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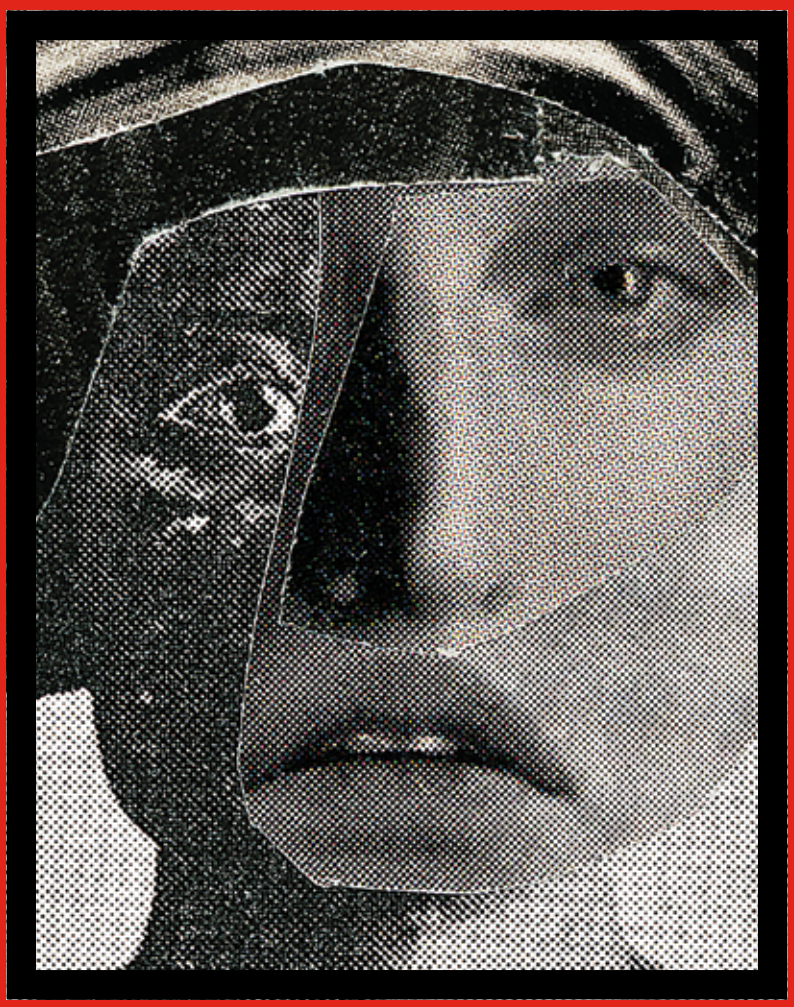

WHAT'S INSIDE:

THE PENDULUM SWINGS IN BOTH DIRECTIONS.

EDUCATION GOES FORWARD.

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AVAILABLE TO PRESCRIBE

Provide pain relief for the intended, **while helping protect against intravenous and intranasal abuse by the unintended**

Abuse of MORPHABOND ER is still possible by intranasal, intravenous, and oral routes

MORPHABOND™ ER

(morphine sulfate) extended-release tablets CII

15 mg • 30 mg • 60 mg • 100 mg

The only single-agent, abuse-deterrent, ER morphine with SentryBond™ Technology[1,2]

Bioequivalent to MS Contin®

Retains its extended-release properties even if manipulated and/or chemically extracted

Expected to deter abuse by both of the following routes:

Abuse of MORPHABOND ER is still possible by intranasal, intravenous, and oral routes

INDICATION

MORPHABOND™ ER (morphine sulfate) extended-release tablets, for oral use, CII is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

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 MORPHABOND ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

MORPHABOND ER is not indicated as an as-needed (prn) analgesic.

IMPORTANT SAFETY INFORMATION

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

Addiction, Abuse, and Misuse

MORPHABOND™ 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 MORPHABOND ER, and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression

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

ER=extended release.

References: 1. MORPHABOND ER [package insert]. Basking Ridge, NJ: Inspirion Delivery Sciences LLC; 2017. **2.** Data on file. Daiichi Sankyo, Inc.

For more information, **visit MORPHABONDhcp.com**

Please see additional Important Safety Information, including **BOXED WARNINGS** on following pages.

IMPORTANT SAFETY INFORMATION

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

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHABOND 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.

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 MORPHABOND 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**

CONTRAINDICATIONS

MORPHABOND ER is contraindicated in patients with: significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days; known or suspected gastrointestinal obstruction, including paralytic ileus; and hypersensitivity (eg, anaphylaxis) to morphine.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

MORPHABOND ER contains morphine, a Schedule II controlled substance, and thus exposes its users to the risks of addiction, abuse, and misuse. As extended-release products such as MORPHABOND 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 morphine present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHABOND ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing MORPHABOND ER, and monitor all patients receiving MORPHABOND ER for development of these behaviors or conditions. Patients at increased risk may be prescribed extended-release opioid formulations such as MORPHABOND ER, but use in such patients necessitates intensive counseling about the risks of proper use of MORPHABOND ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of MORPHABOND ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death. Opioid agonists such as MORPHABOND ER are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing MORPHABOND ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper storage and disposal of unused drug.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended, and 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 MORPHABOND ER, the risk is greatest during the initiation of therapy or following a dosage increase. Closely monitor patients for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases with MORPHABOND ER.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHABOND 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.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of MORPHABOND ER with benzodiazepines or other CNS system depressants (eg, non-benzodiazepine sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, anxiolytics, 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.

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.

Advise both patients and caregivers about the risks of respiratory depression and sedation when MORPHABOND 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.

Please see additional Important Safety Information on following pages.

Please see Brief Summary of full Prescribing Information, including **BOXED WARNINGS** on adjacent pages.

WARNINGS AND PRECAUTIONS

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

The use of MORPHABOND 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: MORPHABOND 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 MORPHABOND ER.

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 MORPHABOND ER and when MORPHABOND ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Interaction with Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. MORPHABOND ER should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

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

MORPHABOND 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 (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of MORPHABOND ER. In patients with circulatory shock, MORPHABOND ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MORPHABOND 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 (eg, those with evidence of increased intracranial pressure or brain tumors), MORPHABOND 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 MORPHABOND ER. Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of MORPHABOND ER in patients with impaired consciousness or coma.

Risks of Use in Patients with Gastrointestinal Conditions

MORPHABOND ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. The morphine in MORPHABOND ER 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 morphine in MORPHABOND 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.

Withdrawal

Avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including MORPHABOND ER. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. When discontinuing MORPHABOND ER, gradually taper the dosage. Do not abruptly discontinue MORPHABOND ER.

Risks of Driving and Operating Machinery

MORPHABOND 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 MORPHABOND ER and know how they will react to the medication.

Adverse Reactions

In clinical trials, the most common adverse reactions with morphine sulfate extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.

Drug Interactions

- Concomitant use of benzodiazepines or other CNS depressants can increase the risk of respiratory depression, profound sedation, coma and death
- The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome
- Mixed agonist/antagonist and partial agonist opioid analgesics may reduce the analgesic effect of MORPHABOND ER and/or may precipitate withdrawal symptoms
- Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression
- MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity
- The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus
- The concomitant use of PGP-inhibitors can increase the exposure to morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death

Daiichi-Sankyo | Inspirion Delivery Sciences

MORPHABOND™ ER (morphine sulfate) extended-release tablets, for oral use CII
Initial U.S. Approval: 1941

BRIEF SUMMARY: See package insert for full prescribing information.

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

Addiction, Abuse, and Misuse

MORPHABOND™ 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 MORPHABOND ER, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

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

Accidental Ingestion

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

Neonatal Opioid Withdrawal Syndrome

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

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 *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of MORPHABOND 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.**

1 INDICATIONS AND USAGE

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

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 *[see Warnings and Precautions (5.1)]*, reserve MORPHABOND 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.
- MORPHABOND ER is not indicated as an as-needed (prn) analgesic.

4 CONTRAINDICATIONS

MORPHABOND ER is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.5)]*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Warnings and Precautions (5.6)/Drug Interactions (7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.10)]*
- Hypersensitivity (e.g., anaphylaxis) to morphine *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

MORPHABOND ER contains morphine, a Schedule II controlled substance. As an opioid, MORPHABOND ER exposes its users to the risks of addiction, abuse, and misuse. Because extended-release products such as MORPHABOND 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 morphine present *[see Drug Abuse and Dependence (9) in the full prescribing information]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed MORPHABOND 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 MORPHABOND ER, and monitor all patients receiving MORPHABOND ER for 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 MORPHABOND ER, but use in such patients necessitates intensive counseling about the risks of proper use of MORPHABOND ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of MORPHABOND ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of morphine and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing MORPHABOND ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper storage and disposal of unused drug *[see Patient Counseling Information (17) in the full prescribing 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.

5.2 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 (10)]*. 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 MORPHABOND 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 MORPHABOND ER.

To reduce the risk of respiratory depression, proper dosing and titration of MORPHABOND ER are essential *[see Dosage and Administration (2) in the full prescribing information]*. Overestimating the MORPHABOND ER dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of MORPHABOND ER, especially by children, can result in respiratory depression and death due to an overdose of morphine.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of MORPHABOND 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 (8.1), Patient Counseling Information (17) in the full prescribing information]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of MORPHABOND ER with benzodiazepines or other CNS system depressants (e.g., non-benzodiazepine sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, anxiolytics, 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 (7)]*.

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 MORPHABOND 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 (7) and Patient Counseling Information (17) in the full prescribing information]*.

5.5 Life -Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
The use of MORPHABOND 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: MORPHABOND 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 MORPHABOND ER *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.2)]*.

Monitor such patients closely, particularly when initiating and titrating MORPHABOND ER and when MORPHABOND ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2, 5.4)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.6 Interaction with Monoamine Oxidase Inhibitors
Monoamine oxidase inhibitors (MAOIs) may potentiate the effects of morphine, including respiratory depression, coma, and confusion. MORPHABOND ER should not be used in patients taking MAOIs or within 14 days of stopping such treatment.

5.7 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.

5.8 Severe Hypotension
MORPHABOND ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is 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 (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of MORPHABOND ER. In patients with circulatory shock, MORPHABOND ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of MORPHABOND ER in patients with circulatory shock.

5.9 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), MORPHABOND 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 MORPHABOND ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of MORPHABOND ER in patients with impaired consciousness or coma.

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

The morphine in MORPHABOND ER 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.

5.11 Increased Risk of Seizures in Patients with Seizure Disorders
The morphine in MORPHABOND 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 MORPHABOND ER therapy.

5.12 Withdrawal
Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including MORPHABOND ER. In these patients, mixed agonists/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms *[see Drug Interactions (7)]*.

When discontinuing MORPHABOND ER, gradually taper the dosage *[see Dosage and Administration (2.4) in the full prescribing information]*. Do not abruptly discontinue MORPHABOND ER *[see Drug Abuse and Dependence (9.3) in the full prescribing information]*.

5.13 Risks of Driving and Operating Machinery
MORPHABOND 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 MORPHABOND ER and know how they will react to the medication *[see Patient Counseling Information (17) in the full prescribing information]*.

6 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 (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]*
- Interactions with Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.7)]*
- Severe Hypotension *[see Warnings and Precautions (5.8)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Withdrawal *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trial Experience

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

MORPHABOND ER may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

Most Frequently Observed Reactions

In clinical trials, the most common adverse reactions with morphine sulfate extended-release were constipation, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoric mood.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain.

Less Frequently Observed Reactions

Cardiovascular disorders: tachycardia, bradycardia, palpitations

Eye disorders: visual impairment, vision blurred, diplopia, miosis

Gastrointestinal disorders: dry mouth, diarrhea, abdominal pain, constipation, dyspepsia

General disorders and administration site conditions: chills, feeling abnormal, edema, edema peripheral, weakness

Hepatobiliary disorders: biliary colic

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: muscle rigidity, muscle twitching

Nervous system disorders: presyncope, syncope, headache, tremor, uncoordinated muscle movements, convulsion, intracranial pressure increased, taste alteration, paresthesia, nystagmus

Psychiatric disorders: agitation, mood altered, anxiety, depression, abnormal dreams, hallucination, disorientation, insomnia

Renal and urinary disorders: urinary retention, urinary hesitation, antidiuretic effect

Reproductive system and breast disorders: reduced libido and/or potency

Respiratory, thoracic and mediastinal disorders: laryngospasm

Skin and subcutaneous tissue disorders: pruritus, urticaria, rash

Vascular disorders: flushing, hypotension, hypertension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of morphine sulfate. 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.

Amenorrhea, asthenia, bronchospasm, confusional state, drug hypersensitivity, fatigue, hyperalgesia, hypertonia, ileus, increased hepatic enzymes, intestinal obstruction, lethargy, malaise, pulmonary edema, thinking disturbances, somnolence, and vertigo.

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 MORPHABOND ER.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

7 DRUG INTERACTIONS

Table 1 includes clinically significant drug interactions with MORPHABOND ER.

Table 1: Clinically Significant Drug Interactions with MORPHABOND ER

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, increase the risk of 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.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue MORPHABOND ER if serotonin syndrome is suspected.
Example:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect 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 (5.6)]*.
Intervention:	Do not use MORPHABOND 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 MORPHABOND ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Morphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MORPHABOND ER and/or the muscle relaxant as necessary.
Cimetidine	
Clinical Impact:	The concomitant use of cimetidine can potentiate morphine effects and increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MORPHABOND ER and/or cimetidine 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.

(continued)

Table 1: Clinically Significant Drug Interactions with MORPHABOND ER

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 MORPHABOND ER is used concomitantly with anticholinergic drugs.
P-Glycoprotein (P-gp) Inhibitors	
Clinical Impact:	The concomitant use of P-gp-inhibitors can increase the exposure to morphine by about two-fold and can increase risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of MORPHABOND ER and/or the P-gp-inhibitor as necessary.
Example:	quinidine

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.3)]*. There are no available data with MORPHABOND ER in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects *[see Human Data]*. In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse. Administration of morphine sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3-4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD *[see Animal Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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 (5.3)]*.

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. MORPHABOND ER is not recommended for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including MORPHABOND ER, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data

Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on a human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of morphine sulfate (35-322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of morphine sulfate to pregnant mice (100-500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day morphine sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day morphine sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg morphine sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10-50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), and decreased

plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered morphine sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day morphine sulfate (9.7 to 19.5 times the HDD) or when female mice treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

8.2 Lactation

Risk Summary

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with extended-release morphine, including MORPHABOND ER. 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 MORPHABOND ER.

Clinical Considerations

Monitor infants exposed to MORPHABOND ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

8.3 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 Adverse Reactions (6.2), Clinical Pharmacology (12.2) in the full prescribing information]*.

In published animal studies, morphine administration adversely effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats *[see Nonclinical Toxicology (13) in the full prescribing information]*.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

The pharmacokinetics of MORPHABOND ER have not been studied in elderly patients. Clinical studies of morphine sulfate extended-release did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. In general, dosage selection for an elderly patient should be cautious, 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 MORPHABOND ER slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.5)]*.

Morphine 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.

8.6 Hepatic Impairment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of MORPHABOND ER and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Renal Impairment

Morphine pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of MORPHABOND ER and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

MORPHABOND ER contains morphine, a Schedule II controlled substance.

