USING MEDICAL TECHNOLOGY TO RELIEVE PAIN AND DISRUPT THE OPIOID EPIDEMIC

LIFE EXPECTANCY in the United States has fallen for three years in a row – with systemic opioid overdose a key driver.[13-15]

Misuse Defined[4]
The use of prescription drugs without a prescription or in a manner other than as directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or for longer than told to take a drug; or use in any other way not directed by a doctor.

PERSPECTIVE SYNOPSIS

Millions of Americans are affected by pain and have been prescribed systemic opioids (typically oral) as part of their treatment plan by healthcare providers.[2] In the pain continuum, chronic pain can start with acute pain. Both pain types prompt an urgency of addressing patients' needs, often with systemic opioids. This is despite the limited evidence on the benefits of long-term systemic opioid therapy and evidence that long-term systemic opioid therapy is associated with increased risk for opioid misuse or addiction.[3] Here's what is known about the misuse of prescription opioids:

- An estimated 11.4 million Americans are misusing opioids with 63% doing so to relieve physical pain.[5]
- An estimated 25% of chronic pain patients are misusing prescription oral opioids.[6]

A CDC review of scientific evidence yielded many mitigation steps to reduce the risks associated with long-term systemic opioid use, including misuse, addiction and overdose.[7] In its guidelines, the CDC recommends patients with acute pain ask their doctors for treatment options that do not involve prescription opioids.[8] In addition, for chronic pain, CDC recommends nonpharmacologic therapy and nonopioid pharmacologic therapy as preferred treatments.[9] The FDA's updated opioid education Blueprint includes the use of approved/cleared medical devices for pain management as one of several nonpharmacologic treatment options healthcare providers should be knowledgeable about as part of a multidisciplinary approach to pain management.[10] Enacted into law on October 24, 2018, the federal SUPPORT for Patients and Communities Act includes provisions to raise provider and patient awareness of alternative, non-oral opioid pain treatments, including medical device-delivered therapies.[11]

> ***"We cannot solve the opioid crisis, until we solve the nation's pain crisis.[1]"***
> -Admiral Brett P. Giroir, M.D.
> Assistant Secretary of Health,
> US Department of Health and Human Services

As part of the comprehensive efforts in the United States to address the opioid epidemic, device-delivered therapies are being considered as an alternative or adjunct to systemic

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MICHELSON TECHNOLOGY AT WORK

Burden of mortality is highest among adults aged 25 to 34 years; in this age group, **1 in 5 deaths in the United States is opioid related.**[22]

opioids in the management of acute and chronic pain. Device-delivered therapies of spinal cord stimulation, intrathecal pain pumps, and vertebral augmentation along with several other procedures have been identified by the U.S. Department of Health and Human Services in The Pain Management Best Practices Inter-Agency Task Force Report as interventional procedures that can be considered singularly or as part of a multimodal approach to the management of chronic and acute pain, depending on the patient and his or her medical conditions.[12] Through greater awareness and use of device-delivered therapies, healthcare providers can reduce pain for many patients, potentially reducing their exposure to high dose opioid and/or long-term systemic opioid use that could lead to opioid misuse and addiction. As more patients effectively take control of their pain, these patients may no longer need to turn to misusing opioids to attempt to control their pain. This could help disrupt the opioid epidemic.

Medtronic Pain Therapies do not treat opioid addiction, but rather offer patients a way of managing their pain as an alternative or adjunct to systemic opioids. Medtronic has already published clinical evidence that shows reduction in the use of systemic opioids in managing and treating chronic pain with Targeted Drug Delivery (i.e. intrathecal pain pumps) and acute pain associated to vertebral compression fractures (VCF) using Balloon Kyphoplasty as a technology for vertebral augmentation.[16,17] It is important to understand that not every patient experience is the same. We continue to invest in clinical trials designed to generate new evidence to help physicians make more informed pain treatment decisions.

Medtronic supports ongoing efforts by stakeholders across the U.S. – patients, providers, payers, regulators, elected officials, patient advocacy groups, and employers – as they pursue approaches for preventing and treating prescription opioid misuse, addiction, and overdose. Medtronic is playing an important role alongside other stakeholders in helping patients take control of their pain by:

- Informing patients with acute and chronic pain of their options for device-delivered pain relief as an alternative or adjunct to systemic opioids so that patients may have an informed discussion with their doctors.
- Partnering with providers to consider non-systemic opioid pain relief in treatment plans for patients with acute and chronic pain.
- Educating payers, policymakers, and regulators to enable greater patient access to medical devices shown to alleviate pain as an alternative or adjunct to systemic opioids.

