients, I am completing chart review consults and teaching pharmacy residents and students." **Persona** "I've had several positive role models and mentors in the chronic pain pharmacy world who have taken me under their wing. With their guidance and knowledge, I have become the practitioner that I am today. With their encouragement I feel poised and ready to step up to the plate when it's my turn." **Social Media Habits** "Facebook allows me to connect with other professionals and keep up with pharmacy and chronic pain news. I enjoy Instagram and Snapchat for more personal connections. I also check updates from PAINWeek and a pharmacy organization that I am a member of." **Contribution** "When a former patient sees me in the hallway and expresses thanks for the care that I provided... that is truly the best reward. I have even had a patient come back to me several months later and thank me for my help in getting him off of opioids—which he was not in agreement with at the time. He said that off of opioids, he still had chronic pain but was able to think more clearly and felt better overall." **People** "Honestly, I am obsessed with Kate Middleton, the Duchess of Cambridge. To me, she emulates such poise, grace, and dignity—qualities I strive to represent. Now that I am also a mom, I enjoy seeing her interact with her children." **Words** "While I don't have much time for reading—between caring for a baby and keeping up with the pain literature—I think it is important to always have something interesting to read, for pleasure and to develop my understanding of the world around me." **Popcorn** "I am a big believer that the book is always better than the film, so I gravitate towards reading the book first. I can't say that any film has changed my life, but I do watch *It's a Wonderful Life* every Christmas with my Dad, and I always cry when George Bailey's friends come to his rescue. After all, it's not about our material wealth or possessions, but the friends and family we love and cherish and how we help them when given the opportunity." **PAINWeek** "I first came to PAINWeek after winning an essay contest...and let's just say the rest is history! I have met so many inspiring pain providers and have had the privilege to lecture for the last 3 years. Dare I say, I look forward to the conference each year because of all the learning opportunities but also because I have fun the entire time. We know that chronic pain can be a tough field to work in and I always leave PAINWeek feeling refreshed and rejuvenated, and ready to conquer another year as a pain practitioner."

CLINICAL PEARLS

By Doug **Gourlay**
MD, MSC, FRCPC, FASAM



The craziest thinking makes perfect sense to the person thinking it at that time.

• • • • • • • • • • • • • • • • • • •

Some patient's lives are in chaos. In that sense, their perception of things may genuinely be skewed.

As an example, a positive UDT result for cocaine is often explained as the result of *someone* putting cocaine in a marijuana cigarette. A more fundamental question to ask that patient is "Why were you in a position where something like that could happen?"

The *action steps* to take here are to tighten the boundaries around the patient in an effort to increase support for someone who is very likely struggling.

Pain by Numbers

In a central poststroke pain study,

8

patients

received **ultrasound-guided peripheral nerve blocks** with

2%

lidocaine solution

in the area of maximal pain.

The injections blocked peripheral sensory afferents and all forms of evoked **mechanical** and **thermal hypersensitivity**.

The intervention completely relieved spontaneous pain in **7** of the **study cohort,** while providing

50%

relief in the remaining subject.[1]

An analysis examined patient records from

14,899

adults covered by **Medicare** undergoing in-center hemodialysis during **2011**.

Median age of participants was **61 years,** and **52**% were **men**.

64%

of the group received a **prescription for opioids** during the study period, and instances in this cohort for **altered mental state** was **11**%, **falls 5**%, and **fractures** requiring in-hospital attention **3**%.[2]

In the US,

>100,000,000

NSAID prescriptions are issued annually.

A **substudy** evaluated records of

~24,000

patients who took daily prescription doses of **celecoxib**, **naproxen**, or **ibuprofen** for >**18** months.

11,000

also took aspirin.

The **addition** of aspirin **diminished** the original safety advantages observed for celecoxib but overall, patients taking a combination of **celecoxib & aspirin** experienced **fewer adverse outcomes** than did those taking both **ibuprofen & aspirin.**[3]

A study assessed records from **475 patients** in **18** surgical centers who had surgery for **adult spinal deformity** between **2008** and **2015**.

Average patient age:

58

years;

79% were **women**;
44% of the study group **self-reported** daily use of **opioid medications** prior to their surgery.

This cohort averaged **16** hours **longer stay** in intensive care, and a **70**% **higher incidence** of **prolonged** hospital stay overall.

They were also **690**% **more likely** to be taking daily opioids at **2** years postprocedure.[4]

The ESPOUSE migraine study: participants self-administered

4

pulses

from the **Spring transcranial magnetic stimulation** device in the morning and at night as required to treat or forestall **migraine attacks**.

The treatment protocol reduced the frequency of headache days by

3

per month, and

46%

of participants reported a

50%

or **greater reduction** in migraine attack incidence.[5]

Researchers surveyed

2,583

patients with **chronic pain** presenting at a pain clinic.

85%

of respondents self-reported as **moderate drinkers**.

Moderate consumption was defined as

1 **drink** per day for **women** and
2 **drinks** per day for **men**.

Chronic pain patients who drank **moderately** reported **less pain** and **symptom severity** compared with **nondrinkers.**[6]

1. https://bit.ly/2FfKUPq **2.** https://bit.ly/2Kf4HlW **3.** https://bit.ly/2HOqqTb **4.** https://bit.ly/2HLMhuz **5.** https://bit.ly/2Jlyyb5 **6.** https://bit.ly/2Fghv7N

One-Minute Clinician

1

Differential Diagnosis of Myelopathies

Charles Argoff MD, CPE

In my experience, the recognition that disorders of the spinal cord can be associated with chronic pain has often been undervalued or underestimated. It's become clear that a variety of disorders that can cause spinal cord dysfunction are present in people who have ongoing pain. We typically think of spinal cord compression, the most common reason for such being cervical spondylosis or spondylotic arthritic degenerative changes that may occur over time. They may ultimately result in bony encroachment of the spinal cord either in the thoracic or, more likely cervical region. We often overlook nonstructural reasons such as vitamin deficiencies, metabolic disorders in general, and various infections. There's quite a long list of potential etiologies to myelopathies that result in ongoing pain, and clinicians should be aware of both structural and nonstructural etiologies. What is important is recognizing the presence of a spinal cord abnormality from the history and the old fashioned physical examination. Clinicians need to recognize the complaints and the physical examination findings that suggest a spinal cord abnormality or a myelopathy and pursue by referring to someone who can further assess. Raising the question before someone undergoes an invasive treatment can actually help in the long run.

2

Denouncing Opioid Use... but What to Use Instead?