9.2 Abuse

Risks Specific to Abuse of MORPHABOND ER

MORPHABOND ER is for oral use only. Abuse of MORPHABOND ER poses a risk of overdose and death. This risk is increased with concurrent abuse of MORPHABOND ER with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved MORPHABOND ER enhances drug release and increases the risk of overdose and death.

Parenteral abuse of MORPHABOND ER can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with MORPHABOND 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 *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

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.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose.

Because the duration of reversal would be expected to be less than the duration of action of morphine in MORPHABOND ER, carefully monitor the patient until spontaneous respiration is reliably reestablished. MORPHABOND ER will continue to release morphine and add to the morphine load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. 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 initiated with care and by titration with smaller than usual doses of the antagonist.

Healthcare professionals can telephone Daiichi Sankyo, Inc. (1-877-437-7763) for information on this product.

Manufactured for: Daiichi Sankyo, Inc.
Basking Ridge, NJ 07920

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PAINWEEK JOURNAL

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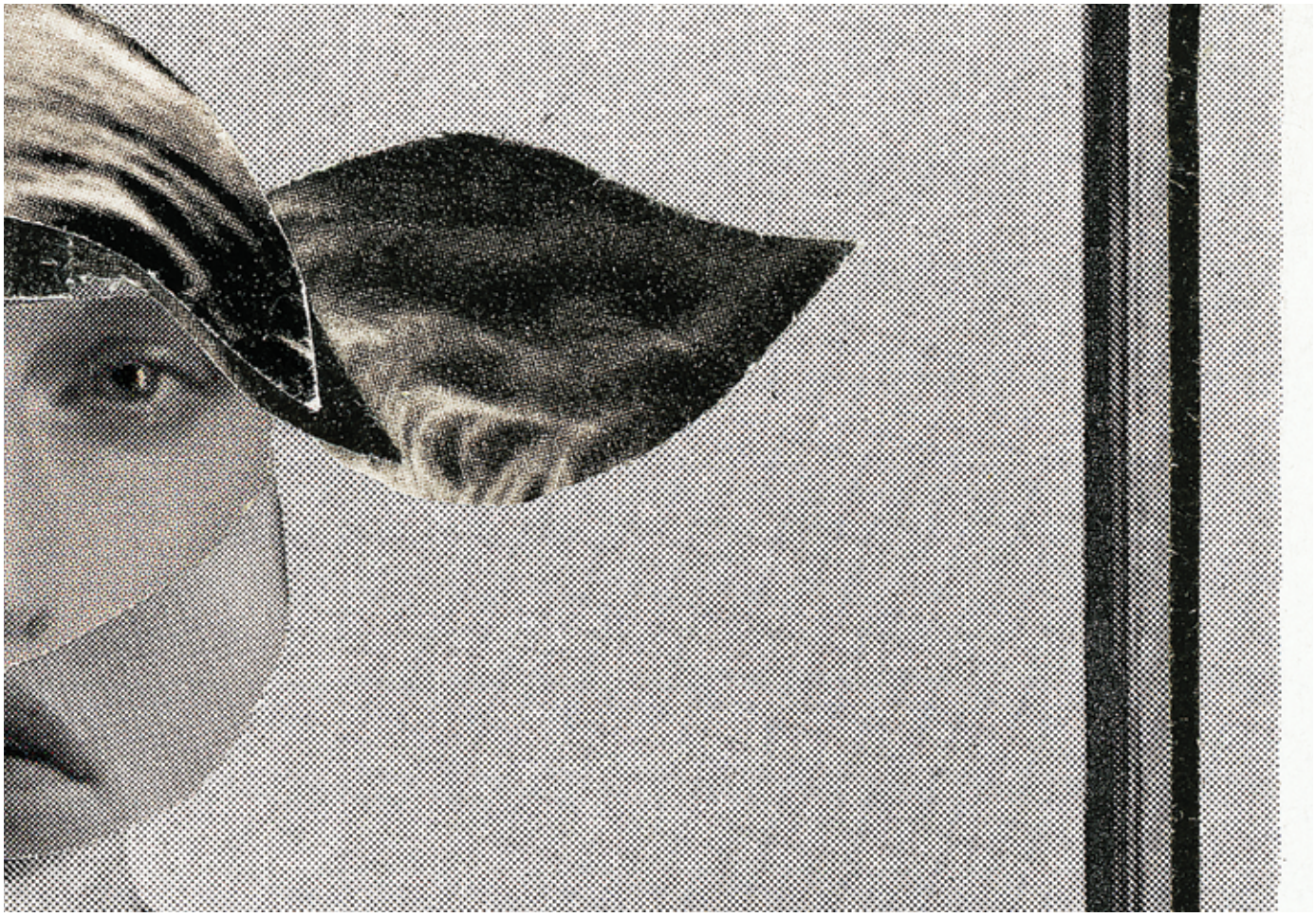

FEATURES

SHORT CUTS

Kevin L. **Zacharoff**

iF someone

asked me 10 years ago (*and someone probably did*) about the progress I expected to be made in the fields of managing chronic pain and pain education, I would have been optimistic in my speculations. I would have projected that in 10 years there would be expert consensus and educational penetration to answer any remaining questions about best practices regarding chronic pain management. Of equal or greater importance, I would have been hopeful that disparities in treatment—and patient outcomes and satisfaction—would be vastly improved. I would have predicted that dialogue about and reimbursement for multidisciplinary, nonprescription, and alternative chronic pain treatments would be more progressive. But here we are, with seemingly more controversy about best practices than ever before; with discussions about what *should not* be done instead of what *should* be done; and more than ever in need for rational, reproducible, beneficial thinking and educational moments. This year, I am rededicated to the notion that education is the only way to make a difference in the quality of care we provide, and here we are with the first issue of PWJ 2018 to help us get to that place we all need to be—for the patients' sake. Let's have a look at what this issue has to offer to help get us there.

Our first article by **Drs. Meryl Alappattu** and **Mark Bishop** presents the reader with a type of pain occurring in women that rivals the prevalence of other common primary care chief complaints like low back pain, migraine headaches, and asthma: persistent nonmalignant pelvic pain. The authors are quick to point out that like many other types of regionally-defined pain conditions, pelvic pain is not homogenous in its pathophysiology. The primary focus of this piece involves pelvic pain of musculoskeletal origin from the physical therapist's perspective. A great amount of detailed information is presented both about common pelvic pain conditions and symptoms as well as their potential impact on patient quality of life… the "holy grail" of pain assessment. If this is not a subject you are familiar with or often consider as part of the differential diagnosis, after reading this article, you will.

We often hear chronic pain described as a challenging medical condition for a variety of reasons, including the fact that pain is a sign and a symptom which can't be seen and at best is subjective in terms of intensity and life impact. When formulating a differential diagnosis based on chief complaint(s), we may sometimes overlook historical contributors that lie outside the realm of physical pathophysiology—things like psychological childhood traumas. **Drs. Christian Washburn** and **Melissa Fledderjohann** provide us with an in-depth look at the long-term effects of adverse childhood events in the context of chronic pain, including everything from neurobiology to treatment. We may often forget that more than 50% of people with a history of psychological trauma, ranging from physical to sexual abuse, go on to develop some type of chronic pain. This should make us all stop and think about how and what we delve into when dealing with patients and their histories.

There is little doubt that relying on nonprescription analgesics in the management of chronic pain is undergoing resurgence, likely resulting from controversies surrounding prescription pain medications and interventional procedures. In fact, it seems as if there may be no prescription based "silver bullet" for patients with chronic pain. Enter my good friends and colleagues **Drs. Alexandra L. McPherson** and **Mary Lynn McPherson**. While it might seem that nonprescription analgesics are the safest choices in almost all cases, this article grounds us with facts, figures, and good "doses" of reality. Two cases are presented, along with risks, benefits, and rationale choices detailed for us to digest. In typical McPherson style, the role of the pharmacist in helping educate both clinicians *and* patients is underscored in meaningful ways. No disappointments in this article regarding relevance, resonance, and value. Enjoy it and keep it handy for future reference and discussions with colleagues.

Plagues to optimal pain care don't always involve the lack of appropriate and efficacious medications, procedures, or other approaches. **Theresa Mallick-Searle** sheds light on preconceptions and biases that may lead to disparate and undermanagement of pain, as well as proposed solutions to promote a higher degree of equity in pain treatment. Oddly enough, sometimes these simplistic biases may be precognitive and not consciously intentional. Further, while practical solutions to these barriers may seem idealistic, reading about them, digesting them, and considering them are all first steps towards effectively eliminating them. I guarantee more of this article may resonate with you than you expect.

This issue's *Pundit Profile* spotlights **Dr. M. Carey Reid, Jr**. A physician working in the field of geriatric medicine, he provides insight into his passion about the treatment of chronic pain in older adults—something we unfortunately don't hear much about. His love of mentoring and educating others is something I have in common with him, along with his desire to make a positive difference at the end of the day. I'm sure you will enjoy this peek behind the curtain of one of our esteemed colleagues.

Our *Next Generation* interviewee is **Dr. Jay Joshi**, a pain physician practicing in Vernon Hills, Indiana. As someone who lives by the motto of practicing based on facts and truth, Dr. Joshi is contributing in paving the way to a better place in caring for our patients with chronic pain. We need our leaders of the future to not back away from controversy and progress, and we have someone here who fits that bill. Enjoy getting to know him.

A lot in this issue pertains to my introduction. Much of it is long overdue from an educational perspective and critical to us moving forward and making progress in chronic pain management and pain education. It may take longer than expected, but we will get there—for the sake of our patients.

—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

Meryl **Alappattu** DPT, PHD **p.26**

Meryl Alappattu is a physical therapist and assistant professor in the University of Florida Department of Physical Therapy and Center for Pain Research and Behavioral Health. She serves as Director of Research for the American Physical Therapy Association Section on Women's Health and on the Advisory Board for the International Pelvic Pain Society. Dr. Alappattu coauthored her article with **Mark Bishop**, PT, PHD, a physical therapist who treats patients with pain. He is an associate professor from the Department of Physical Therapy and faculty in the Center for Pain Research and Behavioral Health, at the University of Florida in Gainesville.

Theresa **Mallick-Searle** MS, RN-BC, ANP-BC **P.50**

Theresa Mallick-Searle is an Adult Nurse Practitioner specializing in acute and chronic pain management at Stanford Health Care in the Department of Pain Medicine, Palo Alto, California. As part of her commitment to bringing awareness to the impact of unmanaged pain, she lectures nationally on topics surrounding both acute and chronic pain.

Alexandra L. **McPherson** PHARMD, MPH **P.40**

Alexandra McPherson is a PGY-2 Pain and Palliative Care Resident at the University of Maryland School of Pharmacy, where she is also an Adjunct Clinical Instructor. Dr. McPherson coauthored her article with **Mary Lynn McPherson**, PHARMD, MA, BCPS, CPE, Professor and Executive Director of Advanced Post-Graduate Education in Palliative Care at the University of Maryland School of Pharmacy, and a Consultant Pharmacist, Hospice and Palliative Care, in Stevensville, Maryland.

Christian **Washburn** PSYD **p.18**

Christian Washburn is a pain psychologist at the interdisciplinary Pain Management Clinic at San Mateo Medical Center in San Mateo, California. She coauthored her article with **Melissa Fledderjohann**, a pain psychologist and director of San Mateo Medical Center's Pain Management Clinic.

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"Meetings come to an end,
but learning never stops.
PWJ keeps you going all year long."

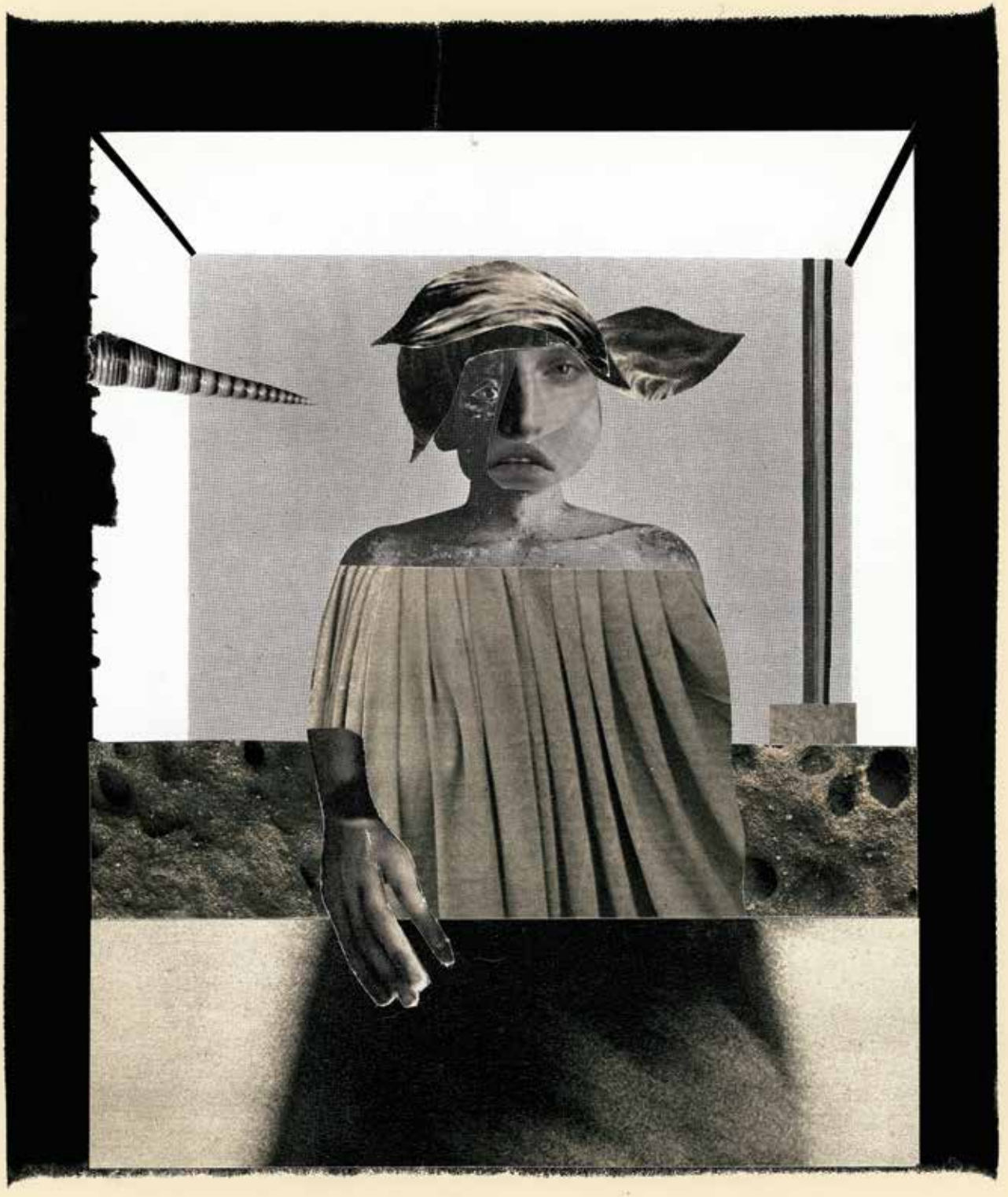
—**Michael R. Clark** MD, MPH, MBA

SCULPTURE BY EMMA CASTER-DUDZICK

trauma:

the lesion that doesn't show up on the scan

By Christian **Washburn** PSYD **&** Melissa **Fledderjohann** PSYD



abstract!