$95 BILLION

Economically, the societal harms of opioid overdoses, deaths, and substance use disorders is estimated to exceed $95 billion annually.[23]

Amongst 500 Human Resource professionals surveyed in America, **67 percent** said their organizations "are impacted by opioid use today or will be in the future," and **65 percent** reported that opioid addiction is having a financial impact on their company.[24]

SYSTEMIC OPIOIDS AND PAIN MANAGEMENT CRISES

There are two interrelated healthcare crises occurring in this area in the United States: the opioid epidemic, and the ongoing public health problem of pain management.

The Opioid Epidemic

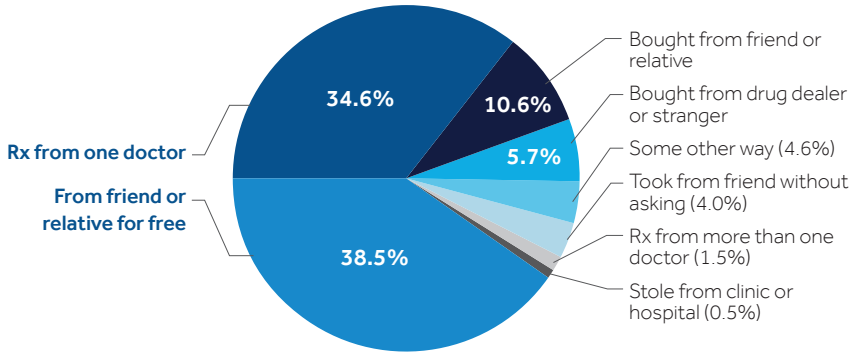
The alarming opioid epidemic has had a devastating impact across the United States with 130 Americans dying every day from an opioid overdose in 2017.[18] In 2017, opioids were involved in 47,600 overdose deaths and represented 67.8% of all fatal drug overdoses (70,237).[13,19] As a result, public officials declared the opioid epidemic "the worst drug crisis in American history."[20] Preliminary analysis by CDC of 2018 opioid involved overdose deaths (47,590) show a flattening but still alarming trend versus prior year.[21]

Urgency of this epidemic has drawn the attention of all American elected officials and regulators. One area that regulators were quick to look at was prescription opioid use for pain relief and how they were then sourced among people whom misused them. In 2017, roughly

37% of people whom misused prescription pain relievers obtained them from one or more doctors.[5] In addition to recommendations on prescribing opioids for pain relief, the CDC recommends non-pharmacological therapy and non-opioid pharmacologic therapy as the preferred treatments of chronic pain.[9] If used, prescription opioids should be combined with other therapies, as appropriate.

An estimated **21% to 29%** of patients prescribed opioids for chronic pain misuse them. And, between **8% to 12%** of these patients develop an opioid use disorder.[6]

The source from where Pain Relievers were obtained among people whom misused prescription Pain Relievers[5] *(Year 2017, 11.1 million people age 12 or older)*



Pain Management Problem

The ongoing public health problem of pain management constitutes a crisis of its own.[2] More than 100 million Americans experience chronic pain lasting greater than 3 months, costing the nation approximately $560-635 billion annually in direct medical treatment costs and lost productivity.[2] Millions more experience pain caused by a specific event (e.g. surgery, broken bones, dental work, or childbirth) that may last for 6 months.[25,26]

Up to **80 percent** of Americans will experience low back pain at some point in their lifetime.[29]

Although research suggests systemic opioids are effective at reducing pain and improving function in the short term, evidence on long-term systemic opioid therapy for relieving pain is limited.[3,7] CDC has identified long-term prescription opioid use and high daily opioid doses as risk factors that could lead to abuse or overdose.[30] An estimated 11.4 million Americans are misusing opioids with 63% doing so to relieve physical pain.[5] Furthermore, risks of prescription systemic opioids are high: prescription systemic opioids contributed to ~35 percent of all U.S. opioid overdose deaths in 2017.[31]

Patients with chronic pain have voiced their frustration with the inability to access effective pain relief and the devastating sociological impacts this has had on their lives.[32,33] These people are victims of chronic pain and the effects of the opioid epidemic on our society. Patients deserve other options for pain management through access to effective alternate and adjunct pain therapies.

An estimated **19.6 million Americans** in 2016 had high impact chronic pain (pain that limited their life or work activities on most days or every day for 6 months).[28]

INSPIRED TO PROVIDE BETTER PAIN MANAGEMENT

Medtronic has more than a 40-year history of developing innovative medical devices that have been shown to alleviate pain in different disease states.[34] Moreover, we have established expertise to demonstrate clinical outcomes and health economics of these products.