David Glick DC, DAAPM, CPE, FASPE

The hot topic with respect to practitioner groups is the denouncing of the fact that there's too much opioid use, and everyone is looking for ideas to minimize these opioids. One of the top suggestions that people will consider is nonopioid and nonpharmacologic treatments, which is fine. The problem is, everyone is overlooking the main problem: How do you address the problem that the patient's in for. Maybe we can alter the treatment to minimize the need to prescribe an opiate or other medication to begin with. There are so many patients where we have done nothing different except to take a step backwards, re-evaluate the patient from an entirely new perspective, and then treat a problem to resolution. I don't necessarily think we have to look for new means of treatments, but we have to look for better ways of triaging the treatments that we have. We group things together like "back pain" as a single entity, when back pain itself is a *symptom* not a diagnosis. The diagnosis should be, let's say, facet-mediated back pain that might be an inflammatory pathology when we should recognize that that same inflammatory pathology with respect to the facet joint might inflame a nerve root causing a radiculitis. So then the most effective treatment would be to somehow control the inflammation of the nerve root and the facet joint so we can treat it to resolve it. Why do we have to mask the pain or overshoot the problem by, perhaps, injecting a facet joint and "Ooh, that didn't work," but we missed part of the problem. Maybe a few weeks later we did a transforaminal epidural, while by that time the facets reinflamed—then we feel like it's the dog chasing its tail. Other times the problem could be something as simple as a patient is overtreated. Some patients are on multiple medications by multiple providers for multiple problems because everybody is looking at the patient from the perspective of their own specialty, which can be very narrow and focused. Sometimes the patients don't even link the pieces together and they're trying to get treatment for each problem as if it's independent. We've seen so many patients that all you literally have to do is address the medication profile they're on for another disease state and all of a sudden their pain issues resolved. The question should be, how do we center our care or create more of a patient-centered model, which I think would improve our outcomes to begin with. Then we can be a little bit more careful with respect to the care that we're providing a patient.

3

Pain in the Emergency Department: Let's Elevate Our Game!

Alexis LaPietra DO

With the current opioid epidemic, practitioners across all subspecialties are looking to find alternatives to treat pain effectively and not solely rely on opiates, especially as a first line treatment. In the emergency department we see a variety of pain, some mild, some severe. For patients who have severe pain, opiates are a fantastic modality to help relieve their suffering. From mild to moderate pain, ankle sprains, or low back pain, it's important not to reflexively prescribe opiates but to appreciate the tool box of medications we have for pain management. It's important in primary care and emergency medicine to utilize a multimodal approach and not solely rely on any one medication to get the job done. Utilizing anti-inflammatory medication combined with acetaminophen has been shown to provide better pain relief than using either alone. Appreciating topical medications and utilizing the skin as a modality for administration has also been shown to be very effective. Things like diclofenac gel or lidocaine patches are a great way to elevate pain management; they can be easily administered and prescribed in an outpatient setting. Another interesting modality that I discovered during my pain management fellowship was trigger point injection which can be performed in the outpatient or emergency department (ED) setting. It's a matter of putting a small gauge needle into the area of severe spasm (which may actually feel like nodule) and just by using the needle to break up that spasm, the patient will have immediate relief. Exploring this modality in a primary care setting will greatly improve pain management in the office and can provide immediate relief in ways that other modalities cannot. What's nice has been looking at the evidence and seeing the studies and reading about patient experiences and appreciating that there's a lot of modalities that cross emergency care as well as primary care. In the ED, we do

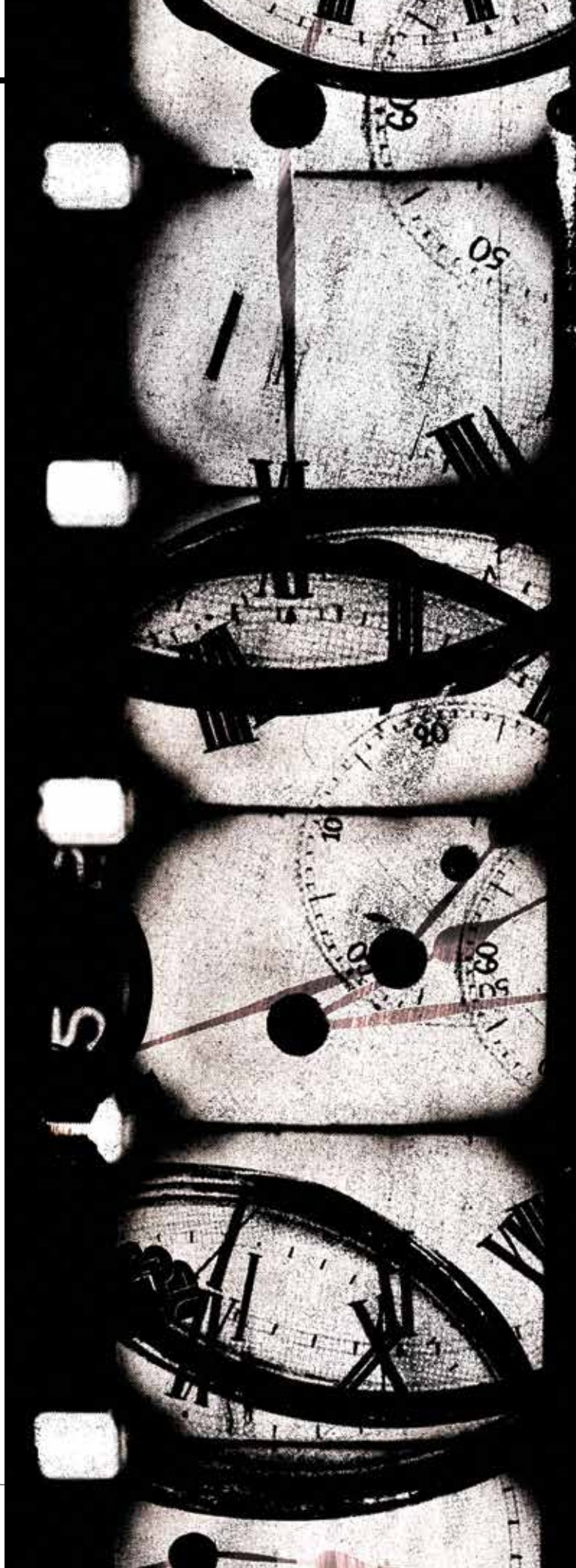
see a large population of people who are maintained on opiates at home for chronic pain. We have to appreciate that it's a delicate balance when prescribing opiates chronically, and then dealing with an acute flair in the ED. In the emergency department, the goal should be to clearly manage the acute issue, but then to collaborate and communicate with the prescribing physician from the community so that you are not adding benzodiazepine or other chronic opiates on top of what a patient is maintained on, because it sets the patient up for adverse events. So we really have to be a team in the ED with the primary care prescriber.