Childhood traumas. For the purposes of this article, "trauma" will be referring to *psychological* trauma, or adverse childhood events (ACE). ACEs—physical, sexual, and emotional abuse; neglect; and household dysfunction—are prevalent within our communities and can lead to a wide range of mental and physical problems, including chronic pain. Assessment and treatment of trauma, however, are often ignored in medical facilities. ACEs are a toxic form of stress that impacts biological foundations. The original Adverse Childhood Experiences research and subsequent studies signified the need to acknowledge and treat trauma. This article explains ACEs and chronic pain, the neurobiology of ACEs, treatment of trauma and chronic pain, and discusses provider education.

introduction and background

We, the authors of this article, are licensed psychologists at a pain management clinic, with challenging patients from both a medical and psychiatric perspective. Our interdisciplinary team stresses that patients need to develop internal resources to manage pain and mood as well as define meaning. While our program is ideal for treatment of chronic pain conditions and despite the team's best efforts, some patients did not improve. It was noted that these patients had a history of trauma, which needed to be addressed.

Individuals who work in the healthcare industry must learn to acknowledge how trauma impacts patients' lives. Patients who have a history of trauma also have histories of chronic medical diseases. It must be noted that it is difficult to manage and treat chronic downstream diseases (chronic pain) if upstream problems (trauma) are ignored.

Everyone experiences stress, and stress impacts pain. Stressors have significant effects on mental health, and most providers will not argue this point. However, it was not until Dr. Vincent Felitti addressed the relationship between childhood trauma (early stressors) and adult diseases that attention was paid. For the first time, Dr. Felitti and his colleagues shed light on the role trauma plays in developing a whole host of physical illnesses, such as diabetes, heart disease, and chronic pain. The ACE *study* was coined as probably the *most* important public health study you never heard of.[1] In the field of psychiatry, the ACE study is as groundbreaking as penicillin.

ACEs and chronic pain

In 1998, Dr. Felitti and his colleagues released the first study of adverse childhood experiences and their toxic form of stress and how it impacts biological foundations. It examined the relationship between several adverse childhood experiences—neglect, household dysfunction, and physical, sexual, or emotional abuse—and adult health consequences.[2] Their research found that two-thirds of participants experienced some form of childhood abuse. In addition, the researchers found a dose-dependent relationship between ACEs and negative health outcomes. Following the Felitti study, other researchers found additional health consequences, such as liver disease, COPD, lung cancer, STDs, and mortality. Participants who reported multiple ACEs also had functional limitations, poor self-rated health, and premature mortality.[3]

In addition, studies demonstrated a strong graded relationship between ACEs and alcohol and substance use. ACEs correspond to early initiation of use,[4] problematic drinking into adulthood,[5] and increased odds of binge and heavy drinking.[6] Additionally, ACEs correlate with lower age of initiation of opioids, increased overdose of opioids, and recent intravenous drug use related to opioids.[7] There is currently an opioid epidemic, and ACEs likely are contributing to it.

Chronic pain is one of the ways childhood trauma manifests in the body, and chronic pain patients have doubled rates of trauma compared to the general population[8]:

90%
of women with fibromyalgia have a history of trauma[9]

66%
of women with chronic headaches have a history of physical or sexual abuse[10]

60%
of women with arthritis have a history of trauma[11]

58%
of migraine sufferers (male or female) have a childhood history of physical or sexual abuse[12]

56%
of patients with chronic pelvic pain have a history of trauma[13]

Childhood stress and current psychosocial stress increases the risk for developing chronic centrally maintained pain.[14]

neurobiology of ACEs

ACEs play a role in contributing and maintaining chronic pain through various mechanisms in the brain and spinal cord. ACEs wound at a foundational level and research shows how inflammatory markers (eg, interleukin-6 and C-reactive protein) are promoted after exposure to trauma(s).[15]

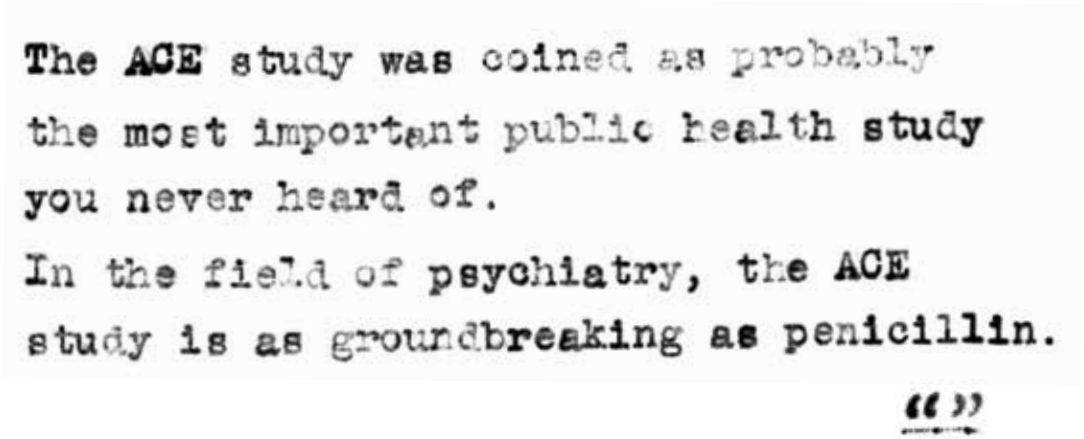
The nervous system is adaptive and change based on experiences. During a stress response, the amygdala sends signals to the hypothalamus (the command center) that in turn regulates the body's autonomic nervous system to cause the fight, flight, or freeze response. Additionally, the hypothalamic-pituitary-adrenal axis (HPA) is activated and various stress hormones are released (cortisol and norepinephrine). Once the threat passes, cortisol levels decrease, and the parasympathetic nervous system calms the stress response.

There are 3 main areas in the brain that are involved in developing and maintaining trauma. These brain areas include the prefrontal cortex (logical thinking, planning, controlling attention, and integrating memories into stories), amygdala (fear response), and the hippocampus (storage and retrieval of memories, which are especially sensitive to stress).[16] Over time, high levels of cortisol damages the HPA axis, medial prefrontal cortex, hippocampus, and amygdala.[17] The central nervous system is especially sensitive during childhood, and damage to it in childhood can later lead to difficulty with planning, problem solving, self-regulation, and emotional regulation. Research has shed light on the role of trauma in accelerating the aging process by shortening telomere lengths.[18]

treatment of trauma and chronic pain

Prior to discussing treatment, it is important to clarify the difference between post-traumatic stress disorder (PTSD) and trauma.

PTSD is a mental health disorder resulting from experiencing or witnessing a life-threatening event. In order to meet criteria for PTSD, patients must have had exposure to actual or threatened death, serious injury, or sexual violence. Patients also have to have intrusion symptoms (eg, recurrent nightmares), avoidant symptoms, negative alteration in cognitions and mood related to the event(s), and alterations in arousal and reactivity associated with the event(s).[19] PTSD is diagnosed by licensed mental health professionals, and it can take up to several visits before clinicians make a formal diagnosis. Patients in healthcare settings may never be formally diagnosed with PTSD, even if they meet criteria. Also, there are patients who do not meet criteria for PTSD but still harbor the ill effects of childhood trauma. Chronic physical illnesses, especially chronic pain, may be one way trauma manifests in the body while PTSD is one way trauma manifests in the brain.



Treating trauma in the setting of chronic pain entails **2 pathways:** top-down vs bottom-up approaches. **Top-down approaches** include traditional psychotherapy and medications because they work on cognition. Evidenced based psychotherapies include cognitive processing therapy (CPT),[20] eye-movement desensitization and reprocessing (EMDR),[21] and prolonged exposure (PE).[22] Medications include SSRIs and SNRIs. Similar to chronic pain, we cannot expect a medication to directly treat the trauma itself. While there are medications to manage symptoms (eg, prazosin for nightmares), the treatment needs to include the biopsychosocial model for both the mind and body. Additionally, patients with a history of trauma may see a specialized trauma therapist. Licensed therapists include clinical social workers, marriage and family therapists, psychologists, and psychiatrists. Mental health professionals who work with patients who have trauma require extra training outside of traditional education.

Bottom-up approaches are mindful-movement therapies that target the central nervous system. Examples of therapies include yoga, tai-chi, biofeedback, mindfulness meditation, progressive muscle relaxation, and physical therapy. These techniques are somatic experiences that bypass the thinking, rational parts of the brain, and help patients reprocess trauma nonverbally. Mindful meditation, in particular, helps mitigate the negative effects of trauma.[23,24] This treatment works through influencing the parasympathetic pathway in the nervous system.[25]

Mindfulness meditation and other relaxation therapies are especially important to the treatment of a dysregulated CNS. Relaxation includes diaphragmatic breathing, progressive muscle relaxation, guided imagery, and mindfulness meditation. Literature reveals that when patients engage with relaxation techniques, genes related to inflammation switch off and reduce risk of inflammatory diseases.[26] Relaxation therapies switch on the following genes: genes linked to mitochondrial functioning, genes linked to the maintenance of telomeres, and genes linked to the release of insulin.[27]

Another important aspect to treatment is to teach patients to appropriately feel bodily sensations. Chronic pain patients are on a spectrum between disconnection from bodily sensations to being hyperfocused on bodily sensations. For example, patients who are disconnected from their bodies have a difficult time describing their pain sensations and are preoccupied with the “just fix it” approach. These patients may be employed in labor intensive jobs and are used to “pushing” through the pain. Patients who are hyperfocused on bodily sensations may have full-body pain or their pain locations change from visit to visit. These patients’ subjective pain ratings are often incongruent to outward manifestations of pain or their pain pathologies. On either side of the spectrum, chronic pain patients learn to not trust their bodies and end up developing a dysfunctional relationship with the body. The goal is to teach patients to establish an accurate relationship with their body and reprocess trauma nonverbally. This goal is also accomplished through mindful movement, meditation, and physical therapy.

Finally, a larger goal to treatment of chronic pain and trauma is to teach patients to shift from an external to an internal locus-of-control. For example, patients shift from looking for a medication or surgery to practicing yoga and mindfulness daily. Daily practice of these treatments helps patients get their own resiliency back online as well as rediscover their own internal resources.[28]

provider education

While treating chronic pain and trauma requires expert training, patients benefit from their providers’ ability to acknowledge trauma. Education alone can be therapeutic and help patients decrease poor self-efficacy and blame. Many patients express relief when hearing how ACEs impact their pain and that the pain is not their fault. Finally, patients need to hear that they can recover from trauma and chronic pain. This discussion can start the healing process.

> The central nervous system is especially sensitive during childhood, and damage to it in childhood can lead to difficulty with planning, problem solving, self-regulation, and emotional regulation.
>
> “”

Various barriers may prevent clinicians from assessing trauma—time constraints, fear of causing re-trauma, vicarious traumatization, not knowing how to respond, and more immediate needs and concerns in the moment.[29] There are several basic principles to assessing trauma, which all include asking open-ended questions. Read and Fraser noted that if not assessed initially, trauma is usually not assessed later in treatment.[30] Assessment should come naturally through a psychosocial history. **Examples include[29]**:

Tell me about your childhood

?

How did you get along with your parents

?

How was discipline dealt with

?

Were there times you felt unsafe as a child

?

Providers need to be aware that it is unrealistic to “fix” the trauma and that the goal is to validate the patients’ experiences. The use of empathy is significantly potent.[31] Hammersley and Rudegeair (2007) recommend checking for safety of the patient and reporting to appropriate authorities as needed.[32] It is important to understand mandating reporting rules in advance. Notably, it is worth attending trainings as well as additional readings on assessing for trauma. Finally, if possible, consider hiring mental health professionals to help manage the assessment or treatment afterwards.

conclusion

Individuals who work in the healthcare industry must learn to acknowledge how trauma impacts our patients’ lives. Patients who have a history of trauma also have histories of chronic medical diseases, including chronic pain. It is difficult to manage and treat chronic downstream diseases if upstream problems are ignored. Dr. Felitti and his colleagues were the first to discover the role of trauma in perpetuating chronic physical diseases. It is important to know that trauma leads to a dysregulated central nervous system, and medications alone will not address this problem. There is hope for treatment, which includes several top-down and bottom-up approaches. However, education also can be therapeutic. Healthcare employees, at any level, can help patients find their voice and provide them with options for treatment for chronic pain and trauma. ◘

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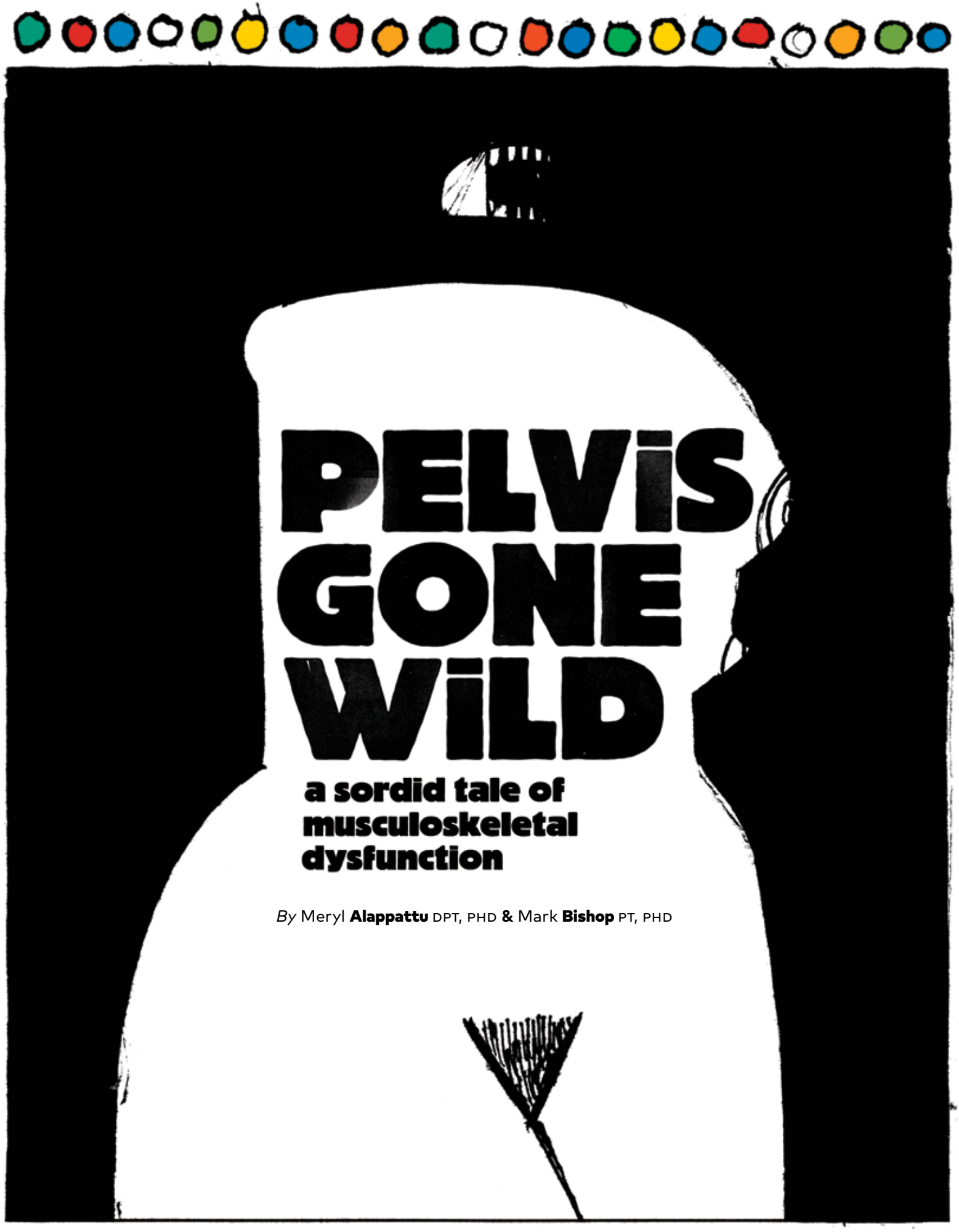
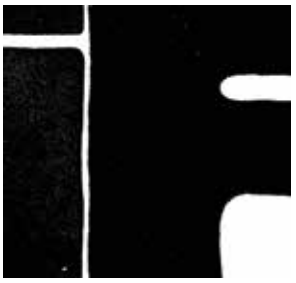