Given the current opioid epidemic and pain management crisis, our work to alleviate pain has never been more critical. That is why we leverage our capabilities and product portfolio in partnership with stakeholders — patients, providers, payers, regulators, elected officials, patient advocacy groups, and employers — to address the unmet needs of pain patients.

PAIN
affects more Americans and is costlier than diabetes, heart disease, and cancer.[27]

We are aware no single entity can solve America's opioid and pain crises alone. It is when we work in partnership that we expand patient access to non-systemic opioid pain management therapies. Therefore, we are pursuing collaboration with others in pain management to:

Broaden Therapy Awareness and Advocacy

- Increase stakeholder **awareness** of the clinical and economic evidence of device-delivered therapies along with the risks of long-term systemic opioid use to treat pain.
- Leverage social media networks, pain advocacy groups, and local treatment clinics to heighten **patient awareness** to device-delivered options that have been shown to treat pain or painful conditions. Only a physician can decide if these therapies are right for a patient.

Deliver Innovation

- Develop **novel payment models** for private and public payers that will help healthcare providers deploy evidence-based clinical workflows, guidelines, and policies for device-delivered therapies to manage pain or painful conditions.
- Explore with industry partners the **use of medical technology** to track objective patient metrics, coupled with clinical workflows, to deliver and monitor non-systemic opioid pain relief.

Advance Clinical and Economic Evidence

- Expand the body of existing **clinical and economic evidence** (independently and through partnerships with providers and payers) on the ability of Medtronic Pain Therapies — coupled with clinical workflows — to reduce or eliminate systemic opioid usage.
- Educate state and federal government officials about the need for **policies to ensure patient access** to the clinical and economic benefits of device-delivered therapies for pain or painful conditions.

MISSION-DRIVEN TECHNOLOGY TO IMPROVE OUTCOMES

With our company mission to alleviate pain, restore health, and extend life, Medtronic strives to be at the forefront of medical device innovation, challenging ourselves to develop high-quality therapies for pain or painful conditions. Our view is that medical technology should not be only for reducing pain, but also for improving quality of life. And at every stage of the process — from technology advancements to physician training — we strive to understand the patient experience through the principles of human-centered design.[35]

The Medtronic Pain Therapies portfolio includes implantable medical devices for Targeted Drug Delivery (TDD) and Spinal Cord Stimulation (SCS) for chronic pain. Our portfolio also includes products indicated for: vertebral augmentation therapies such as Balloon Kyphoplasty (BKP) for vertebral compression fractures (VCF) due to osteoporosis, cancer or benign lesion; Osteocool™ radiofrequency ablation of painful bone tumors; and Sacroplasty for the treatment of pathological sacral fractures. These minimally invasive technologies treat these conditions, which are associated with acute pain. To date, over a million patients have received treatment from Medtronic Pain Therapies.[36] In addition to the risks of surgery, the medical devices discussed in this paper carry significant risks. Please refer to the important safety information at the end of document.

While these therapies do not treat addiction, they can help patients manage their pain. Medtronic is committed to providing clinical evidence and in studying the use of systemic opioids in managing and treating chronic pain with TDD and acute pain associated to VCF with BKP.[16,17] Through our medical education and ongoing clinical support programs, we continuously strive to educate about device therapies as an option in pain management with the goal that fewer patients will need to rely on long-term systemic opioid use.

Two retrospective claims analyses found that **43 and 51 percent**, respectively, of chronic non-malignant pain patients eliminated systemic opioids within one year of TDD therapy.[16,45]
In the second study, overall (regardless of discontinuation), **84% reduced** their average daily morphine milligram equivalents (MME) in the year following start of TDD therapy relative to one-year baseline MME values.[45]
In the first study, elimination was correlated with a **10% to 17% reduction** in yearly inpatient, outpatient, and drug expenditures.[16]

A smaller, single-center, retrospective chart review (n=99) of patients with chronic non-malignant pain who agreed to transition from systemic opioids to TDD with the goal of eliminating systemic opioids, demonstrated that **84 percent of patients were able to eliminate systemic opioids after 12 months** when using TDD to relieve their chronic pain.[51]

Along with clinical evidence demonstrating pain relief, we have strong coverage and reimbursement in the United States for clinical indications recognized and covered by government and non-government payers. For example:

- TDD and SCS are covered by Medicare under national and local coverage determinations.
- BKP has coverage from all Medicare MAC's via Local Coverage Determinations.
- Most commercial payers have published coverage determinations for all our Medtronic Pain Therapies.