4

Biofeedback: Misconceptions and Resistance

Anthony Whitney MS, LHMC, BCB

When we run into resistance with biofeedback, usually we first start by explaining exactly what biofeedback is. It's a term that gets used a lot that either people don't know about or there are misperceptions or misrepresentations. The biggest thing I start with is just making sure the person understands that they're not going to be injured or harmed. That there's no electricity or needles. I then explain that we use computer technology to get information from their body, and then provide that information back to them in a way that empowers them and increases what they can do to enhance how they cope and live, rather than just survive with chronic pain. One of the major goals with biofeedback, at least based on the way I've been trained, is to help patients get to a point where they don't need to continue with the therapist or the equipment. That they gain increased body awareness, mindfulness, and other tools to help improve anything from muscle tension to circulatory dynamics, or other aspects that can contribute to the management of chronic pain. As relaxation is definitely a strong component of biofeedback, I try to help people understand how to actually truly relax physically, mentally, and emotionally...not just the mental side that we tend to think of. Because with the biofeedback component we're not approaching the person as if the pain is in their head. The pain is real, and we want to treat it as such and give them real tools to be able to improve their quality of life. Unfortunately insurance companies may be driving healthcare more than our medical recommendations. With biofeedback, the reimbursement rates are equivalent to any psychological treatment or therapy. Most insurance companies have a level of requirement to provide at least some mental health treatment, and biofeedback is a tool which can be incorporated at least through the mental health window. I often use it in conjunction with counseling or psychological training or treatment. Biofeedback tends to be competitive with most other nonpharmacological tools, and even though it's still categorized as an alternative treatment, it fits within the category of accepted tools such as psychotherapy.



PUNDiT PROFiLe

with
ramon l.
cuevas-trisan
md

"...other residents dreaded working in the pain clinic and I would volunteer to switch assignments with them to spend more time there."

Q What inspired you to become a healthcare provider?

A Being raised by my parents. They are both in their 80s and still practicing psychiatry. My father always says that he has never worked in his entire life because he enjoys his job so much.

Q Why did you focus on pain management?

A During my PM&R residency's pain clinic rotations at the West Los Angeles VA, I thought it was fascinating... We knew so little about chronic pain. As I read classics by Gordon Waddell, Wilbert Fordyce, and John Bonica among others, my interest kept on growing. I remember how some of the other residents dreaded working in the pain clinic and I would volunteer to switch assignments with them to spend more time there.

Q Who were your mentors?

A First and foremost my parents. Dr. Francisco Muñiz at the University of Puerto Rico SOM and the San Juan VA; Dr. Peter Moulder at the Tulane SOM; Dr. Richard Riggs at Cedars-Sinai in Beverly Hills; and Dr. Daniel Shin at Rancho Los Amigos Medical Center in Downey. All taught me hard work, selflessness, and perseverance.

Q If you weren't a healthcare provider, what would you be?

A I would have been in the space program at NASA, hands down. I studied engineering and had my sights on being an astronaut with the space shuttle program from a very young age.

Q What is your most marked characteristic?

A I believe that I am a good listener. It comes in very handy as a clinician and administrator but also as a friend and person. You do not learn by talking but do learn a lot by listening.

Q What do you consider your greatest achievement?

A Professionally, I would say that it was in 2000 when I took over as director of the PM&R Residency Training Program at the San Juan VA after it was placed on probation by the

"You do not learn by talking but do learn a lot by listening."

Accreditation Council for Graduate Medical Education. In just over a year I was able to turn it around and get it fully accredited. Lots of blood, sweat, tears, and invaluable support from my family and colleagues.

Q **What is your favorite language?**

A Spanish. It is so rich. There are so many words to describe the simplest of things. The abundance of regionalisms add amazing depth and character to it.

Q **If you had to choose one book, one film, and one piece of music or art to take into space for an undetermined amount of time, what would they be?**

A That's a very tough one, especially when it comes to music. I love all kinds of music and would hope that I could at least be able to take my iPod mini (it's small and would be easy to sneak in) with some of my favorite playlists. I would have a hard time choosing among the TOTO IV, Sting's *Fields of Gold* compilation album, *Seal I*, and Don Henley's *Actual Miles*. I would be remiss if *Siembra* by Ruben Blades and Willie Colon was not in the mix. Regarding a movie, it would be either *Gladiator* or *Traffic*, but preferably both. As far as a book I would have to say *The Immortal Life of Henrietta Lacks* by Rebecca Skloot.

Q **What would you like your legacy to be?**

A It is and has always been to leave a place in better shape than I found it.

Q **What is your motto?**

A I have several. "Choose your battles" and "Actions speak louder than words." As I have become more involved in healthcare management, my motto is: "If you are not at the table, you may be on the menu."

Ramon L. Cuevas-Trisan, MD, is Affiliate Assistant Professor, University of Miami Miller School of Medicine; Chief, Physical Medicine, Rehabilitation & Pain Management Service, West Palm Beach VA Medical Center, Florida.

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NEW WORKSHOPS

Cannabis and Cannabinoids:
Kissing Cousins or Good Cop/Bad Cop?

Douglas L. Gourlay MD, MSC, FRCPC, FASAM ● Mary Lynn McPherson PHARMD, MA, MDE, BCPS, CPE

Presented Tuesday/9.4 1:40p – 4:40p

Registration Fee: $165

This fast paced, case based course will take learners on a journey exploring the scientific evidence that supports or refutes the use of cannabinoids, including clinical pharmacology, acute and chronic adverse effects, and the appropriate use of FDA-approved and other cannabinoids. Also to be explored: the interrelationship between cannabis and opioids, the management of long-term consequences of cannabis use, and how practitioners can use our growing evidence base to recommend cannabis products in states where cannabis is approved for medical use. Participants will leave this session with a commonsense approach to this complicated topic—complications being both therapeutic and regulatory!