PELVIS GONE WILD

a sordid tale of musculoskeletal dysfunction

By Meryl **Alappattu** DPT, PHD **&** Mark **Bishop** PT, PHD



you went to a conference of women with vulvodynia and talked to each attendee, you will likely find that each woman's pain, how it affects her personally, physically, and sexually may be very different despite the fact that all of these women were diagnosed with ***vulvodynia.***

“ ”

abstract: Persistent or chronic, nonmalignant pelvic pain is a debilitating, costly condition described as a "clinical nightmare" by health professionals[1] with primary care prevalence estimates comparable to low back pain, migraine, and asthma.[2] The direct annual costs of physician visits alone related to pelvic pain are estimated exceeding $167 million dollars.[3] Women with pelvic pain report sleep disturbances, depression, anxiety, and limitations in physical mobility.[4,5] Like other pain conditions, pelvic pain is not homogenous. If you went to a conference of women with vulvodynia and talked to each attendee, you will likely find that each woman's pain, how it affects her personally, physically, and sexually may be very different despite the fact that all of these women were diagnosed with "vulvodynia." Many report a variety of symptoms, including the presence of pelvic pain with dyspareunia (pain with sexual intercourse) or pelvic pain with dysmenorrhea (pain with menstruation), for example, rather than a single issue of dysmenorrhea or dyspareunia alone. Physical therapists have long been recognized for their role in the management of other musculoskeletal pain conditions, including spinal and extremity pain. Over the last several decades, a specialty practice of physical therapists includes those who work closely with physicians, psychologists, nurses, and counselors to manage musculoskeletal aspects of pelvic pain. The information in this article provides both referring providers and patients with an idea of what to expect as part of the initial examination and subsequent treatment interventions performed by a physical therapist.

THE BEGINNING

Where does this sordid tale of musculoskeletal dysfunction begin when the pelvis goes wild? Despite differences in the suspected or apparent pathophysiology of different pelvic pain diagnoses, they share common pain-specific features, including sexual pain,[6-9] painful menstruation,[10,11] and pain of the pelvic floor muscles and surrounding tissues.[7,12-14] This pain of the pelvic floor muscles and surrounding tissues is considered musculoskeletal pelvic pain. Simply put, musculoskeletal pain is pain of the muscles of the pelvic cavity. These muscles include the pelvic diaphragm (aka, the pelvic floor muscles), obturator internus and piriformis, and muscles of the urogenital triangle. The pelvic diaphragm is comprised of the levator ani and coccygeus muscles while the urogenital triangle is comprised of the bilateral bulbospongiosus and ischiocavernosus muscles and the bilateral deep and superficial transverse perineal muscles. These muscles support the pelvic viscera, and play key roles in urination, defecation, and sexual function. While genitalia differ, both males and females share these internal and external muscles.

However, dysfunction need not originate solely from pelvic musculature to be perceived as pain in the pelvic region. Dysfunction in the neighboring abdominal, lumbar, hip, and/or sacroiliac regions may also refer pain to the pelvis, groin, and buttocks.[15] Conversely, when assessing a patient with pain in these neighboring regions, it may be necessary to include screening questions specific to pain or dysfunction of the pelvic floor muscles, including pain with intercourse and changes in bowel or bladder habits.

Sexual pain, or dyspareunia, is a common problem for women with musculoskeletal pelvic pain. Dyspareunia affects 6.5% to 45% of older women and 14% to 34% of younger women.[16] What impact does sexual pain have on women and their sexual function? Imagine that having sexual intercourse is so painful that it leaves you feeling debilitated and in pain for hours or even days following intercourse. Imagine that because it's so painful, the last thing you want to do is have intercourse and you avoid it at all costs. Now imagine the stress this puts on your relationship with your partner and how the whole situation might make you feel—anxious, depressed, and lonely. Women who experience pelvic pain during sexual intercourse may think about and react to intercourse differently than women without pelvic pain. This is hardly surprising. Sexual pain is associated with significant fear and/or anxiety that may be present before, during, or after penetration. Previous work suggests that this distress imparts physiological and biological changes associated with sensitization of pain processing pathways[17,18] which likely contributes to both local (ie, vaginal)[19,20] and widespread[21,22] pain sensitivity in women with pelvic pain. As a result of this actual or anticipated pain, women with sexual pain avoid intercourse[23,24] and report higher levels of pain related psychological distress related to intercourse, including catastrophizing,[22-24] fear,[25,26] and anxiety.[27]

COMMUNICATION

Asking a patient about the pain she experiences during intercourse may be difficult and somewhat taboo and, similarly, patients don't always offer such information without prompting. Therefore, if providers believe or suspect that a patient's pelvic pain may be musculoskeletal in nature, it's critical to explicitly ask about sexual pain. Educating patients on the basic musculoskeletal anatomy of the pelvic region, and its proximity to surrounding areas (eg, low back, sacroiliac joint, hip) may be an appropriate way to frame these questions or transition into the topic of sexual function and pain without being perceived as intrusive. Questions that should be asked directly include:

▼

"Are you having pain during sexual intercourse?"

▼

"Please rate the [average, worst, and least] pain intensity you experience with intercourse from 0 to 10, with 0 being no pain and 10 being your worst imaginable pain."

▼

"How long have you had this pain with sexual intercourse?"

▼

"How would you describe this pain?"

▼

"Is your pain with deep or superficial penetration?"

▼

"How long does your pain last following intercourse?"

▼

"Have you tried anything (eg, lubricant, medication, ice) that lowers your pain, either during intercourse or after intercourse?"

▼

"How is this pain impacting your relationship with your partner?"

A patient's responses to these questions will provide insight into the location of pain, pain intensity and quality, positions that cause pain, and the impact of this pain. These responses can be used to direct treatment, including consulting with and referral to other healthcare providers.

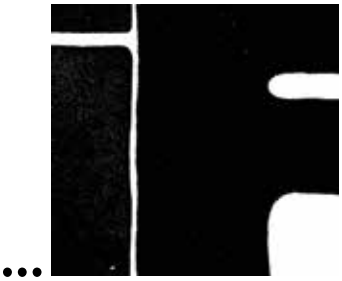
TREATMENT

Existing treatment guidelines for pelvic pain call for multidimensional care.[28,29] Inclusion of physical therapists on the care team of patients with pelvic pain is growing, given the presence of muscle pain, altered neuromuscular control, and pelvic floor muscle weakness in these women. Physical therapists are experts in musculoskeletal dysfunction and pain. In addition to entry level training in orthopedic musculoskeletal dysfunction, physical therapists who work in pelvic rehabilitation undergo specialized training in the assessment and management of musculoskeletal pelvic pain. Treatment by a physical therapist for pelvic pain is largely directed at dysfunction and pain in the pelvic floor and surrounding soft tissues,[30] and may include patient education, manual therapy, graded exposure, and/or general aerobic and local (ie, pelvic floor) exercises. Finally, as best practice and consistent with clinical guidelines, physical therapists collaborate with other members of the healthcare team, including physicians, clinical psychologists, and sexual therapists.

What does a physical therapist musculoskeletal evaluation of a patient with pelvic pain look like? And why should you care? As healthcare providers, we have an important role in shaping patients' expectations of healthcare and other healthcare providers. Most patients have no idea physical therapists should be included as part of the healthcare team managing their pain, despite multiple clinical guidelines recommending that physical therapists be included in the multidisciplinary care of patients with pelvic pain. This specialty area of the physical therapist practice is established and providers' and patients' awareness continues to grow. If you refer or recommend a patient to a pelvic physical therapist, it's important to give that patient an idea of what to expect from the assessment.

THE PHYSICAL THERAPIST EXAM

A physical therapist's musculoskeletal evaluation of a patient with pelvic pain begins with a patient centered interview to obtain information about the duration, description, and location of pain, the type of onset (triggering and/or traumatic event or insidious onset), frequency of pain, triggering activities or movements, the patient's medical and surgical history, and any other areas of bodily pain. The physical therapist will also obtain from the patient the patient's goals and expectations with physical therapy. During the intake, it is also appropriate for the PT to ask the patient if she has previously experienced sexual or physical abuse. If the patient reports a history of abuse, the physical therapist may refer the patient to a provider with the training to address this history. In addition to the questions in the patient interview, the physical therapist may also ask patients to complete standardized questionnaires related to their pain. The responses to these measures, in addition to the goals identified by the patient, will be used by the physical therapist to identify benchmarks for success in treatment. These questionnaires should be



providers believe or suspect that a patient's pelvic pain may be musculoskeletal in nature, it's critical to explicitly ask about ***sexual pain.***

readministered throughout the episode of care and at discharge from the episode of care to obtain a complete picture of the patient's progress with therapy.

The clinical examination will consist of screening the hips, low back, and sacroiliac regions for pain, strength, flexibility, and any reproduction of symptoms. After obtaining consent from the patient, the physical therapist will perform a musculoskeletal pelvic examination consisting of **1 visual examination of external tissues to evaluate scar tissue, erythema, or discoloration; 2 palpation of the muscles comprising the urogenital triangle, the vaginal introitus, and the mucosa overlying the deeper pelvic diaphragm; 3 ability to contract and relax the pelvic floor muscles with a pelvic floor muscle contraction**. The purpose of palpation to these muscles is to identify the intensity and quality of pain with palpation and to determine if palpation reproduces the pain for which the patient is seeking care. See Apte et al (2012)[15] for a more thorough overview of the physical therapist pelvic examination.

It's important to note that while this pelvic examination is commonly performed at the initial evaluation, it is not required to be done then, particularly if the patient is uncomfortable or overly anxious about the exam. As with any clinical examination, obtaining informed consent from a patient is required prior to initiating the examination, and the patient should know that she can ask for the examination to stop at any time. It's also important to share with patients that the physical therapist pelvic examination is not the same as a gynecological pelvic examination. As with gynecological pelvic examinations, patients will be draped for modesty. However, patients are positioned supine with their knees bent and feet flat on the table rather than in stirrups, and physical therapists do not use speculums.

The physical therapist will also complete a systems review, which is a brief assessment of the cardiovascular/pulmonary, integumentary, musculoskeletal, and neuromuscular systems and it is related to identifying red and yellow flags. Red flags include signs and/or symptoms that may mimic common musculoskeletal pain conditions but are associated with serious medical pathology. Yellow flags, identified through self-report questionnaires and/or during the patient interview, may indicate negative beliefs or expectations of treatment for pain, including treatment offered by a physical therapist. Yellow flags may also indicate high levels of emotional distress or difficulty coping with the pain for which the patient is seeking care. The presence of red flags warrants a referral to a licensed physician trained to manage such conditions. Yellow flags may also warrant a referral to licensed mental health providers, including clinical psychologists or counselors, and their presence may

affect a patient's prognosis with physical therapy. Any indication of clinical depression or psychopathology also warrants a referral to a licensed mental health provider as these conditions are outside the scope of physical therapist practice. The systems review, along with the information obtained from the interview, tests, and measures, and clinical examination will allow a physical therapist to determine the patient's physical therapy diagnosis, prognosis for physical therapy, and the plan of care. The plan of care may involve any of the following:

▼

Management of pelvic pain for a predetermined frequency and duration with a plan for treatment interventions

▼

Referral to another provider if the symptoms are not musculoskeletal in nature or if the therapist believes the presence of red or yellow flags contraindicate physical therapist care

▼

Referral to another provider for comanagement the patient's pain

Patients are reassessed at every visit and the plan of care has the potential to change if the patient's symptoms fail to improve or worsen.

CONCLUSION

Where does this sordid tale end? Musculoskeletal pelvic pain is a common problem in women with persistent pelvic pain. This pain is also associated with sexual dysfunction and negative impacts on mood and psychological well-being. Providers who treat women with pelvic pain must be explicit in asking about the impact of pain on sexual and physical function and psychological and emotional well-being. Best practice for caring for women with pelvic pain involves a multidisciplinary team that addresses the medical, psychological, physical, and sexual consequences of pain. Communication between all members of the team is important to evaluate the patient's progress and identify potential gaps in treatment. To locate a physical therapist who specializes in pelvic health, the American Physical Therapy Association Section on Women's Health PT Locator is available for providers and members of the public.[31] ◘

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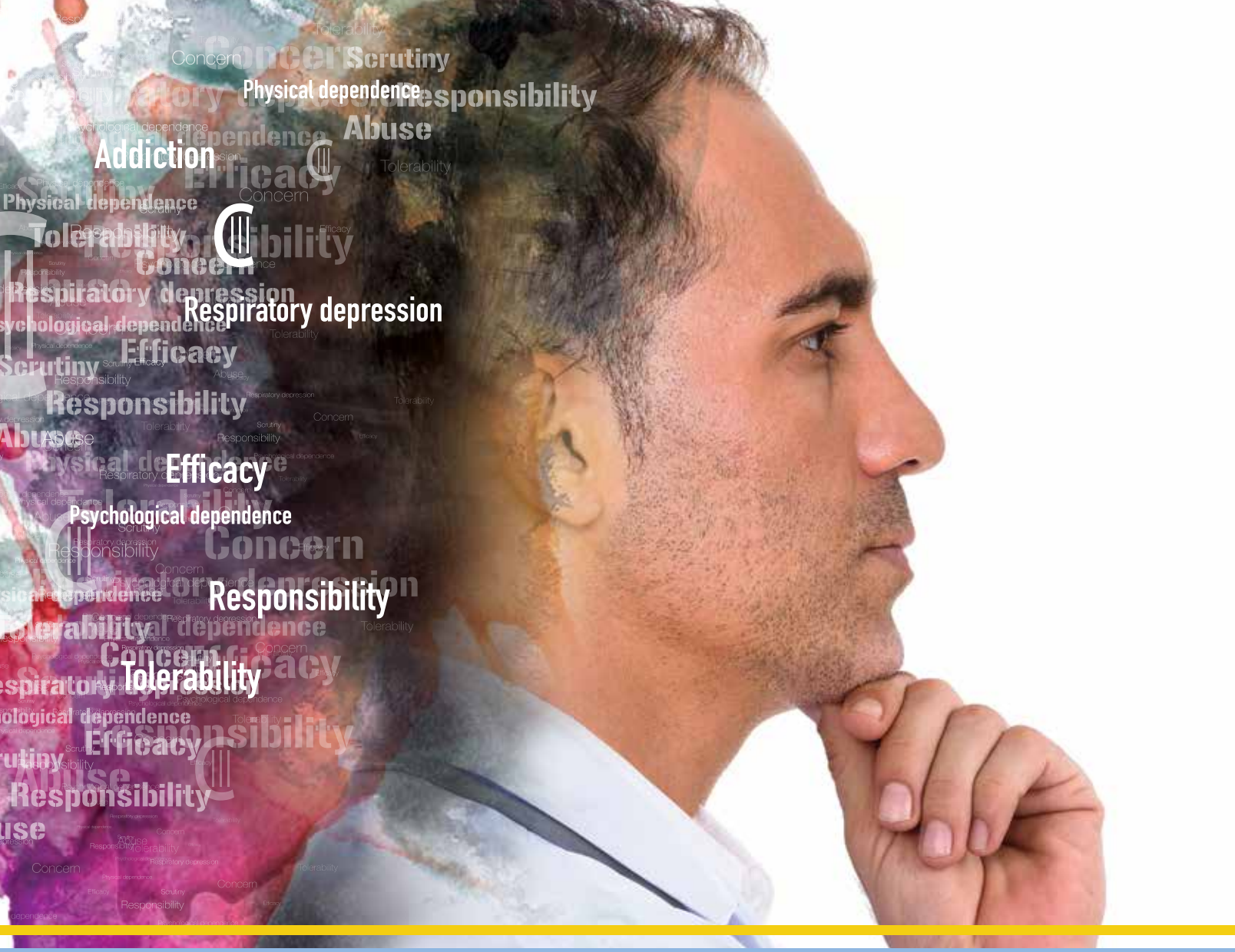
where does this sordid tale end?