Knowing how and when to use alternative and adjunctive therapies to systemic opioids is more important than ever. That is why, before committing to long-term treatment, physicians will have their patients undergo a trial for some therapies (i.e. TDD and SCS) to experience the therapy.

MEDTRONIC PAIN THERAPIES

Targeted Drug Delivery
Targeted Drug Delivery (TDD) with SynchroMed™ II, also known as a pain pump or intrathecal drug delivery system (IDDS), for the treatment of chronic intractable pain, including intractable cancer pain, provides pain relief at a fraction of the oral medication dose.[37-40] An implanted, programmable pump and catheter releases prescribed amounts of pain medication directly into the intrathecal space, near pain receptors in the spine instead of the circulatory system. The CONTROL Workflow℠ in combination with SynchroMed™ II encourages systemic opioid elimination and is an alternative to long-term systemic opioids.

Intrathecal drug delivery has been shown to improve patients' ability to function, return to work, and participate in activities of daily living.[37,39,41,42] In addition to effective pain relief, TDD has been shown to reduce or eliminate use of oral pain medication and to reduce side effects compared to systemic pain medication.[16,37-40,43-45]

TDD is often viewed as a "salvage therapy" when high dose systemic opioid therapy has not worked. This is despite success of the therapy as demonstrated in randomized controlled trials, and the demonstrated cost effectiveness of the therapy.[16,38,46-50]

The implanted pump stores and dispenses medication inside the body, reducing the opportunity for diversion of the drug, for misuse by individuals who are not prescribed the opioids. Additionally, the physician programs the pump to deliver a certain amount of medication, allowing more physician control compared to systemic opioid therapy, reducing the opportunity for misuse of prescribed opioids.

Medtronic developed The Control Workflow℠ for TDD providing a pain relief option utilizing a low-dose protocol with the SynchroMed™ II intrathecal drug delivery system and as guidance for eliminating systemic opioids. This workflow assists physicians with patient selection and includes oral opioid weaning and treatment protocols that can be tailored to individual patients. By having an outlined workflow for physicians, we are working to simplify the therapy and expand patient access to TDD therapy.

Medtronic is currently sponsoring the Embrace TDD Post Market Clinical Study that will evaluate the use of the SynchroMed™ II intrathecal drug delivery system as an alternative to oral opioids for patients with chronic intractable non-malignant primary back pain with or without leg pain.[52] The study will follow patients who wean completely from all oral opioids and have a positive response to an intrathecal drug trial. The study will assess pain control and opioid-related side effects at six months following a route of delivery change to intrathecal

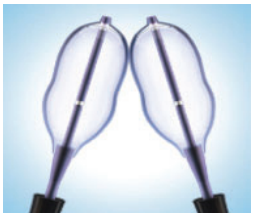
preservative-free morphine sulfate.

Spinal Cord Stimulation

Medtronic's Intellis™ implantable neurostimulator for Spinal Cord Stimulation is the smallest spinal cord stimulator implanted under the skin to deliver mild electrical pulses to the spine. Spinal Cord Stimulation (SCS) is a therapy that modifies pain messages before they reach the brain and has proven to provide long-term effective pain relief and improve quality of life. [53-55] In addition to pain relief, spinal cord stimulation is more cost-effective than conventional medical management and reoperation.[56,57] Multiple studies have provided clinical evidence to suggest some patients treated with Spinal Cord Stimulation (SCS) may be able to reduce oral opioid consumption.[58-60] Spinal cord stimulation is more effective than repeat surgery for persistent radicular pain after lumbosacral spine surgery.[61]

As a platform technology, Medtronic is providing more than just pain relief with the Intellis neurostimulator. This is the only platform that has embedded measurable activity data through Snapshot™ reporting, which tracks and shares activity, body positions and therapy usage continuously. Snapshot complements patient self-reporting with an objective look at their mobility. By reporting objective activity data, Intellis offers physicians insights into patient treatment beyond patient-reported pain scores. This may enable better treatment personalization to support improvement in function.