Patient Centered Opioid Reduction

Beth Darnall PHD ● Ming-Chih Kao PHD, MD ● RICHARD STIEG MD, MPH

Presented Tuesday/9.4 1:40p – 4:40p

Registration Fee: $165

Come learn strategies to enhance your partnership with patients as a pathway to reduce their opioid health risks. This workshop will introduce critical behavioral and medical aspects of an evidence based patient centered approach to *voluntary* opioid reduction, including transforming the messaging in the clinic environment, using the right approach and language, partnering with patients, setting them up for success with a tapering schedule, and helping patients feel and be in control. Both provider-level and clinic-level strategies will be discussed. This course will be led by faculty who received national funding to implement a patient centered voluntary opioid reduction clinical program. To encourage active participation in behavioral pain management, several tip sheets will be provided, and an audience Q&A is sure to enlighten.

Working With Old Molecules:
Lipstick on the Pig...or Mama's Got a Brand New Bag

Douglas L. Gourlay MD, MSC, FRCPC, FASAM ●
Mary Lynn McPherson PHARMD, MA, MDE, BCPS, CPE

Presented Wednesday/9.5 9:30a – 12:30p

Registration Fee: $165

Practitioners today are fairly comfortable dealing with traditional opioids such as morphine, oxycodone, hydromorphone, and fentanyl. But what about buprenorphine and methadone? This case based session will provide attending practitioners with hard and fast skills that can be implemented immediately upon return to work! Contemporary issues with monitoring and dosing methadone will be addressed, including risk stratification for candidate selection, the implication of drug interactions, and the nuances of monitoring. Buprenorphine's intriguing pharmacology will be covered, along with dosing guidance for chronic pain. Importantly, participants will learn how to treat acute pain in a patient receiving methadone or buprenorphine as part of an opioid agonist recovery program.

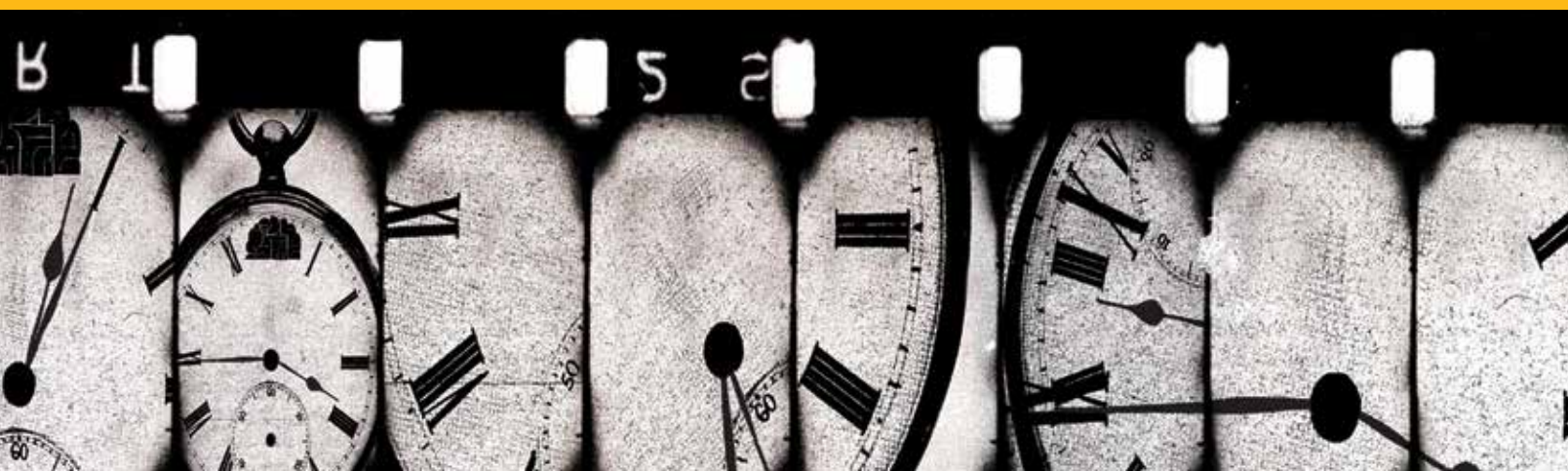
Palliative Care Bootcamp:
You're in the Army Now!

Frank D. Ferris MD, FAAHPM, FAACE ● Jessica Geiger-Hayes PHARMD, BCPS, CPE ● Alexandra L. McPherson PHARMD, MPH ● Mary Lynn McPherson PHARMD, MA, MDE, BCPS, CPE

Presented Saturday/9.8 P1: 9:30a – 12:30p P2: 1:40p – 4:40p

Registration Fee: $195

Soldier up! This 2-part all-day program is jam packed with clinical pearls to manage pain and nonpain symptoms associated with advanced illness. Taught by leading experts, you will learn how to conduct a thorough assessment of pain in a verbal and nonverbal patient (with plenty of practice!) and how to use this information to determine the most likely pathogenesis of pain, which drives drug-therapy decision making. Considerable time will be spent exploring difficult-to-control syndromes, including painful wound care and complicated neuropathic/multipathology pain. The use of ketamine, methadone, and lidocaine will be addressed. Importantly, tips and tricks to develop and support informal caregivers in the medication management process will be explored as well.



Featured Sessions

The Other Opioid Crisis:
Fentanyl and Heroin

Kevin L. Zacharoff MD, FACIP, FACPE, FAAP

There is a significant amount of media, political, and public attention paid to the opioid crisis/opioid epidemic in the United States today. With the seemingly ever-increasing number of opioid related overdoses and fatalities, there has been a feverish push by stakeholders to diminish the amount of opioids prescribed in order to help stem these worrisome trends. Unfortunately, there may be a lack of focus regarding the true definition and characterization of the opioid epidemic. There may also be a rush to judgment about the role of appropriately prescribed opioid analgesics in the addiction crisis we face today. This presentation will discuss the roles and statistics of both prescription and illicit opioids (namely fentanyl and heroin) in today's "opioid overdose epidemic" with the intention of clarifying important differences and similarities between these competing epidemics including concerns and clinical considerations specific to each of them. Additionally, this program will examine and identify how these medications and drugs share potentially tragic adverse effect profiles in many cases. However, it is important for clinicians to make sure that appropriate chronic pain patients who may be candidates for opioid analgesic therapy aren't penalized, and still get the treatment they deserve.