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.

BELBUCA®
(buprenorphine) Buccal Film
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg

A Responsible Choice

When managing chronic pain*...

RETHINK RELIEF

BELBUCA® is the first and only Schedule III long-acting opioid that uses novel buccal film technology to deliver buprenorphine for appropriate patients living with chronic pain[1]*

- **Proven efficacy and sustained chronic pain* relief[1]**
- **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.

BELBUCA®
(buprenorphine) Buccal Film
75 • 150 • 300 • 450 • 600 • 750 • 900 mcg

Rx Only

Printed in USA. BEL-0060.1 January 2018

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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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THE 411 ON NONPRESCRIPTION ANALGESICS: WHEN TO HOLD 'EM, WHEN TO FOLD 'EM

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INTRODUCTION

Nonprescription, or over-the-counter (OTC), analgesics are the most frequently used of all OTC products. Over 80% of adults have used OTC analgesics in the past year and approximately 20% use them on a weekly basis.[1,2] Since these medications are available without a prescription and can be found anywhere from your pharmacy to a vending machine, they are often (and unsurprisingly) perceived as safe. These are medications that cause side effects, drug interactions and, in certain patient populations, should be avoided altogether. To make matters worse, 50% of patients who use OTC analgesics do not read the labels of these products.[3] As a result, patients often end up exceeding recommended doses and using combinations of medications that magnify the risk of adverse effects. Given the ubiquity of these products, it is essential that patients and healthcare providers alike are well educated on the selection, administration and self-monitoring of nonprescription medications.

CASE 1. HEADACHE

Let's meet our first patient. Jason is a 26-year-old African American man who presents to his pharmacy asking for advice on how to treat the "relentless" headache he has had for the past several days. Jason recently graduated from law school and is studying furiously for the bar exam. He describes the pain as bilateral, extending over the top of his head and the base of his skull. He says the pain is constricting and feels like his hat is too tight. He states the pain evolved gradually over 4 to 6 hours and has been present for 2 days. He denies any throbbing sensations, pressure behind his eyes or face, and the pain is not worsened by light or sound. He denies having chronic headaches but notices a pattern of headache when he is stressed and anxious (like now). He reports having no chronic medical conditions or allergies. How can we best help Jason? **What are our options?**

a Recommend a nonpharmacologic intervention such as meditation

b Recommend acetaminophen 1000 mg by mouth every 6 hours

c Recommend nonprescription ibuprofen but advise the patient to take the prescription dose (800 mg by mouth 3 times daily)

d Contact Jason's primary care practitioner to get an emergency supply of oxycodone/acetaminophen

Acetaminophen

Acetaminophen (Tylenol®) is an analgesic and antipyretic medication indicated for treatment of fever and mild-to-moderate pain. Although acetaminophen has been around for quite a long time (it was discovered in 1880s and introduced to the US market in 1955), its mechanism of action is complex and is still being researched and debated. There are multiple potential mechanisms of action including peripheral (cyclooxygenase [COX] inhibition) and central (COX, serotonergic descending neuronal pathway, L-arginine/nitric oxide pathway, endocannabinoid system) antinociceptive processes.[4]

Acetaminophen is usually well tolerated, with the most common side effects being nausea, vomiting, and headache. Although rare, acetaminophen is also associated with severe skin reactions, including acute generalized exanthematous pustulosis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. More controversial are the risks of hyperkinetic offspring and childhood asthma when used during pregnancy.

Acetaminophen has a dose-dependent risk of hepatotoxicity and is the leading cause of acute liver failure in the US.[5,6] According to the FDA, the total daily dose of acetaminophen should not exceed 4 grams due to the risk of hepatotoxicity **(see Table 1)**. However, the manufacturer recommended maximum daily OTC dose ranges from 3 to 3.9 grams depending on the individual product (eg, Tylenol Regular Strength, Tylenol 8 Hr Arthritis Pain, Tylenol Extra Strength, etc). Due to an increased risk of acetaminophen-induced hepatotoxicity, acetaminophen should be used with caution in patients taking other hepatotoxic medications and those who drink ≥3 alcoholic beverages/day. In patients with less severe hepatic impairment, the total daily dose should not exceed 2 grams. Repeatedly exceeding the recommended total daily dose, using multiple acetaminophen-containing products, and concomitant alcohol use increase the risk for developing acute liver failure.[5]

Early symptoms of acetaminophen toxicity include nausea, vomiting, and abdominal pain; however, these symptoms are not always present. In mild-to-moderate toxicity, there may be increases in plasma aspartate aminotransferase and alanine aminotransferase which can range from mild to marked and typically peak 2 to 3 days postingestion. Signs of severe hepatotoxicity include coagulopathy, hepatic encephalopathy, renal injury, coma, hyperglycemia, and lactic acidosis.[7]

Table 1. Oral nonprescription analgesics[7,12-14]

Medication	Usual Adult Dosing/ Maximum Daily OTC Dose (MDD)	Available Dosage Forms	Comments
Acetaminophen (Tylenol®)	325–1000mg Q4–6H FDA MDD: 4g/24H Manufacturer MDD: 3–3.9g/24H*	Tablets (IR/ER), capsules, suspensions, elixirs, solutions, rectal suppositories	Lacks anti-inflammatory effects of NSAIDs; no adverse effects on gastric mucosa or platelets; preferred in elderly patients
Ibuprofen (Motrin®)	200–400mg Q4–6H MDD: 1.2g/24H	Tablets, capsules, suspensions	
Naproxen sodium (Aleve®)	IR: 220mg Q8–12H MDD: 660mg/24H	Tablets (regular and enteric coated), capsules	
Aspirin (Ecotrin®, Bayer®)	325–650mg Q4H MDD: 4g/24H	Tablets (regular and enteric coated), rectal suppositories	Binds irreversibly to COX-1 and COX-2; rectal bioavailability ≈ 60%

*Manufacturer recommended maximum dosage based on individual product; IR: Immediate release; ER: Extended release

Given that acetaminophen is well tolerated and has few drug-drug interactions **(see Table 2)**, it is the preferred analgesic in the elderly. Acetaminophen does not affect platelet function like the NSAIDs, therefore it is also preferred in patients taking warfarin or other anticoagulants. However, 2 prospective, randomized, double-blind, placebo-controlled studies have concluded that long-term concurrent use of acetaminophen at doses of 2 to 4 grams daily for 4 weeks may increase the INR (International Normalized Ratio, or how long it takes blood to clot) and risk of bleeding.[8,9] Therefore, it is suggested that the maximum total daily dose of acetaminophen in patients taking warfarin should be 2 grams; for patients requiring >2 grams/day of acetaminophen, more frequent INR monitoring is recommended.[10]

Believe it or not, acetaminophen is found in over 600 prescription and OTC products. In order to prevent an unintentional overdose, patients must be educated to always read the label of their medications and to inform their healthcare providers of all the medications they're taking. As the most accessible healthcare provider, pharmacists are a valuable resource for patients seeking guidance regarding whether acetaminophen is a safe option.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Nonprescription NSAIDs include aspirin (Bayer®, Ecotrin®), ibuprofen (Motrin®, Advil®), and naproxen sodium (Aleve®), which have analgesic, antipyretic, and anti-inflammatory properties. NSAIDs act by inhibiting the COX enzymes COX-1 and COX-2. Inhibition of COX-2 prevents the conversion of arachidonic acid (AA) to prostaglandins E2 and I2 which are responsible for pain and inflammation. Inhibition of COX-1 prevents the conversion of AA to thromboxane (responsible for platelet aggregation) and prostaglandins in the gastric mucosa (responsible for inhibiting gastric acid).[11]

NSAID dosing information can be found in **Table 1**. The most common adverse effects associated with NSAIDs include nausea, dyspepsia, and epigastric pain.[12-14] These side effects can usually be mitigated by instructing patients to take NSAIDs with food or milk. NSAIDs carry a Black Box Warning for increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, and gastrointestinal (GI) events, including bleeding, ulceration, and perforation of the stomach or intestines. NSAIDs can also cause acute kidney injury, especially in patients with pre-existing renal dysfunction or those taking other nephrotoxic medications concomitantly. The **3 figures shown below** illustrate the adjusted relative risk of NSAID-related complications based on dose.[15-17] The low-medium dose includes ibuprofen ≤1200 mg/day (maximum recommended OTC dose) and naproxen 500 mg/day (less than maximum recommended OTC dose). As you can see, NSAID use increases the relative risk of GI, cardiovascular, and renal complications and the risk is dose-dependent. A commonly held belief is that these complications only occur with *chronic* NSAID use, but that is simply not the case. These serious complications can occur as early as 1 to 14 days of use, and they persist throughout the duration of use. Patient counseling should emphasize this point.[15-17]

NSAID Dose and Adjusted Relative Risk of:	Low-Medium	High Dose
Upper GI bleed and perforation	2.4	4.9
Cardiovascular complication and NSAID dose	1.2	1.6
Serious renal complications and NSAID dose	2.5	3.4

Strategies to prevent gastric mucosal damage in chronic NSAID users include use of proton pump inhibitors (PPI; eg, omeprazole, pantoprazole), histamine-2 receptor antagonists (eg, ranitidine, famotidine), and misoprostol. Use of COX-2 selective NSAIDs (eg, celecoxib; Rx only) or topical NSAIDs are other potential options. Studies have shown that use of naproxen plus a PPI provides equivalent GI protection as celecoxib.[18,19] Combination NSAID/PPI products such as Vimovo® (naproxen/esomeprazole) are currently available (Rx only) but are considerably more expensive than taking an NSAID and PPI separately. Risk reduction strategies should especially be considered in patients at an increased risk for NSAID-related GI toxicity, including those with a history of peptic ulcer disease or upper GI bleed, ≥65 years old, receiving hemodialysis, and concomitant use of anticoagulants, aspirin, corticosteroids, or selective serotonin reuptake inhibitors (SSRIs).[20]

NSAIDs and salicylates, including aspirin should generally be avoided in patients with the following:

- **Asthma or nasal polyps**
- **Chronic/recurrent GI ulcers**
- **Gout**
- **Coagulation disorder or anticoagulant therapy**
- **Hypertension**
- **Congestive heart failure**
- **Kidney disease**
- **History of allergy**
- **<12 years old (naproxen)**
- **≤15 years old with symptoms of viral illness (aspirin/salicylates)**

Given the sheer prevalence of NSAID use, we need to be vigilant in educating patients regarding their associated risks, including the fact that they can occur almost immediately. This is especially true for our elderly patients who we know are at a higher risk of NSAID-related adverse events and are more likely to be taking multiple medications. Clinically important drug-drug interactions involving NSAIDs are in **Table 2**.

Let's not forget about Jason! Does Jason have any exclusions to self-treatment? Using **Table 3**, you can see that Jason is appropriate for self-treatment. He is likely suffering from a tension-type headache and since he is not taking any interacting medications, you would be safe in recommending either acetaminophen or an NSAID for this patient (but at the OTC dose, ibuprofen not to exceed 1200 mg per day), making answer **B** from the multiple-choice question above the most appropriate option. Nonpharmacologic therapy, including relaxation exercises and physical therapy which emphasizes stretching and strengthening of head and neck muscles, may also be considered in conjunction with an OTC analgesic. Patients should be counseled to limit the use of OTC analgesics to 3 days per week to reduce the risk of developing medication overuse headaches.

> "...50% of patients who use OTC analgesics do not read the labels of these products. As a result, patients often end up exceeding recommended doses and using combinations of medications that magnify the risk of adverse effects."

Table 2. Clinically important drug-drug interactions with nonprescription analgesics[21,22]

Analgesic	Interacting Drug	Interaction	Action
Acetaminophen	Alcohol	Increased risk of hepatic dysfunction	Avoid concurrent use
	Warfarin	Increased INR	Limit acetaminophen dose to 2 g daily; closely monitor INR
	Isoniazid	Increased risk of hepatotoxicity	Avoid concurrent use; if not, limit dosage of acetaminophen and closely monitor hepatic function
NSAIDs	Anticoagulants	Increased risk of GI bleeding	Avoid concurrent use
	Alcohol	Increased risk of GI bleeding	Avoid concurrent use
	Bisphosphonates	Potential increased risk of GI toxicity	Avoid concurrent use
	Corticosteroids	Increased GI side effects, including ulceration and hemorrhage	Avoid concurrent use or consider use of a PPI for gastroprotection
	Methotrexate	Increased plasma concentration of methotrexate; increased risk of renal dysfunction and pancytopenia	Avoid NSAIDs with high-dose methotrexate (≥150 mg daily)
	SSRIs	Increased risk of bleeding	Avoid concurrent use
	Lithium	Increased steady state concentrations of lithium; increased lithium toxicity	Monitor lithium levels and signs/symptoms of lithium toxicity (eg, tremor, nausea/vomiting, renal insufficiency, ataxia, slurred speech, lethargy, and sedation). Interactions are less likely to occur with aspirin than they are with naproxen or ibuprofen
	Antihypertensives	Decreased efficacy of antihypertensive medication; increased risk of renal dysfunction (ACE inhibitors); increased risk of hyperkalemia (potassium-sparing diuretics and ACE inhibitors)	Monitor blood pressure and renal function; dose of antihypertensive medication may need to be increased.
	Thiazide and Loop Diuretics	Diuretics can cause fluid depletion, which increases the risk of renal dysfunction	Avoid concurrent use; if not, regularly monitor renal function
	Cyclosporine	Increased concentrations of cyclosporine; increased risk of renal dysfunction	Avoid concurrent use; if not, regularly monitor renal function
	Aspirin	Decreased antiplatelet effects of aspirin; additive risk of bleeding	Aspirin should be taken at least 30 minutes before or 8 hours after ibuprofen; use of acetaminophen is preferred in patients receiving aspirin

Table 3. Exclusions to self-treatment of adult headaches[23]

Severe head pain
Headaches that persist for 10 days with or without treatment
Last trimester of pregnancy
High fever or signs of serious infection
History of liver disease or consumption of ≥3 alcoholic drinks per day
Headache associated with underlying pathology (secondary headache), except for minor sinus headache
Symptoms consistent with migraine but no formal diagnosis

CASE 2. MUSCULOSKELETAL INJURY

Meet our second patient, Sally. Sally is a 68-year-old Caucasian woman with a past medical history of hypertension (uncontrolled), dyslipidemia, and osteoarthritis. She presents to her local community pharmacy with complaints of an aching back and is inquiring as to what she can take to "make the pain go away!" She states that since the weather was so beautiful on Saturday, she spent all day outside gardening. Then on Sunday, she babysat her toddler grandson and was constantly chasing him around and bending over to pick him up. Upon further questioning, she stated her pain was located in her mid-to-lower back, and she denied radiation elsewhere. When asked to describe what the pain *feels* like, she states it is "achy" and "sore." She rates her current pain severity as 5/10. She denies other signs and symptoms, including weakness. She reports having tried the ThermaCare® HeatWrap but has not experienced any significant relief. **What would you recommend for Sally?**

a Refer to a pain specialist for a trigger point injection

b Advise Sally to stay in bed for a week so her back can heal

c Contact Sally's primary care physician for an emergency 3 day supply of oxycodone/acetaminophen

d Recommend a topical counterirritant and gentle remobilization of the back

e Recommend OTC acetaminophen, or preferably a NSAID

Counterirritants

Counterirritants are a class of topical analgesics that exhibit a paradoxical pain relieving effect—that is, they produce a less severe pain to counteract a more intense one (your brain gets so confused!). These agents reduce pain indirectly by stimulating cutaneous receptors to induce sensations of cold, warmth, or even itching and distracting from deep-seated pain in muscles, tendons, and joints. There may also be a psychological component in the form of distraction.