Interventional Pain



As a minimally-invasive vertebral augmentation technology, Kyphon™ Balloon Kyphoplasty (BKP) uses orthopedic balloons to restore vertebral height and correct angular deformity due to vertebral compression fractures (VCF) from osteoporosis, cancer or benign lesion. After reduction, the balloons are deflated and removed. The resulting cavity (void) allows for a controlled deposition of Kyphon bone cement forming an internal cast and stabilizing the fracture. Risks of the procedure include cement leakage, which may cause tissue damage, nerve or circulatory problems, and other serious adverse events. Studies have shown BKP offers better pain relief and quality of life for patients with acute VCF compared to non-surgical pain management.[17,62]

The BKP procedure has been shown to reduce systemic opioid usage: a two-year prospective, randomized, controlled trial (n=300) showed that **31 percent fewer Kyphoplasty patients (29.8%) used opioid medications at 6 months** compared to patients treated with non-surgical management (42.9%) (p=0.042).[17]

TOGETHER TO FIND LASTING SOLUTIONS

Millions of Americans are affected by the opioid epidemic, and their best hope is partners in healthcare coming together to create lasting solutions.[2] Healthcare providers, payers, elected officials, regulators and patient advocacy groups all hold important pieces to the puzzle and must work together. It starts with novel care pathways and personalized treatment options to help these patients break their cycle of misuse or dependency. Solutions must also help the approximately 7.2 million patients who misuse opioids to alleviate pain, and these patients need effective policies and programs that will expand access to medical devices shown to relieve pain as an alternative or adjunct to systemic opioids.[5]

Partnership is the path forward in addressing the systemic opioid and pain management crises. All stakeholders must work together, pursuing effective policies and programs that will expand patient access to medical technologies shown to relieve pain as an alternative or adjunct to systemic opioids.

SynchroMed® II Drug Infusion System Brief Statement:

Review product technical manuals, including information about EMI, and the appropriate drug labeling prior to use for detailed disclosure.

Indications: US: Chronic intrathecal infusion of Infumorph® preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, Prialt® chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

Drug Information: Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration, screening procedures, and under-/overdose symptoms and methods of management. Patients should be informed of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions, and signs and symptoms that require medical attention.

Contraindications: System implant is contraindicated in the presence of an infection; implant depth greater than 2.5 cm below skin; insufficient body size; and spinal anomalies. Use of the system with drugs with preservatives and drug formulations with pH ≤3. Use of CAP kit for refills or of refill kit for catheter access and use of PTM to administer opioid to opioid-naïve patients.

Warnings: Non-indicated formulations may contain neurotoxic preservatives, antimicrobials, or antioxidants, or may be incompatible with and damage the system. Failure to comply with all product instructions, including use of drugs or fluids not indicated for use with system, or of questionable sterility or quality, or use of non-Medtronic components or inappropriate kits, can result in improper use, technical errors, increased risks to patient, tissue damage, damage to the system requiring revision or replacement, and/or change in therapy, and may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug under- or overdose.

An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients carefully for any new neurological signs or symptoms, change in underlying symptoms, or need for rapid dose escalation. Monitor patients appropriately after refill if a pocket fill is suspected. Failure to recognize signs and symptoms of pocket fill and seek appropriate medical intervention can result in serious injury or death. Overinfusion may lead to underdose or overdose symptoms. Strong sources of electromagnetic interference (EMI) can negatively interact with the pump and cause heating of the implanted pump, system damage, or changes in pump operation or flow rate, that can result in patient injury from tissue heating, additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose. The SynchroMed II system is MR Conditional; consult the labeling for MRI information.

Precautions: Monitor patients after pump or catheter replacement for signs of underdose/overdose. Infuse preservative-free saline at minimum flow rate if therapy is discontinued for an extended period to avoid system damage. EMI may interfere with programmer telemetry during pump programming sessions.

Adverse Events: In addition to procedure-related risks, the following may occur: pocket seroma; hematoma; erosion; infection; pump inversion; post-lumbar puncture risks (spinal headache); CSF leak and rare central nervous system pressure-related problems; radiculitis; arachnoiditis; spinal cord bleeding/damage; meningitis; neurological impairment (including paralysis) due to inflammatory mass; allergic response to implant materials; surgical replacement due to end of service life or component failure; loss of therapy, drug overdose, or inability to program the pump due to component failure; catheter complications resulting in tissue damage or loss of or change in therapy; potential serious adverse effects from catheter fragments in intrathecal space.

For full prescribing information, please call Medtronic at 1-800-328-0810 and/or consult Medtronic's website at www.medtronic.com

Infumorph® is a registered trademark of West-Ward Pharmaceutical. Prialt® is a registered trademark of TerSera Therapeutics LLC. Lioresal® is a registered trademark of Saol.

USA Rx Only

Rev 1118

Neurostimulation Systems for Pain Therapy

INDICATIONS Spinal cord stimulation (SCS) is indicated as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain.

CONTRAINDICATIONS Diathermy - Energy from diathermy can be transferred through the implanted system and cause tissue damage resulting in severe injury or death.