The Medical Stasi:
When the Best of Intentions Lead to Unexpected Outcomes

Douglas L. Gourlay MD, MSC, FRCPC, FASAM ●
Howard A. Heit MD, FACP, FASAM

The debate over the existence of an opioid crisis is over: with more than 150 deaths per day being attributed to the use of opioids, there is *clearly* an opioid crisis in America. The debate rages over the cause, but little attention has been paid to a clear definition of the intended consequences of the proposed guidelines, nor has there been a willingness to examine the unintended consequences of the solutions that have been proposed. Guidelines are being enshrined in state regulations and, in some cases, being elevated in criminal proceedings as "standards of care," even though there is little evidence to suggest these guidelines, no matter how desperate the need or how well intentioned the effort, are helping. Worse still, guidelines are being implemented with no provision for review to examine these intended and unintended consequences, allowing for iterative changes to be made. **Note:** the position of this panel is neither pro, nor con, opioid use.

Year of the Locusts:
The Impact of the CDC Guidelines on Practitioners and Patients

Gary W. Jay MD, FAAPM, FACFEI ●
Robert L. Barkin MBA, PHARMD, FACP, DAPM

The CDC guidelines have caused controversy and spurred heated discussion. Produced with a paucity of evidence based medicine, they were never evaluated and iterated in the manner of more appropriate guidelines. In this course, we will examine the guidelines and their effect on practitioners—primary care physicians, pain specialists, etc—and chronic pain noncancer patients as well as some chronic cancer patients. Many functioning patients have had their opioid dosages diminished, either in concert with their physician or forcibly, without any say in the matter. This, along with a marked reduction in the amount of legal opioid medications that can be produced, has led to significant unintended consequences: practitioners are leaving the field; some refuse to even prescribe opioids, mostly due to fear of overregulation; once functional patients are being abandoned by the medical field; patients are searching for something to return them to functionality, which can lead to overdose and death, particularly from heroin and illicit fentanyl. Indeed, the opioid crisis has now become the heroin and fentanyl crisis. During this presentation, solutions, and the changes necessary to bring them about, will be discussed.

Embrace Changes and Prevent Overdose:
A Basic Blueprint for Legal Risk Mitigation and Response

Jennifer Bolen JD

Overdose—a small word that packs a major punch, and a big reason for many recent legal regulatory changes in controlled substance prescribing and pain management. Too many physicians and allied healthcare practitioners are caught unawares by the legal issues surrounding overdose events, fatal and nonfatal. Often, prescribers are the last to learn about an overdose event and, worse yet, fail to take action once notified. Through a series of case examples, attendees will learn how to develop and implement overdose event

"PainWeek is not only for specialists. It is essential for primary care!"

—**Douglas L. Gourlay** MD, MSC, FRCPC, FASAM

policies and protocols. Attendees will receive copies of sample policies and protocols and learn how to tailor them to their respective practices and state licensing board framework. Professional licensing board and criminal cases involving overdose events do not usually end well for the prescriber, but there is much the prescriber can do proactively to signal his/her intent to get things right. While prescribers cannot control what their patients do once they leave the medical office, they are responsible for establishing a safe framework for opioid prescribing, including a proper response when something goes wrong.

Pain Management at Ground Zero

Mark Garofoli PHARMD, CPE

West Virginia continues to lead the nation, and world, in drug overdoses, which makes one ponder what is being done at the "ground zero" of the opioid epidemic to save and improve lives. Where else but where it's "worst" should some of the possible solutions come from? In 2016, an interprofessional panel of experts in pain management—ranging from medicine, osteopathy, nursing, pharmacy, and dentistry, to public health, the state PDMP, and representatives from insurance providers—was developed with aims of doing just that. The West Virginia Safe & Effective Management of Pain (SEMP) Guidelines (www.sempguidelines.org) were developed to facilitate the shift of best practices in pain management becoming the new standard of care. The SEMP Guidelines include 2 main components including the risk reduction strategy and clinical treatment algorithms. Pain management algorithms are not available anywhere else in the entire world! Thus, welcome participants to "the West Virginia Way" and see just how we are approaching the opioid epidemic from a true ground zero. After all, if it works where it's worst, how could it not help your state or your practice?

Fear & Loathing in the Bedroom:
A Savage Journey Into Sexual Pain

Meryl Alappattu PT, DPT, PHD

When sexual pain strikes, the impact goes beyond pain during intercourse. Painful sex is associated with significant cognitive, emotional, and physical consequences that affect women even outside the bedroom. This common condition, affecting nearly 45% of older women and 34% of younger women, is linked to local (ie, pelvic) and widespread pain sensitivity, in addition to other areas of bodily pain. Sexual pain is also associated with significant intercourse related distress, including fear and anxiety that may be present before, during, or after vaginal penetration. Unfortunately, this topic remains taboo among patients and providers; patients often suffer in silence for years before receiving treatment from a provider with knowledge of sexual pain. This talk will cover the proposed mechanisms of sexual pain and how this type of pain impacts sexual and physical function, partner dynamics, and health related quality of life. Participants will learn how to screen for sexual pain and how to engage other providers to provide the multidisciplinary care warranted for managing this condition. Participants will also learn the key components of a musculoskeletal pelvic examination for sexual pain.

SCHEDULE AT A GLANCE

MONDAY/9.3

Sessions presented from 6:00p – 8:00p

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- **PAINWeek 101** is a noncertified primer for first time attendees—or anyone seeking a refresher on the conference agenda, faculty, onsite technology, and venue logistics. Moderated by PAINWeek staff and faculty with Global Education Group, all questions as they pertain to course selection and CME protocol will be answered. With so much packed into the 5-day conference, PAINWeek 101 will make sure that you're fully briefed and oriented to navigate, plan, select, and make the most of your PAINWeek experience!

Not certified for credit.

Visit **www.painweek.org** for more information.

TUESDAY/9.4

Sessions presented from 7:00a – 6:30p

BEHAVIORAL PAIN MANAGEMENT

- **The Carrot and the Stick:** Values Based Interdisciplinary Pain Management
- **Unveiling the Mask:** The Relationship of Chronic Pain and Psychopathology
- **Sleep and Pain:** Friends or Foes
- **The Science of Pain Relief and Opioid Reduction**
- **The Psychology Toolbox:** Evidence Based Treatments for Pain Management
- **Being Held Hostage?** Use Psychological Strategies for Resolving Difficult Patient Behaviors

CHRONIC PAIN SYNDROMES

- **The Weight of the World:** Evaluation and Management of Sacroiliac Joint Dysfunction
- **Mirror, Mirror on the Wall:** Graded Motor Imagery to Treat Complex Regional Pain Syndrome
- **Neck and Upper Extremity Pain Syndromes**
- **Neurogenic Thoracic Outlet Syndrome**