Counterirritants can be grouped into 4 categories—Group A, B, C, and D—based on their precise mechanism of action **(see Table 4)**. The agents in Group A, which includes methyl salicylate, are rubefacients, they work by increasing blood flow. Group B includes camphor and menthol, which work by producing a cooling sensation. Group C includes histamine dihydrochloride and methyl nicotinate, which work by causing vasodilation. Finally, Group D includes capsaicin, which works by inciting irritation without rubefaction. For the treatment of acute pain, these agents should be applied no more than 3 to 4 times daily for up to 7 days. For chronic pain, capsaicin can be applied 3 to 4 times daily for the duration of pain. There are many different counterirritants available without a prescription, including IcyHot®, Biofreeze®, Salonpas®, and BENGAY®, to name a few.[23]

The most common adverse effects associated with counterirritants include skin irritation, rash, and erythema. Other potential adverse effects include blistering, thermal hyperalgesia, and systemic reactions. Systemic reactions are of particular

Table 4. Classification of counterirritants[23]

Group	Ingredients/Concentration	Mechanism of Action	Frequency and Duration of Use
A	Allyl isothiocyanate / 0.5% to 5% Ammonia water / 1% to 2.5% Methyl salicylate / 10% to 60% Turpentine oil / 6% to 50%	Rubefacients (redden skin, increase blood flow)	Apply no more than 3–4 times daily for ≤7 days
B	Camphor / 3% to 11% Menthol / 1.25% to 16%	Produce cooling sensation	Same as group A
C	Histamine dihydrochloride / 0.025% to 0.1% Methyl nicotinate / 0.25% to 1%	Cause vasodilation	Same as group A
D	Capsicum / 0.025% to 0.25% Capsicum oleoresin / 0.025% to 0.25% Capsaicin / 0.025% to 0.25%	Incite irritation without rubefaction; are as potent as group A ingredients	Acute pain: Same as group A Chronic pain: Apply 3–4 times daily for duration of pain

concern with products containing salicylates, as they can lead to salicylate toxicity. To reduce the risk of dermal adverse effects, patients should be educated on the following key points[23]:

- **If pain, swelling, or blistering of the skin occurs after application of a topical analgesic, patients should immediately discontinue use of the product and seek medical attention.**
- **Do not bandage the area tightly where the product has been applied.**
- **Do not use any heat where the product has been applied.**
- **Do not apply to wounded, damaged, broken, or irritated skin.**
- **Do not allow these medications to come in contact with the eyes, or inside the nose, mouth, or genitals.[23]**

When it comes to musculoskeletal pain, how do you know when self-treatment is appropriate vs when you need to refer the patient? Exclusions for self-treatment are listed in **Table 5**. Does Sally have any exclusions for self-treatment? No, she does not; however, she is elderly and has a history of uncontrolled hypertension. As we learned, NSAID-related GI, cardiovascular, and renal effects can occur almost immediately, not just with chronic use; therefore, avoiding NSAIDs is recommended. Instead, the patient could try acetaminophen, not exceeding 3 to 4 grams daily. A topical analgesic would be equally appropriate. For instance, you could recommend applying the Salonpas® original patch (methyl salicylate 6.3%, menthol 5.7%, and camphor 1.2%) to her back 3 to 4 times daily for up to 7 days. You would want to educate the patient not to use heat when she is using this medication. Gentle remobilization is important too; we don't want Sally taking to the bed for days on end.

Table 5. Exclusions to self-treatment of adult musculoskeletal pain[23]

Moderate-to-severe pain (pain score >6)
Pain that lasts >10 days; or >7 days after treatment with a topical analgesic
Increased intensity or change in character of pain
Pelvic or abdominal pain (other than dysmenorrhea)
Accompanying nausea, vomiting, fever, or other signs of systemic infection
Visually deformed joint, abnormal movement, weakness in any limb, or suspected fracture
Third trimester of pregnancy

Heat/Thermal Wraps

Heat/thermal wraps represent a very useful nonpharmacologic option for the treatment of musculoskeletal pain. Osteoarthritis guidelines recommend heat as adjunct treatment for pain and

> ...acetaminophen is found in over 600 prescription and OTC products. ...to prevent an unintentional overdose, patients must... always read the label...and to inform their healthcare providers of all the medications they're taking. ...pharmacists are a valuable resource for patients seeking guidance regarding whether acetaminophen is a safe option.

stiffness.[24] They may help reduce pain by increasing blood flow, and have been studied in the treatment of acute low back pain (<4 weeks in duration) with promising effects. In general, heat/thermal products can be applied for 15 to 20 minutes 3 to 4 times daily (regular heat). ThermaCare® products are an exception, as they can be worn for up to 8 to 12 hours (depending on the specific product). Of note, heat/thermal wraps should not be applied to recently injured (<48 hours) or inflamed areas. They should also not be used with other topical agents or over broken skin.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) units are a Class II Medical Device FDA-approved for the relief of pain associated with sore, aching muscles, joint pain, or chronic intractable pain. Both low frequency (LF) and high frequency (HF) TENS devices are available, and they are typically used for 15 to 30 minutes up to 3 times daily. These devices work by altering pain transmission and increasing production of natural endorphins. Three factors influence the efficacy of TENS: tolerance to repeated TENS, intensity of the stimulation, and electrode placement. Analgesic tolerance can occur with repeated application of TENS at the same frequency, intensity, and pulse duration. This can be mitigated by switching between LF and HF TENS within a single treatment session and by increasing the intensity of TENS daily as tolerated. Intensity is also critically important, therefore TENS should be applied at the individual's maximally tolerated intensity. In terms of placement, application of TENS at acupoints may be more effective than nonacupoint sites. Of note, HF TENS may be more effective in patients taking opioids. Overall, TENS devices are considered safe, noninvasive, patient friendly interventions, but they should not be used in patients with internal or attached medical devices (eg, pacemakers, defibrillators), pregnant patients, or in the pediatric population.[25]

So what's the best solution for our friend Sally's aching back? While the *most* correct answer to our multiple-choice question would be **D** (topical counterirritant and gentle remobilization), I'd argue answer **E** could be considered as well, either alone or in conjunction with **D**. Sally does have a history of uncontrolled hypertension, but that does not preclude her from using acetaminophen and a dose or two of an NSAID may alleviate her pain enough to get her up and moving.

Conclusion

Nonprescription analgesics can be helpful in treating moderate painful complaints, and in reducing fever. Patients should carefully review the indications and contraindications to therapy, and consult the pharmacist if there are questions about the appropriateness of a nonprescription medication. Patients should follow dosing instructions provided in the package labeling, and not exceed the recommended dose or duration of therapy. Also, patients should confirm they are not also taking acetaminophen or an NSAID in their prescription medications,

which could inadvertently cause them to exceed the maximum daily dose. As a final note, the pharmacist is always available to triage a pain complaint, and review the patient's medication profile to make recommendations and determine if a nonprescription analgesic is appropriate. ◘

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By Theresa **Mallick-Searle** MS, RN-BC, ANP-BC

THE GREEN-EYED MARTIAN

HEALTHCARE DISPARITIES IN PAIN MANAGEMENT

... 

ealth disparities [are defined] as differences among specific groups, in terms of incidence, prevalence, mortality, and burden of disease.

Studies have shown that there are many often overlooked risk factors—including race, socioeconomic background, and healthcare provider bias—for the undermanagement of pain in vulnerable patient population groups.[1-3] Disparities in pain management undermine affected individuals and their families, and contribute to higher rates of disability, increasing healthcare utilization and spending.[1,4] The overwhelming impact of undermanaged pain in selected patient groups has made it one of the key areas addressed in the National Pain Strategy.[5] This article focuses on defining the magnitude of the problem facing vulnerable groups, offers problem-solving solutions to overcoming disparities in pain management, and includes the utility of evaluating the mismanagement of pain as a medical error, applying a systems approach to resolve the problem.

defining the issue

The National Institutes of Health (NIH) and Institute of Medicine (IOM) define health disparities as differences among specific groups, in terms of incidence, prevalence, mortality and burden of disease.[6]

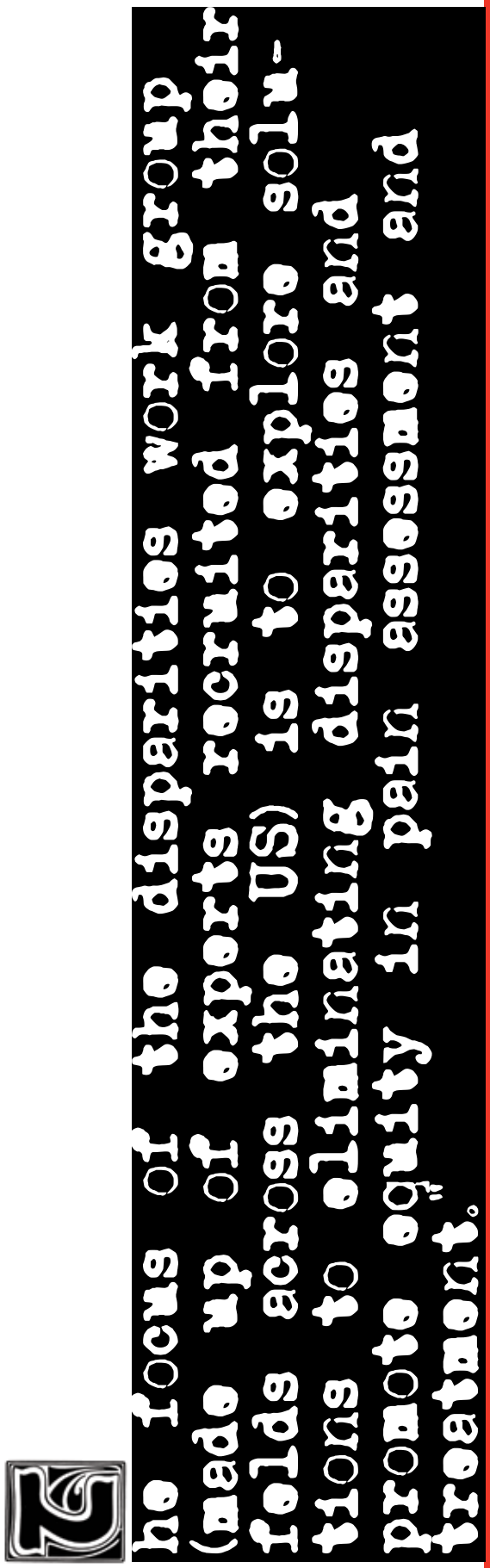
In the 2003 publication *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*, the IOM described healthcare inequalities in the delivery of services, including pain therapies, among racial and ethnic minorities being related in part to discrimination, biases, and stereotypes amongst providers.[7] These findings have direct legal and regulatory consequences on healthcare systems. The literature suggests that reasons for disparities in pain treatments are multifactorial.[8-15] Patient factors include cultural beliefs about the reporting of pain, low literacy, and a lack of understanding regarding "patient's rights" regarding pain treatments.[9-11] Provider factors include personal bias, fear of opioid prescribing, and lack of education regarding options available for pain treatment.[12] Healthcare systems or institutional factors include patient satisfaction, concerns over litigation, resources, education, and cost.[13-16]

The National Pain Strategy (NPS) is a comprehensive population health-level tactical approach to pain treatment. It was the product of a coordinated effort directed by the Department of Health and Human Services (HHS) and IOM for the development of activities to increase the recognition of pain as a significant public health problem; identify and reduce barriers to appropriate care; evaluate the adequacy of assessment, diagnosis, treatment, and management of acute and chronic pain across the population; and improve pain care research and education.[3] The recommendations of the NPS are meant to create change in the issues mentioned above through the engagement of various stakeholders (patients, healthcare professionals, the public, government), ultimately to improve pain management in the community. The **6 key areas** addressed in the NPS are **1 population research, 2 prevention and care, 3 disparities, 4 service delivery and payment**, **5 professional education and training,** and **6 public education and communication.**[5] Although all 6 key areas hold importance in the improvement of pain education and treatment, this article will focus on only the work of the NPS surrounding the understanding and management of disparities.

The focus of the disparities work group (made up of experts recruited from their fields across the US) is to explore solutions to eliminating disparities and promote equity in pain assessment and treatment. The NPS recommends efforts aimed at

- **Increasing understanding of the impact of bias and supporting effective strategies to overcome it**
- **Increasing access to high-quality pain care for vulnerable population groups**
- **Improving communication among patients and health professionals**[5]

The working premise is that "Pain is more prevalent or disabling and/or care is inadequate in certain vulnerable populations."[5]



THE NATIONAL PAIN STRATEGY: 4 OBJECTIVES

1

Reduce bias and its impact on pain treatment by improving the understanding of its effects, and supporting strategies to overcome it.

- *The accomplishment of these goals requires*: support of key stakeholders including Agency for Healthcare Research and Quality (AHRQ), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH).
- *The collaborators and investigators are responsible for*: working to meet the established metrics of identifying knowledge gaps on the effects of provider bias, and implementation of practices to minimize these effects, include professional medical organizations and other providers involved in the care of patients with pain, patient advocacy organizations, state and federal policymakers, along with individuals living with pain.

2

Facilitate communication among patients and healthcare providers.

- *The accomplishment of these goals requires*: support of key stakeholders including those mentioned above, as well as Administration for Community Living (ACL) and Office of the Assistant Secretary for Health (OASH).
- *The collaborators and investigators are responsible for*: working to meet the established metrics of establishing models of payment for direct translation services include healthcare professional training programs, healthcare organizations, accrediting bodies, patient advocacy organizations, and social service providers.

3

Improve the quality and availability of data to assess the impact of pain and under- or overtreatment for vulnerable populations and the costs of disparities in pain care.