WARNINGS Sources of electromagnetic interference (e.g., defibrillation, electrocautery, MRI, RF ablation, and therapeutic ultrasound) can interact with the system, resulting in unexpected changes in stimulation, serious patient injury or death. An implanted cardiac device (e.g., pacemaker, defibrillator) may damage a neurostimulator, and electrical pulses from the neurostimulator may cause inappropriate response of the cardiac device.

PRECAUTIONS Safety and effectiveness has not been established for pediatric use, pregnancy, unborn fetus, or delivery. Avoid activities that put stress on the implanted neurostimulation system components. Recharging a rechargeable neurostimulator may result in skin irritation or redness near the implant site.

ADVERSE EVENTS May include: undesirable change in stimulation (uncomfortable, jolting or shocking); hematoma, epidural hemorrhage, paralysis, seroma, infection, erosion, device malfunction or migration, pain at implant site, loss of pain relief, and other surgical risks.

Refer to www.medtronic.com for product manuals for complete indications, contraindications, warnings, precautions and potential adverse events.

USA Rx Only

Rev 0119

Kyphon Balloon Kyphoplasty and Sacroplasty Important Safety Information

Kyphon Xpede™ Bone Cement and Kyphon HV-R™ Bone Cement are indicated for the treatment of pathological fractures of the vertebral body due to osteoporosis, cancer, or benign lesions using a cementoplasty (i.e. kyphoplasty or vertebroplasty) procedure. It is also indicated for the fixation of pathological fractures of the sacral vertebral body or ala using sacral vertebroplasty or sacroplasty. Cancer includes multiple myeloma and metastatic lesions, including those arising from breast or lung cancer, or lymphoma. Benign lesions include hemangioma and giant cell tumor. Pathologic fracture may include a symptomatic vertebral body microfracture (as documented by appropriate imaging and/or presence of a lytic lesion) without obvious loss of vertebral body height.

Risks of acrylic bone cements include cement leakage, which may cause tissue damage, nerve or circulatory problems, and other serious adverse events, such as: cardiac arrest, cerebrovascular accident, myocardial infarction, pulmonary embolism, or cardiac embolism.

Osteocool Important Safety Information

The OsteoCool™ RF Ablation System is intended for the palliative treatment in spinal procedures by ablation of metastatic malignant lesions in a vertebral body and of benign bone tumors such as osteoid osteoma. It is also intended for coagulation and ablation of tissue in bone during surgical procedures, including palliation of pain associated with metastatic lesions involving bone in patients who have failed or are not candidates for standard therapy.

Risks of the system include damage to surrounding tissue through iatrogenic injury as a consequence of electrosurgery; pulmonary embolism; nerve injury including thermal injury, puncture of the spinal cord or nerve roots potentially resulting in radiculopathy, paresis, and paralysis.