INTERVENTIONAL PAIN MANAGEMENT

- **Electroceuticals:** The Future of Interventional Pain Management
- **Injections, Nerve Blocks, Pumps, and Spinal Cord Stimulation**
- **Stem Cells and Regenerative Medicine for Chronic Pain**
- **Procedures or Medication Management?** When to Refer to a Specialist
- **Central Sensitization and Ketamine**

MASTER CLASS

- **When Stars Collide:** Diagnosis and Pathophysiology of Minor Traumatic Brain Injury & Post-Traumatic Headache

MEDICAL/LEGAL

- **I'm a Doctor, Not a Detective!**

SPECIAL INTEREST SESSIONS

- **Brain Based Biomarkers for Pain:** Objective Measures of Pain or a Journey Down the Rabbit Hole?
- **Hello Darkness My Old Friend:** Tapping Into Temperament and Pain With Music Psychotherapy
- **Involuntary Tapers:** Legal, Ethical, and Clinical Concerns
- **The Emperor's New Clothes:** Multimodel Engagement & Improving Access to Care

WORKSHOPS

- **Cannabis and Cannabinoids:** Kissing Cousins or Good Cop/Bad Cop?
- **Patient Centered Opioid Reduction**

WEDNESDAY/9.5

Sessions presented from 7:00a – 6:30p

ACUTE PAIN MANAGEMENT

- **Relax, All Antispasmodics are the Same**—Right?
- **The Role of Acute Care in the Opioid Epidemic**
- **Emerging Trends in Acute Pain Management**
- **The Dynamics of Managing Acute Postoperative Pain in the Current Opioid Sparing Environment**

INTERNATIONAL PELVIC PAIN SOCIETY

- **A Spy in the House of Love:** Unraveling the Mysteries of Misplaced Cells and Cyclical Pain in Endometriosis
- **Pregnancy Related Pain:** Sciatica My Ass!
- **Fear & Loathing in the Bedroom:** A Savage Journey Into Sexual Pain
- **The Razor's Edge:** Evaluating Pelvic Pain Caused By Peripheral Nerve Injury

PAIN EDUCATORS FORUM

- **Pain Terminology:** Knowing the Difference Makes a Difference!
- **Pain Pathways Made Simple**
- **Chronic Pain Assessment**
- **Pain Therapeutics**
- **Clinical Pearls:** Unraveling the Secrets of Imaging Studies

SPECIAL INTEREST SESSIONS

- **Full-Metal Jacket:** Examining the Psychedelic Side of Ketamine
- **The Other Opioid Crisis:** Fentanyl and Heroin
- **The Yin and the Yang of Pain Research:** Matching Disease Mechanisms with Interventions
- **The Outer Limits:** Analgesics of the Future

WORKSHOP

- **Working With Old Molecules:** Lipstick on the Pig...or Mama's Got a Brand New Bag

THURSDAY/9.6

Sessions presented from 7:00a – 6:30p

ADVANCED PRACTICE PROVIDER

- **Practicing Multidisciplinary Pain Management in the Community Setting**
- **Caring for the Clinicians:** Preventing Burnout and Promoting Wellness
- **Complex Cases in Pain Management**
- **Case Studies in Aberrant Drug Taking Behaviors**

AMERICAN HEADACHE SOCIETY

Chronic Migraine Education Program (CMEP)

PART 1 (2 hours)

- **Diagnosis of Chronic Migraine and Episodic Migraine**
- **Transitions, Risk Factors, and Barriers to Care**
- **Case Studies and Q&A**

PART 2 (2 hours)

- **Pathophysiology of Chronic Migraine and Episodic Migraine**
- **Acute Treatment Strategies**
- **Preventive Treatment Strategies**

Medical/Legal

- **Get Your Specimens in Order:** The Importance of Individualized Test Orders and Timely Test Utilization
- **Embrace Changes and Prevent Overdose:** A Basic Blueprint for Legal Risk Mitigation and Response
- **Trusted But Not Busted:** Staying Compliant in a Litigious Environment

Neurology

- **Evaluation and Management of Painful Neuromusculoskeletal Conditions**
- **Not So Silent Screams:** Managing Pain in Demyelinating Disorders
- **Big News in Small Fiber Neuropathies**
- **The Pompatus of Pain:** Living Through Postherpetic Neuralgia

Pain Educators Forum

- **Teamwork Through Common Language**—A CPE Approach to Engaging Patients in a Multimodal Care Plan
- **Using Gagne's Nine Events of Instruction to Shape Your Presentation**
- **Plan Before You Leap!** Instructional Design for Clinicians
- **It's a Bird! It's a Plane! No, it's a Case Manager!** Utilizing Complex Care Case Managers in a Pain Clinic Setting

Scientific Poster Session

Not certified for credit.

Special Interest Sessions

- **Year of the Locusts:** The Impact of the CDC Guidelines on Practitioners and Patients
- **Solutions to Counterfeit Medicine**
- **Pain, Drugs, and Ethics**
- **Pain Clinical Trials**
- **Dangerous Liaisons:** Regimens, Regimes, and Rapprochements
- **Do As I Say!** Facilitating Treatment Adherence in Pain Medicine

Friday/9.7

Sessions presented from 7:00a – 6:30p

American Pain Society

- **The Knee Bone's Connected to the...** Peripheral and Central Mechanisms in Knee Osteoarthritis
- **Oh, My Aching Back:** Assessment and Management of Low Back Pain
- **Here a Pain, There a Pain, Everywhere a Pain Pain:** Widespread Pain and Fibromyalgia
- **Exercise Your Demons:** The Benefits of Exercise as a Treatment for Musculoskeletal Pain

Master Class

- **Differential Diagnosis of Low Back Pain**

Medical/Legal

- **The Intersection of Law Enforcement and Healthcare:** Increased Utilization of PDMPs
- **Nontraditional Law Enforcement Solutions to the Misuse, Abuse, and Diversion of Opioids**

Medical Marijuana/Cannabinoids

- **Cannabinoid Hyperemesis Syndrome**
- **Reefer Madness Revisited:** Taking the Insanity Out of Medical Cannabinoids
- **An Unexpected Valentine:** Cannabis for Painful Skin Conditions
- **Medical Cannabis:** Focus on Pain Management

Pharmacotherapy

- **Walking the Line:** Opioid Dose De-Escalation
- **Thug Drugs**
- **Opioid Conversion Calculations**
- **ADFs:** Gimmick or Godsend?
- **Nonopioid Analgesics, Adjuvants, and Antidepressants**
- **Topical Analgesics**

Podium Poster Presentations

Not certified for credit.