- *The accomplishment of these goals requires*: support of key stakeholders including those mentioned above as well as Centers for Disease Control (CDC) and Office of the National Coordinator for Health Information Technology (ONC).
- *The collaborators and investigators are responsible for*: working to meet the established metrics of identifying the number of existing and new studies published using the data standards and definitions developed to assess prevalence of disparities in pain management and treatment outcomes include the pain research community, private entities, and patient advocacy organizations.

4

Improve access to high-quality pain services for vulnerable population groups.

- *The accomplishment of these goals requires*: support of key stakeholders including those previously mentioned as well as Centers for Medicare & Medicaid Services (CMS), Department of Defense (DoD), and Veterans Health Administration (VHA).
- *The collaborators and investigators are responsible for*: working to meet the established metrics of improving access, utilization, and quality of telehealth programs include professional medical organizations, private entities with expertise in information technologies, healthcare organizations, patient advocacy groups, and people living with pain.

Research unfortunately continues to indicate that providers' implicit beliefs may nonetheless lead to unintended discrimination. Therefore, healthcare providers must also learn to be aware of their bias and constantly work to disengage from those conditioned judgments that can affect patient care.

proposed solutions

The fundamental way to reduce bias is through education and self-reflection. All bias will not be corrected through education, as bias is individual and a learned behavior generally deeply entrenched from life experience. Explicit discrimination by healthcare professionals, however, has greatly decreased through the educational efforts of institutions and professional societies. Research unfortunately continues to indicate that providers' implicit beliefs may nonetheless lead to unintended discrimination.[17] Therefore, healthcare providers must also learn to be aware of their bias and constantly work to disengage from those conditioned judgments that can affect patient care.

One strategy to reduce the impact of disparities in pain management and improve outcomes is to understand the role that provider factors play in suboptimal pain management. A survey undertaken by Bekanich et al sought to identify healthcare provider attitudes, knowledge, and practices regarding the treatment of chronic pain in vulnerable patient populations to assess whether a certified continuing medical education (CME) intervention could improve knowledge in this area. The survey discovered the following: respondents (providers) identified language barriers, miscommunication, fear of medication diversion, and financial barriers as major obstacles to optimal pain management for this patient population.[1] In this study, the participants were asked to complete a self-directed learning module and then complete a series of questions to assess their new confidence and gained knowledge about disparities in pain management. Of the 400 participants who completed the CME-certified activity on pain management disparities, 99% demonstrated some degree of increased confidence in caring for disadvantaged patients, but only 1 of 3 knowledge items improved: communication related barriers associated with specific patient populations.[1] Of the other 2 knowledge items, there was no statistically significant change after completion of the module in respondent's knowledge regarding the effects of interventions designed to increase guideline-directed pain management strategies, or the use of cross-cultural training to reduce disparities in clinical decision making.

National Pain Strategy[5]

As mentioned above, "The focus of the disparities work group is to explore solutions to eliminating disparities and promote equity in pain assessment and treatment." Accomplishing the aim of bringing about awareness to reduce disparities in pain management required clarifying objectives **(see Sidebar)**, identifying stakeholders and collaborators, establishing short (within 1 year) to medium (within 2 to 4 years), and longer-term (within 5 years) goals, and finally identifying the metrics by which the accomplishment of stated goals is measured.

systems approach

In 2001, Starck et al proposed a systems framework for the study of pain management errors, as an approach to reducing disparities.[18] Building on the theme of "reframing the mismanagement of pain into one of medical error that requires a new systems approach" to reduce the incidents of disparities in pain management in an acute care setting, McNeill et al conducted a secondary analysis examining pain outcomes.[19] Data was collected from 964 hospitalized adult patients in the southwestern United States. The study findings supported conceptualizing the mismanagement of pain as a medical error. An intervention model was used to describe the use of a systems approach to identify high risk patients and ensure effective pain management practices.[19] The

study concluded that errors (discrepancies) in pain assessment and documentation could be reduced through the use of standardized scales, identification of vulnerable patient populations (nonwhite, elderly, female, low literacy), providing culturally/linguistically appropriate tools for assessment, and regularly reassessing pain after each intervention.

Errors in pain treatment and management can be reduced by:

- **Using the appropriate analgesic and route of administration for the reported pain complaint**
- **Considering employing around-the-clock dosing vs as-needed**
- **Closer monitoring of higher risk patients for poorly managed pain**

Errors in patient education can be reduced by:

- **Informing all patients that effective pain management is important for their recovery**
- **Fostering effective communication and collaboration with the patient and family**
- **Providing culturally sensitive and linguistically appropriate written and verbal instruction**
- **Reinforcing patient education with verbal information, frequent assessment, and wall charts**

conclusion

Disparities in pain management not only undermines the overall well-being of affected individuals and their families, but also contributes to higher rates of disability. This in turn increases healthcare utilization and has a greater impact on healthcare spending.[1,4]

Race, ethnicity, socioeconomic background, and healthcare provider bias are all risk factors for the undermanagement of pain in vulnerable patient population groups.[1-3]

To overcome these disparities, healthcare professionals must recognize their own personal biases and provide a standard of care that is of the same high quality amongst all groups of patients. Using evidence based models will help promote unbiased clinical expertise, while holding providers accountable to quality outcome measures. Quality evidence based models can be achieved by including a cross-section of individuals from all ages, races, genders, and health status in clinical trials.

Education "as the best medicine" helps reduce disparities in pain management by increasing the pain literacy of healthcare providers and well as their patients. Patients should be involved in developing culturally appropriate training materials, media, and educational tools for a range of diverse audiences. Finally, patient information about pain therapies should be provided in their own language, using interpretative services when appropriate, along with written instructions and other forms of educational media. ◘

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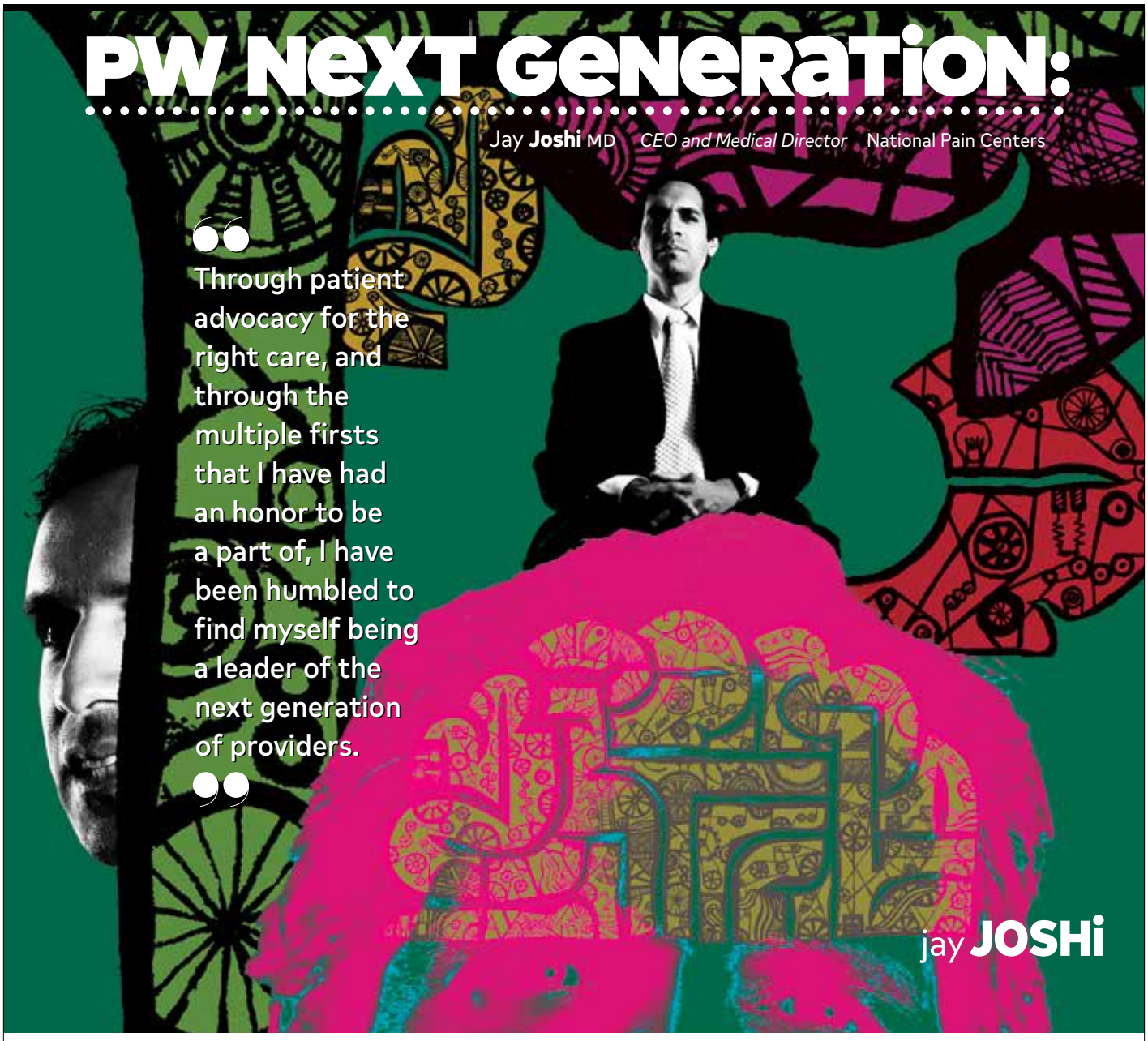
PW Next Generation:

Jay **Joshi** MD *CEO and Medical Director* National Pain Centers



GPS Vernon Hills, Indiana **Typical Day** "My typical day at work is, like many other practitioners, nonstop! Between seeing patients, documenting in the chart, answering messages and phone calls, paperwork and prior authorization requests, and running the business side of the practice, there is no time for rest. The work doesn't stop on the weekend or at night either. But knowing that you are making a positive transformation in someone's world makes the thrill of the physician lifestyle worth it." **Persona** "There is an old saying that you can lead, follow, or get out of the way. I'm not going to follow the errors of the previous generation. I have no plans to get out of the way of progress and innovation." **Social Media Habits** "I stay current on what is going on in the world today, including healthcare, science, technology, social issues, popular culture, and of course the social media feeds of the National Pain Centers." **Contribution** "I've always been an advocate for facts and the truth. Medicine has been practiced with stereotypes, egos, lies, and corporate malfeasance for years. Through patient advocacy for the right care and through the multiple firsts that I have had an honor to be a part of, I have been humbled to find myself being a leader of the next generation of providers." **People** "I admire people who are intelligent, intellectual, visionaries, creative, talented, and able to create something from scratch. I admire people who are the first in the world to accomplish something special. I know the hard work, courage, planning, and luck that those achievements involve." **Words** "Anything that involves facts, science, and peaceful philosophies." **Popcorn** "*Contact* (1997) is a great movie pinning science vs religion, fact vs ignorance, intellectual curiosity vs fear. Issues from 2 decades ago are still relevant today. " **PainWeek** "It is broad based, multifaceted, and nonpartisan. It's not cliquey like some other conferences. Participants can learn about a variety of topics. In some cases, there may be conflicting opinions, which is not a bad thing. It allows for the facts to emerge."

CLINICAL PEARLS

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

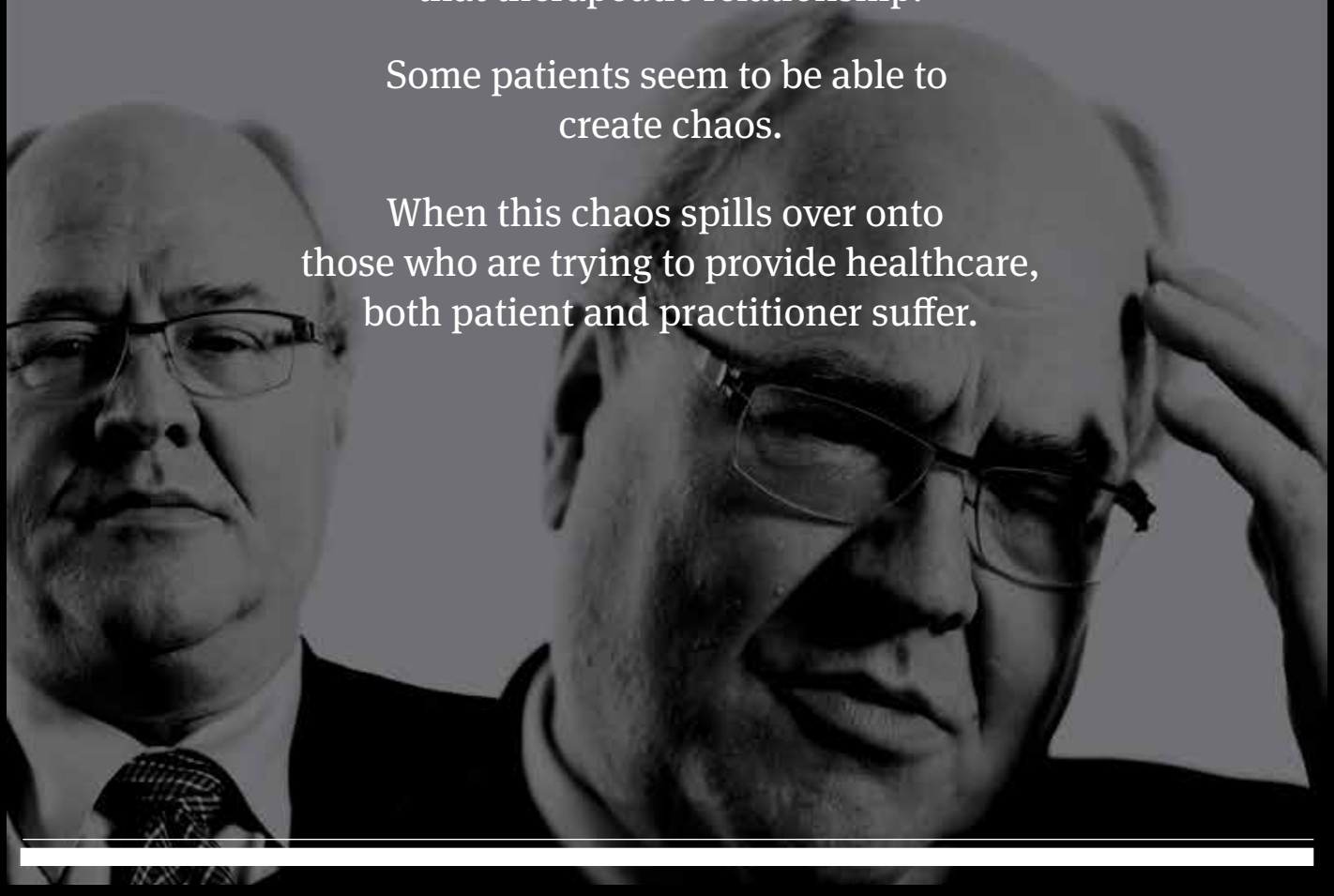
Who's working harder?

• • • • • • • • • • • • • • • • • • •

When your staff find themselves repeatedly expending a disproportionate amount of effort on one patient, it's time to reevaluate that therapeutic relationship.

Some patients seem to be able to create chaos.

When this chaos spills over onto those who are trying to provide healthcare, both patient and practitioner suffer.