References

1. Pain Management Best Practices Inter-Agency Task Force Third Meeting, Opening Remarks, Time Stamp 48:39;. 2019; https://www.youtube.com/watch?v=xGpzw7jFOmg&list=PLrl7E8KABz1GUeYTPG9_3Xnvq23noOTQQ&index=2&t=0s. Accessed June 2019.
2. *Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research.* Washington DC, United States: The National Academies Press; 2011.
3. Chou R, Deyo RA, Devine B, et al. *The effectiveness and risks of long-term opioid treatment of chronic pain: evidence report/technology assessment No. 218. AHRQ publication no. 14-E005-EF.* Rockville, MD: Agency for Healthcare Research and Quality; 2014.
4. Centers for Disease Control and Prevention. Commonly used terms. https://www.cdc.gov/drugoverdose/opioids/terms.html. Accessed July 2018.
5. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2016 national survey on drug use and health. HHS publication no. SMA 17-5044, NSDUH Series H-52. 2017; Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm. Accessed July 2018.
6. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain.* 2015;156(4):569-576.
7. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA.* 2016;315(15):1624-1645.
8. Centers for Disease Control and Prevention. Opioids for acute pain: what you need to know. https://www.cdc.gov/drugoverdose/pdf/patients/Opioids-for-Acute-Pain-a.pdf. Accessed July 2018.
9. Centers for Disease Control and Prevention. Guideline for prescribing opioids for chronic pain: improving practice through recommendations. https://www.cdc.gov/drugoverdose/pdf/Guidelines_Factsheet-a.pdf. Accessed July 2018.
10. US Food and Drug Administration. FDA's opioid analgesic REMS education blueprint for health care providers involved in the treatment and monitoring of patients with pain, January 2018. https://www.regulations.gov/contentStreamer?documentId=FDA-2017-D-2497-0683&attachmentNumber=1&contentType=pdf. Updated January 2018. Accessed July 2018.
11. SUPPORT for Patients and Communities Act, (2018).
12. US Department of Health and Human Services. Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. 2019; https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf. AccessedJuly 2019.
13. Hedegaard H, Warner M, Minino A. Drug overdose deaths in the United States, 1999-2016. NCHS data brief no. 294. National Center for Health Statistics publications and information products: data briefs. https://www.cdc.gov/nchs/products/databriefs/db294.htm. Updated December 21, 2017. Accessed July 2018.
14. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci U S A.* 2015;112(49):15078-15083.
15. Solly M. US Life Expectancy Drops for Third Year in a Row, Reflecting Rising Drug Overdoses, Suicides. https://www.smithsonianmag.com/smart-news/us-life-expectancy-drops-third-year-row-reflecting-rising-drug-overdose-suicide-rates-180970942/. AccessedJune 2019.
16. Hatheway JA, Caraway D, David G, et al. Systemic opioid elimination after implantation of an intrathecal drug delivery system significantly reduced health-care expenditures. *Neuromodulation.* 2015;18(3):207-213.
17. Boonen S, Van Meirhaeghe J, Bastian L, et al. Balloon kyphoplasty for the treatment of acute vertebral compression fractures: 2-year results from a randomized trial. *J Bone Miner Res.* 2011;26(7):1627-1637.
18. Centers for Disease Control and Prevention. Understanding the epidemic. Opioid overdose: opioid basics. https://www.cdc.gov/drugoverdose/epidemic/index.html. Updated August 30, 2017. Accessed July 2018.
19. Centers for Disease Control and Prevention. Drug overdose death data. Opioid overdose: data. https://www.cdc.gov/drugoverdose/data/statedeaths.html. Updated December 19, 2017. Accessed July 2018.
20. Howe N. America's opioid crisis: a nation hooked. *Forbes*. https://www.forbes.com/sites/neilhowe/2017/11/30/americas-opioid-crisis-a-nation-hooked/#9b4f2c96a570. Accessed July 2018.
21. Ahmad FB, Escobedo LA, Rossen LM, Spencer MR, Warner M, P S. Provisional Drug Overdose Death Counts. National Center for Health Statistics. 2019; https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm. AccessedJuly 2019.
22. Gomes T, Tadrous M, Mamdani M. The burden of opioid-related mortality in the United States. *JAMA Network.* 2018.
23. Rhyan C. The potential societal benefit of elimination opioid overdoses, deaths, and substance use disorders exceeds $95 billion per year. Center for Value in Healthcare; https://altarum.org/sites/default/files/uploaded-publication-files/Research-Brief_Opioid-Epidemic-Economic-Burden.pdf. November 16, 2017. July 2018.
24. Opioids In The Workplace: New Survey By The Hartford Shows Growing Impact And Increasing Need For Employers To Act Now. [press release]. November 27 2018.
25. Sinatra R. Causes and consequences of inadequate management of acute pain. Pain Med. 2010;11(12):1859-1871.
26. Cleveland Clinic. Acute vs. chronic pain. https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain. Updated January 26, 2017. Accessed July 2018.
27. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain.* 2012;13(8):715-724.
28. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. *MMWR. Morbidity and mortality weekly report.* 2018;67(36):1001-1006.
29. Rubin DI. Epidemiology and risk factors for spine pain. *Neurol Clin.* 2007;25(2):353-371.
30. Centers for Disease Control and Prevention. Guideline for prescribing opioids for chronic pain: promoting patient care and safety. https://www.cdc.gov/drugoverdose/pdf/guidelines_at-a-glance-a.pdf. Accessed July 2018.
31. Centers for Disease Control and Prevention. Opioid overdose. https://www.cdc.gov/drugoverdose/. Updated October 23, 2017. Accessed August 2018.
32. US Food and Drug Administration. Public meeting on patient-focused drug development for chronic pain. July 9, 2018. https://www.fda.gov/Drugs/NewsEvents/ucm603093.htm. Accessed July 2018.
33. Pain Management Best Practices Inter-Agency Task Force Second Meeting, September 25-26, 2018, Day 2, Pain Management Patient Testimonies. 2018; https://www.youtube.com/watch?v=3PXyV_9j-Vg&list=PLrl7E8KABz1FlXVYxbOxTMBvX_vDqbqXa&index=9&t=0s. AccessedJune 2019.
34. Deer T. *Atlas of implantable therapies for pain management.* New York, NY: Springer Science and Business Media, LLC; 2011.
35. US Food and Drug Administration. Human factors considerations. Device advice: comprehensive regulatory assistance: human factors (medical devices). https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/ucm124829.htm. Updated December 23, 2017. Accessed July 2018.
36. Medtronic. Data on file.
37. Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med.* 2012;13(10):1304-1313.
38. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol.* 2002;20(19):4040-4049.
39. Deer T, Chapple I, Classen A, et al. Intrathecal drug delivery for treatment of chronic low back pain: report from the National Outcomes Registry for Low Back Pain. *Pain Med.* 2004;5(1):6-13.
40. Atli A, Theodore BR, Turk DC, Loeser JD. Intrathecal opioid therapy for chronic nonmalignant pain: a retrospective cohort study with 3-year follow-up. *Pain Med.* 2010;11(7):1010-1016.
41. Roberts LJ, Finch PM, Goucke CR, Price LM. Outcome of intrathecal opioids in chronic non-cancer pain. *Eur J Pain.* 2001;5(4):353-361.