Special Interest Sessions

- **The Medical Stasi:** When the Best of Intentions Lead to Unexpected Outcomes
- **Bridges to Babylon:** Assessing & Managing Comorbidities in Chronic Pain Patients
- **Common Threads in Pain and Chemical Dependency**
- **Benzodiazepines and "Z" Drugs for Pain Patients:** The Problem of Prolonged Withdrawal Syndrome (PWS)
- **Solutions to Counterfeit Medicines**
- **Fudin Vs Gudin:** Can Overprescribing Be Defended in Court?
- **The Right Drug, the Right Patient, the Right Time**
- **Policies and Practicalities:** Focusing on the Patient, Not the Opioid

Saturday/9.8

Sessions presented from 7:00a – 4:30p

Electroceuticals

- **Physics Based Electric Cell Signaling in Pain Management:** A Historical Perspective
- **Real Evidence Medicine Makes the Ethical Care of the Patient Its Top Priority**
- **Clinical Applications of Electronic Signal Treatment and the Combined Electrochemical Treatment**
- **Quantum Therapeutics for Pain:** The Future for Patients and Physicians

Integrative Pain Management

- **Battlefield Acupuncture Protocol Combined with Microcurrent for Stress and Pain Reduction**
- **Managing Chronic Noncancer Pain:** The Role of the Multidisciplinary Neurological Rehabilitation Team
- **Scars & Traumas:** Their Hidden Influence on Chronic Pain, Health, and Disease
- **This is Us!** Interdisciplinary vs Integrative Pain Management

Pharmacotherapy

- **What's All the "GABA" About?** Pregabalin and Gabapentin Abuse
- **Are Bootleg Fentanyls the New Pill Mills?**
- **To Dream the Impossible Dream:** Acute Pain Management for Patients on Buprenorphine
- **The Trifecta:** Central Sensitization, Opioid Tapering, and Educational Support for Chronic Pain Management

Physical Therapy

- **Change the Narrative for Improved Outcomes**—Words Matter in Pain Care
- **Dry Needling and Trigger Points:** The Science Behind How Dry Needling Might "Work"
- **Addressing Altered Sensory Perception:** A Missing Piece to the Pain Puzzle
- **Unstable Core or Unstable Theories?** Steadying Our Understanding With the Evidence

Special Interest Sessions

- **Pain Management Strategies for the Geriatric Population:** How to Live in Your Discomfort Zone Without Opioids
- **Pain from Head to Toe:** The Challenge of Multiple Comorbidities
- **Mistaken Identity:** Spasms vs Spasticity

Workshop

- **Palliative Care Bootcamp:** You're in the Army Now!

Note: Courses and faculty are subject to change.

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Conference rate **$165** + tax per night. This rate is applicable to healthcare providers only, and can only be guaranteed if reserved by July 29, 2018.

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"PAINWeek brings together many experts in pain and provides education to practitioners that can be easily used and implemented in practice."

—Courtney **Kominek** PHARMD, BCPS, CPE

"PAINWeek has always been receptive to the needs of advanced practice providers. I think one of the key takeaways is collaborative practice in terms of pain management."

—Theresa **Mallick-Searle** MS, NP-BC, ANP-BC

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but learning never stops.
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—**Michael R. Clark** MD, MPH, MBA

SCULPTURE BY EMMA CASTER-DUDZICK

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

CONTRAINDICATIONS:
NUCYNTA ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including 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 of MAOIs 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. Because extended-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. 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 and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) 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 opioids 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.

Opioids 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 the 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 opioids, even when used as recommended. Respiratory depression, 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 dosage increase. Monitor patients closely for respiratory depression especially within the first 24-72 hours of initiating therapy with and following dosage increases of NUCYNTA ER.

To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA ER are essential. Overestimating the NUCYNTA ER dosage 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 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risk from Concomitant Use with Benzodiazepines or Other CNS 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.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of NUCYNTA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

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

Risk from Concomitant Use with Benzodiazepines or Other CNS Depressants (continued)

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NUCYNTA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressants have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of NUCYNTA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: NUCYNTA ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of NUCYNTA ER.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Alternatively, consider the use of non-opioid analgesics in these patients.

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

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of tapentadol with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range.

Serotonin syndrome symptoms 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, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue NUCYNTA ER if serotonin syndrome is suspected.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Severe Hypotension

NUCYNTA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. 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 these patients for signs of hypotension after initiating or titrating the dosage 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.

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

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In 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), NUCYNTA ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA ER.

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.

Risks of Use in Patients with Gastrointestinal Conditions

NUCYNTA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The tapentadol in NUCYNTA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Risk of Use in Patients With Seizure Disorders

The tapentadol in NUCYNTA ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA ER therapy.

Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., 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. Do not abruptly discontinue NUCYNTA ER.

Risks of Driving and Operating 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.

Risk of Toxicity in Patients with 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.

Risk of Toxicity in Patients with 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:

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

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

NUCYNTA® ER (tapentadol) EXTENDED-RELEASE TABLETS CII

COLLEGIUM Pharmaceutical
Ingenuity in Medicine

NUCYNTA® ER
(tapentadol) EXTENDED-RELEASE TABLETS CII

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 (tapentadol) 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) 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 (*see Warnings and Precautions*), 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.

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4), (7).**

CONTRAINDICATIONS

NUCYNTA ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity (e.g. anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product *(see Adverse Reactions)*.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *(see Drug Interactions)*.

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. Because extended-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 (*see Drug Abuse and Dependence*).

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NUCYNTA ER. 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 and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) 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 opioids 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 (*see Overdosage*).

Opioid 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 *(see Patient Counseling Information)*. Contact the 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 opioids, even when used as recommended. Respiratory depression, 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)*. 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 dosage increase. Monitor patients closely for respiratory depression especially within the first 24-72 hours of initiating therapy with and following dosage increases of NUCYNTA ER.

To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA ER are essential *(see Dosage and Administration)*. Overestimating the NUCYNTA ER dosage 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 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. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *(see Use in Specific Populations, Patient Counseling Information)*.

Risk from Concomitant Use with Benzodiazepines or Other CNS 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 *(see Clinical Pharmacology)*.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of NUCYNTA ER with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (*see Drug Interactions)*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NUCYNTA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (*see Drug Interactions and Patient Counseling Information)*.

Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of NUCYNTA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: NUCYNTA ER treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of NUCYNTA ER *(see Warnings and Precautions)*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *(see Warnings and Precautions)*. Alternatively, consider the use of non-opioid analgesics in these patients.