Pain by Numbers

Of the

>1,000,000

joint replacements
done each year in the US,
some

10,000

are **complicated**
by postsurgical infection and may result in
repeat surgery
to clean or even **replace the implant.**

But a newly developed
microsphere coating
applied to the implant can
release high levels of antibiotic
for

3 to **6**
weeks

following surgery,
the time window when risk for
infection is greatest.[1]

Physicians should not

be hesitant to recommend surgery
in cases of **rectosigmoid endometriosis**
that is unresponsive to
conservative treatment.

Research from Denmark analyzed data
from

175
women

who underwent laparoscopic bowel resection
for **endometriosis**,
tracking pain and quality of life scores
before and 1-year postsurgery.

Patients' pain medication usage **dropped**
from

94% to **62%**

and hormone treatment **declined**
from

81% to **56%**

during the interval.[2]

Patient education

can forestall pain medication diversion.
In 2017,
of

334
surgical patients

studied at Washington University,

170

were provided educational material on
safe medication disposal and

164

were not.

22% of **patients**
in the **1st cohort** correctly
disposed of unwanted opioids,
compared to just

11% of **patients**
from the **2nd group.**[3]

Patients who live alone

can safely recover
from total joint arthroplasty
at home,
vs discharge to
an inpatient rehabilitation facility.

An evaluation of outcomes
for

769
patients
found that of

138

who lived alone and were sent home
following their procedure,
scores for **postdischarge complications**
were comparable to patients with
in-home companions,

at **8%**.

Researchers noted that

79%
of **single patients**
had access to help within

15 minutes,
if needed.[4]

Even moderate weight loss

in obese patients can **significantly**
improve pain, and not just in back and joints.

123

participants were placed
on a weight reduction regimen
and evaluated for 12 weeks.

99

of the study cohort achieved

10%

or more weight loss

and reported significant
improvements in pain levels,
mental health, and energy levels.

A possible explanation:
Blood samples from

25%

of participants
found increased concentrations
of **anti-inflammatory molecules.**[5]

Medical marijuana is legal

in **29 states** and the **District of Columbia,**
but clinician education on its use
is lacking.

172

medical school deans were surveyed
and **101 responded.**

66%

said their students were ill prepared
to recommend medical cannabis and only

25%

believed they could answer patient
questions about the modality.

A survey of

258

residents and fellows confirmed
the deficit—**85% stated** they had
received **no training** during
medical school or residency.[6]

1. http://bit.ly/2GBi7Gc **2.** http://bit.ly/2EO8dAF **3.** http://bit.ly/2sJ4m6s **4.** http://bit.ly/2BJy91x **5.** http://bit.ly/2sQGmym **6.** http://bit.ly/2EWKpOb

One-Minute Clinician

1

The Complexity of the Opioid Situation

Jeremy A. Adler MS, PA-C

Opioid issues are complex because it's not a single problem. I think that the rhetoric and concern and issues surrounding this have really boiled up because people recognize there's a problem, and the problem affects everybody. It affects certainly those who have been harmed, and their families that have been harmed. It affects patients who legitimately need access and healthcare providers who may be portrayed one way but certainly don't want to contribute to this ever-growing problem. I think one of the critical issues is to define what it is we're trying to do and understand that there's different solutions for different problems and really break it down and try to work on each of these kind of subsets of problems specifically. The approach where it's an all-or-none is not adequate or appropriate, where you just say "No, we don't use opioids" or "Opioids for all." That to me is certainly not the approach. It's that we need to know how to use these, who to use them on, how to monitor them, how to incorporate technologies available to try to improve safety, have access to nonopioid therapies and behavioral therapies and physical therapies and really know how to best treat our patients while at the same time recognize the impact of diversion. The majority of people out there who misuse and nonmedically take opioids that we're concerned about are not sitting in front of healthcare providers receiving them as prescriptions. Until we fundamentally recognize how these drugs are actually moving through our communities, only then will we develop solutions that'll achieve the desired outcome for all parties.

2

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 different 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 the nonstructural reasons such as various vitamin deficiencies, metabolic disorders in general, and also 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 when evaluating that. 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 help in the long run.

3

Back and Spinal Pain—Where do Interventional Procedures Apply?

Ignacio Badiola MD

Spinal pain is very difficult to diagnose, the more so as patients get older. They present with different things on their MRI, different findings on exam, and they've had chronic pain for many years. Unfortunately, a lot of the physical exam and history findings are very generalizable, so it's hard to tease out where the actual pain is coming from. The most common procedures that we do for spinal pain are epidural steroid injections, lumbar facet interventions, including medial branch blocks (numbing the nerves that go to these facet joints), as well as radiofrequency ablation (burning those nerves that go to the facet joints) to hopefully provide longer pain relief than just the facet joint blocks. For epidural steroid injections, the most common indication is pain that travels down the legs from either spinal stenosis or a herniated disc that is impinging on a nerve root. Facet joint pain typically presents with more lower back pain and so unfortunately physical exam and history findings are not very specific. Doing diagnostic nerve blocks or medial branch blocks can help make that diagnosis and, if positive, a radiofrequency ablation may provide the patient with longer term relief. Patients at risk for poorer outcomes from interventional procedures would include those on high-dose opioids or on chronic opioid therapy; also, those who have failed every other modality...patients you've sent to physical therapy, acupuncture... you've tried medications on them. Typically, interventional procedures don't tend to do as well in these patients. It doesn't mean we don't do them, but typically your outcomes are going to be less favorable than somebody who's responded in the past to other procedures.

4

Stress, Fatigue, and Chronic Pain

Hal Blatman MD, DAAPM, ABIHM

We're stressed in so many ways and our body tries to compensate for that stress and keep us on an even keel. It compensates in an analogous way, as if you were running—your heart beats faster, you prepare yourself for fight or flight, you try to keep your body together and you have many mechanisms through your body to help. Not all stressors affect any/all people in the same way. Some people are more affected by this stressor or by that stressor, and our biologic response to that stress may even be different. There are very few people with chronic pain who don't have any stress,

and having pain causes even more stress. When you're under stress your muscles tighten and you have more pain. Here you are in the circle that you need to get out of. So, we work to get out of it by starting with food, by using herbal and specific protein medicines, and then by working directly on the body and with the mind. Herbal medicines can be very helpful in restoring adrenal gland function and helping mute a stress response. There is an amino acid called theanine that I tell patients is a form of Valium off the grid. It's not going to be as strong as Valium or Xanax, but it's certainly going to help. There are also toxic foods that we need to avoid—bread, sugar, potatoes—not eating things that drive or hurt our ability to handle stress. Our microbiome is a key factor in helping us maintain homeostasis for stress, and with these nutritional interventions, we can mute responses to stress and help the body restore its homeostasis without resorting to dangerous combinations of drugs.

5

What's Happening With Interdisciplinary Teams?

Elaine S. Date MD

I think the resources are not there for us to continue to use interdisciplinary teams as much as we want to. It's difficult for us sometimes to try to get an interdisciplinary pain program authorized, for example, in an industrial medicine setting. But I think the fact that the outcome measures we've been using...there's been many studies that support the use of interdisciplinary teams for pain management to reduce the use of opioids and to improve function. Those are really important factors to help support the upcoming hope of interdisciplinary teams. It is a financial issue, however. We use the interdisciplinary team in the functional restoration programs, so they work together. It is a multidisciplinary team, but the team members have to work together very closely and the #1 team member, of course, is the patient. The team will usually involve a physician, oftentimes it involves a nurse practitioner who's very well trained in pain medicine and addiction medicine. We often use an addictionologist in our team setting. We also need a physical therapist, we need of course psychology; we need pain psychiatry; we use different types of social worker services; and we use other types of what we call movement team members, such as tai chi and yoga instructors, all trained in the specific movement of patients with chronic pain. So together, they can form a team and actually help patients manage their pain with nonpharmacologic methods.

6

The Fifth Vital Sign and Pain Scores

Abhishek Gowda MD

I think we have to go back to before a lot of these scores, before the fifth vital sign. How did we treat patients before we had all these medications, interventions, surgeries at our disposal that were meant to help pain? I think a lot of what we're applying to chronic pain management has been evolved from acute pain management, such as through our anesthesia colleagues. We're applying a lot of the same principles to a disease process that is more global than just focal. Eliminating pain as a fifth vital sign or from HCAHP scores is only going to be beneficial because then we release that back and see the bird's eye view in how to treat this in a more comprehensive manner than just by a numbers game. We've been spending a lot of our careers just saying "How do I get that pain score down?" And when we medicate it, we're finding the caveat to be true: we're actually inducing pain, such as opioid induced hyperalgesia, tolerance to certain medications, and we're hitting a wall with a lot of our conventional treatments. Those treatments come from the acute pain management philosophies. They don't really translate into when patients have pain for greater than 3 months.

7

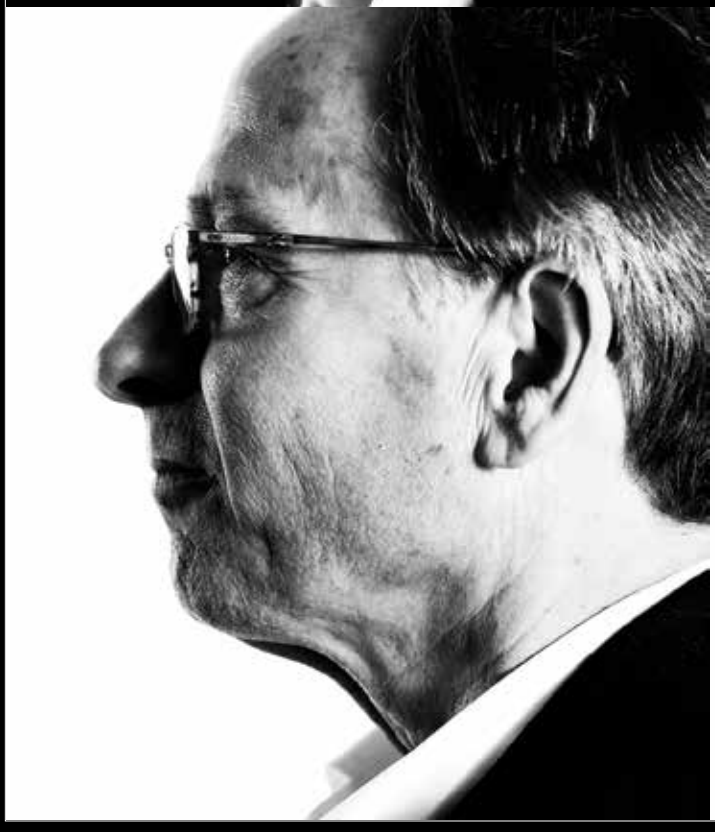
The Psychology of Pain: For Patients and Practitioners

Ravi Prasad PHD

In terms of biopsychosocial treatment, providers must know that it's critically important to look at all the factors affecting a patient's pain condition. Any time we pigeonhole ourselves in any one category—whether it's the medical piece, the psychological piece, or the physical piece—we're losing sight of the bigger picture. So, everybody needs, and would benefit from, that biopsychosocial paradigm. How much does each component vary from one individual to the next? It's critically important that providers are looking at things from that paradigm, as they look at the etiology of pain and the treatment of pain and the perpetuation of pain. As for psychologic vs psychogenic factors, there's sometimes a misconception that when you bring psychology into pain, you're doing it because the pain is just in the person's head or the pain is not real. There are some pain conditions that are rooted 100% in psychogenic factors where it is related to psychiatric issues. Even if that's the case, though, that person's experience of pain is still real. There's really not any such thing as pain that doesn't exist or pain that's not real. It's just that what's causing it could be something different. But that's just a small number of patients that have that type of true psychogenic pain. What we know of with virtually all patients living with pain is that psychological factors can directly influence the onset and the maintenance of the pain condition. Even if it's not what caused the pain, we know that depression, anxiety, stress levels, sleep patterns, activity patterns, all these things can affect the overall pain intensity and how engaged a person is with life. And so, we have to take a look at these things if we want to help patients move forward. Even though a patient's pain may not be rooted in 100% psychogenic factors, psychological factors can always affect the pain that a person has and influence that bottom line.

PUNDiT PROFiLe

with
m. cary
reid jr
md, phd



"...one of the true joys of practicing medicine is the learning that occurs through the care of patients (experiential learning), particularly the stories shared by them about their health, their worries, joys, regrets, and accomplishments."

Q What inspired you to become a healthcare provider?

A I was drawn to the field of medicine because of role models at an early age, a chance to serve others, the opportunity to merge the practice of science with delivery of patient care, a view of myself as a life-long learner, and a sense that medicine selects individuals who see themselves in this vein—and have a need for continuous learning throughout life. This learning happens passively (through reading, taking courses) and actively (through patient care). For me one of the true joys of practicing medicine is the learning that occurs through the care of patients (experiential learning), particularly the stories shared by them about their health, their worries, joys, regrets, and accomplishments.

Q Why did you focus on pain management?

A In the field I work in, geriatric medicine, pain care is suboptimal. Physicians receive little training in pain assessment and management in general. There are many barriers that complicate the management of later-life pain, including older adults' beliefs and attitudes about pain, and physicians' worries about causing harm with treatment. Clearly, we need to do a better job in both assessing and treating pain in older adults. I am gratified that since I began my career as a physician researcher focused on pain care in older adults nearly 2 decades ago, a whole new generation of younger researchers has emerged to address important questions in this field.

Q Who were your mentors?

A I have been fortunate to have many mentors along the way, some professional and some personal. The most inspirational by far was Alvan Feinstein, a Yale-based physician researcher considered by many to be the father of modern clinical epidemiology. Alvan demanded much of his mentees, but was incredibly giving of his time and profoundly supportive of my continued growth and development. I learned a lot about what it means to be a good mentor from Alvan.

"It [the book Zorba the Greek*] is very much a call to all of us to live life to the fullest while we can."*

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

A A musician, language translator, and/or art dealer, which are more right-brained functions than what is typically required in the work I currently do. When I win the lottery, I fully intend to pursue all three on a full-time basis!

Q What is your most marked characteristic?

A Perseverance.

Q What do you consider your greatest achievement?

A I would say serving as a mentor to trainees at various levels—medical students, residents, fellows, and junior faculty—which is work I find incredibly gratifying. It is one of the many reasons I look forward to getting to work each day.

Q What is your favorite language?

A Romance languages by far, with French and Italian being the most pleasing to my ear.

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

A Incredibly tough choices: I would select *Zorba the Greek*, a book written by one of my all time favorite writers, Nikos Kazantzakis. It is very much a call to all of us to live life to the fullest while we can. The characters in this novel are indelibly etched into my brain, while his descriptions of the Crete landscape and sea are breathtaking. For music, it would have to be Miles Davis' *Kind of Blue*. I learn something new every time I listen to this incredible piece of jazz. Selecting one piece of art is incredibly tough, but if I had to choose it would be van Gogh's *Wheatfield with Crows*. Every time I see it, I am filled with joy and reminded of the extreme beauty and 'aliveness' of life.

Q What would you like your legacy to be?

A I would like to be remembered as someone who made a difference in the lives of my family, patients, and trainees. I would also like to be viewed as someone whose research led to decreased suffering and improvement on the part of older adults with pain.

Q What is your motto?

A Carpe diem!

M. Cary Reid, Jr, MD, PhD, is Associate Professor of Medicine at Weill Cornell Medicine in New York.

Not only can you take our faculty home with you—now you can also bring them to the gym 365 days a year!

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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

COLLEGIUM Pharmaceutical
Ingenuity in Medicine

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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