42. Winkelmuller M, Winkelmuller W. Long-term effects of continuous intrathecal opioid treatment in chronic pain of nonmalignant etiology. *J Neurosurg.* 1996;85(3):458-467.
43. Grider JS, Etscheidt MA, Harned ME, et al. Trialing and maintenance dosing using a low-dose intrathecal opioid method for chronic nonmalignant pain: a prospective 36-month study. *Neuromodulation.* 2016;19(2):206-219.
44. Onofrio BM, Yaksh TL. Long-term pain relief produced by intrathecal morphine infusion in 53 patients. *J Neurosurg.* 1990;72(2):200-209.
45. Bansal M, Nichols C, Hatheway JA. Systemic opioid reduction and elimination following implantation of intrathecal drug delivery systems for chronic pain. *Neuromodulation.* 2019;22(3):E248.
46. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. *JAMA.* 2004;291(1):63-70.
47. Wallace MS, Charapata SG, Fisher R, et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial. *Neuromodulation.* 2006;9(2):75-86.
48. Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manage.* 2006;31(5):393-406.
49. Kumar K, Hunter G, Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. *J Neurosurg.* 2002;97(4):803-810.
50. Kumar K, Rizvi S, Bishop S. Cost effectiveness of intrathecal drug therapy in management of chronic nonmalignant pain. *Clin J Pain.* 2013;29(2):138-145.
51. Caraway D, Walker V, Becker L, Hinnenthal J. Successful Discontinuation of Systemic Opioids After Implantation of an Intrathecal Drug Delivery System. *Neuromodulation.* 2015;18(6):508-516.
52. Medtronic enrolls first patient in clinical study to assess pain control and oral opioid elimination with Targeted Drug Delivery [press release]. Dublin, Ireland, January 17 2019.
53. Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. *Eur J Pain.* 2005;9(4):363-373.
54. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg.* 2008;108(2):292-298.
55. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. *Neurosurgery.* 2008;63(4):762-770.
56. North RB, Kidd D, Shipley J, Taylor RS. Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized, controlled trial. *Neurosurgery.* 2007;61(2):361-369.
57. Taylor RJ, Taylor RS. Spinal cord stimulation for failed back surgery syndrome: a decision-analytic model and cost-effectiveness analysis. *Int J Technol Assess Health Care.* 2005;21(3):351-358.
58. Sharan AD, Riley J, Falowski S, et al. Association of opioid usage with spinal cord stimulation outcomes. *Pain Med.* 2018;19(4):699-707. *A non-randomized analysis of Truven Health Marketscan databases from January 2010 to December 2014 based on the first occurrence of an SCS implant (N= 5,476).*
59. Gee L, Smith HC, Ghulam-Jelani Z, et al. Spinal Cord Stimulation for the Treatment of Chronic Pain Reduces Opioid Use and Results in Superior Clinical Outcomes When Used Without Opioids. *Neurosurgery.* 2019;84(1):217-226. *A non-randomized prospective cohort study of SCS patients between September 2012 and August 2015 (N=86 [n=53 on opioids]).*
60. Pollard EM, Lamer TJ, Moeschler SM, et al. The effect of spinal cord stimulation on pain medication reduction in intractable spine and limb pain: a systematic review of randomized controlled trials and meta-analysis. *J Pain Res.* 2019;12:1311-1324. *A research review summarising SCS studies with respect to opioid use and a further meta-analysis of comparative SCS RCTs of 1 year or greater duration (N=489).*
61. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurgery.* 2005;56(1):98-107.
62. Berenson J, Pflugmacher R, Jarzem P, et al. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: a multicentre, randomised controlled trial. Lancet Oncol. 2011;12(3):225-235.

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