Monitor such patients closely, particularly when initiating and titrating NUCYNTA ER and when NUCYNTA ER is given concomitantly with other drugs that depress respiration *(see Warnings and Precautions)*.

Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of tapentadol with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic

antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *(see Drug Interactions)*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms 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, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue NUCYNTA ER if serotonin syndrome is suspected.

Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Severe Hypotension
NUCYNTA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. 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) *(see Drug Interactions)*. Monitor these patients for signs of hypotension after initiating or titrating the dosage 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.

Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
In 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), NUCYNTA ER may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA ER.

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.

Risks of Use in Patients with Gastrointestinal Conditions
NUCYNTA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The tapentadol in NUCYNTA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

Increased Risk of Seizures in Patients with Seizure Disorders
The tapentadol in NUCYNTA ER may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA ER therapy.

Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., 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 *(see Drug Interactions)*.

When discontinuing NUCYNTA ER, gradually taper the dose *(see Dosage and Administration)*. Do not abruptly discontinue NUCYNTA ER *(see Drug Abuse and Dependence)*.

Risks of Driving and Operating 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 *(see Patient Counseling Information)*.

Risk of Toxicity in Patients with 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 *(see Dosage and Administration and Clinical Pharmacology)*. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression when initiating and titrating NUCYNTA ER.

Risk of Toxicity in Patients with 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 *(see Clinical Pharmacology)*.

ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:
- Addiction, Abuse, and Misuse *(see Warnings and Precautions)*
- Life-Threatening Respiratory Depression *(see Warnings and Precautions)*
- Neonatal Opioid Withdrawal Syndrome *(see Warnings and Precautions)*
- Interaction with Benzodiazepine or Other CNS Depressants *(see Warnings and Precautions)*
- Serotonin Syndrome *(see Warnings and Precautions)*
- Adrenal Insufficiency *(see Warnings and Precautions)*
- Severe Hypotension *(see Warnings and Precautions)*
- Gastrointestinal Adverse Reactions *(see Warnings and Precautions)*
- Seizures *(see Warnings and Precautions)*
- Withdrawal *(see Warnings and Precautions)*

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.

Please see full Prescribing Information for ADRs occurring in ≥ 1% of patients.

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.

Please see full Prescribing Information for ADRs occurring in ≥ 1% of patients.

Postmarketing Experience
The following adverse reactions have been identified during post approval use of tapentadol.

Psychiatric disorders: hallucination, suicidal ideation, panic attack

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in NUCYNTA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids (*see Clinical Pharmacology)*.

DRUG INTERACTIONS

Clinically Significant Drug Interactions with NUCYNTA ER

Alcohol	
Clinical Impact:	Concomitant use of alcohol with NUCYNTA ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol.
Intervention:	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on NUCYNTA ER therapy.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions 5.6]*.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue NUCYNTA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	Do not use NUCYNTA ER in patients taking MAOIs or within 14 days of stopping such treatment
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of NUCYNTA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

NUCYNTA ER (tapentadol) extended-release tablets, CII
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION (continued)

Muscle Relaxants (continued)	
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of NUCYNTA ER and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when NUCYNTA ER is used concomitantly with anticholinergic drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C

Risk Summary
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *(see Warnings and Precautions)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy can occur regardless of the health of the mother or the use of medications.

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. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *(see Warnings and Precautions)*.

Labor or Delivery
Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. NUCYNTA ER is not recommended for use in pregnant women during and immediately prior to labor. Opioid analgesics, including NUCYNTA ER, can prolong labor.

Lactation
Risk Summary
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 serious adverse reactions including excess sedation and respiratory depression in a breastfed infant, advise patients that breast feeding is not recommended during treatment with NUCYNTA ER.

Clinical Considerations
Monitor infants exposed to NUCYNTA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Females and Males of Reproductive Potential
Infertility
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

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.

Elderly patients (aged 65 or older) may have increased sensitivity to tapentadol. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of NUCYNTA ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *(see Warnings and Precautions)*.

Hepatic Impairment
Use of NUCYNTA ER in patients with severe hepatic impairment (Child-Pugh Score 10-15) is not recommended. In patients with moderate hepatic impairment (Child-Pugh Score 7 to 9), dosage reduction of NUCYNTA ER is recommended *(see Dosage and Administration)*.

Renal Impairment
Use of NUCYNTA ER in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) is not recommended.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
NUCYNTA ER contains tapentadol, a Schedule II controlled substance.

Abuse
NUCYNTA ER contains tapentadol, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. NUCYNTA ER can be abused and is subject to misuse, addiction, and criminal diversion (*see Warnings and Precautions)*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

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.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: 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 in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers, and people suffering from untreated addiction. 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. Healthcare providers 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 state and federal 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.

Risks Specific to Abuse of NUCYNTA ER
NUCYNTA ER is for oral use only. Abuse of NUCYNTA ER poses a risk of overdose and death. The risk is increased with concurrent use of NUCYNTA ER with alcohol and other central nervous system depressants.

With intravenous abuse the inactive ingredients in NUCYNTA ER can result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, 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.

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 dosage 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 (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., 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 *(see Dosage and Administration)*. If NUCYNTA ER is abruptly discontinued in a physically-dependent patient, a withdrawal 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 Use in Specific Populations)*.

OVERDOSAGE

Clinical Presentation
Acute overdosage with NUCYNTA ER can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose
In case of overdose, priorities are the reestablishment 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.

NUCYNTA® ER
(tapentadol) EXTENDED-RELEASE TABLETS
II

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Not an actual patient.

NUCYNTA® ER
(tapentadol) EXTENDED-RELEASE TABLETS
CII

TIME TO DUAL

TWO SOURCES OF PAIN | ONE SOURCE OF RELIEF

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).

Visit Nucynta.com for more information and to download a NUCYNTA® ER savings card

INDICATIONS AND USAGE

NUCYNTA ER (tapentadol) 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) 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

IMPORTANT SAFETY INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

NUCYNTA 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 NUCYNTA ER, and monitor all patients regularly for the development of these behaviors and conditions.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA ER. Monitor for respiratory depression, especially during initiation of NUCYNTA ER or following a dose increase. Instruct patients to swallow NUCYNTA ER tablets whole; crushing, chewing, or dissolving NUCYNTA ER tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Ingestion

Accidental ingestion of even one dose of NUCYNTA ER, especially by children, can result in a fatal overdose of tapentadol.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of NUCYNTA 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.

Interaction With Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA ER. The co-ingestion of alcohol with NUCYNTA ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of NUCYNTA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

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

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