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Pain Consult

DEPARTMENT OF PAIN MANAGEMENT | 2016

Stemming the Tide of Opioid Dependence

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Dear Colleagues,

As pain practitioners, many of us have seen the ravages of opioid addiction. Over the past decade, this problem has grown exponentially worse. Today we are making every effort to reduce opioid usage and find alternative medications and therapies to address pain.

Over the past two years, Cleveland Clinic has changed its opioid medication prescribing practices, based on recommendations of the Ohio Governor's Cabinet Opiate Action Team and the Centers for Disease Control and Prevention. We are doing all we can in Pain Management to contribute to efforts to stop and reverse the staggering trend of opioid addiction and deaths from overdose here in Ohio. However, as a whole, the volume of narcotics being dispensed is still far too high, and we must find a way to fight this battle on every front.

In July, during the Republican National Convention, I was honored to be part of a health policy forum in Cleveland on the national opioid epidemic alongside Ohio Sen. Rob Portman and Ohio Attorney General Mike DeWine. The panel also included Ohio Department of Mental Health and Addiction Services Director Tracy Plouck and Anthem Blue Cross and Blue Shield of Ohio President Erin Hoeflinger.

Sen. Portman announced that the Senate had just passed a federal bill that includes 18 provisions aimed squarely at reducing opioid usage and abuse. (It was immediately signed into law by the president.) DeWine said the ultimate solution will be working with kids at a young age to educate them on the dangerous addictive qualities of certain painkillers. Ms. Plouck and Ms. Hoeflinger each spoke on the numerous initiatives their respective organizations are implementing, including online documentation of events, and programs to help people beat their addiction.

With the public and private sectors' laser-like focus on this national crisis, we have opened the lines of communication. As physicians we must do our part to curtail the proliferation of inappropriate opioid prescriptions. It requires that we change the focus from passive pain management to active wellness with improved function.

For more on the opioid epidemic, see my feature article on page 3 of this issue; and in another article, meet pain pharmacist Elizabeth Casserly, PharmD, RPh, BCPS, who is an important part of Cleveland Clinic's efforts to improve patient care and minimize opioid usage.

Also in this issue, learn about dorsal root ganglion stimulation for reducing pain in the lower extremities, and meet Jianguo Cheng, MD, PhD, whose stem cell research could revolutionize pain management therapies in the future.

I hope you find this issue stimulating, and I urge you to contact me and my colleagues featured on these pages with your feedback and thoughts.



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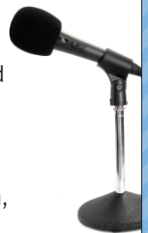
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The Opioid Epidemic: A Status Update

Opioid Prescriptions Drop; New CDC Guidelines Published



// BY RICHARD W. ROSENQUIST, MD //

› *Dr. Rosenquist is Chairman, Department of Pain Management.*

Two years ago, I reported that pain specialists had dramatically reduced use of opioids for noncancer-related chronic pain, and explained how we address dependency.

These efforts, along with the new CDC Guideline for Prescribing Opioids for Chronic Pain¹ issued in March, seem to be paying off, with a reported 12 to 18 percent decrease in opioid prescriptions nationally (see “Opioid Prescriptions Drop for First Time in Two Decades,” *New York Times*, May 21, 2016). Yet overdoses of prescription opioids, fentanyl and heroin continue to claim far too many lives.

More than 165,000 people died from an overdose related to opioid pain medication in the United States from 1999 to 2014, according to the Centers for

Disease Control and Prevention. And while death rates for leading causes of death such as heart disease and cancer have decreased substantially in the past decade, the death rate associated with opioid pain medication has increased markedly.²

HOW WE GOT HERE

The opioid epidemic is the result of a confluence of factors. In the late 1980s, we saw a push to destigmatize and promote the use of opioids as a means of treating chronic pain. At the same time, several small studies — now discredited — claimed that opioids relieved chronic pain without a significant risk of addiction. In parallel, a large pharmaceutical manufacturer began a major sales effort in the 1990s for a sustained-release formulation of oxycodone. The effectiveness of this medication is now being questioned on multiple fronts as well.

In the mid-1990s, the idea emerged that pain should be considered the fifth vital sign. We asked about pain at every visit, reducing the pain score became a major objective, and we prescribed medication, including opioids, for minor bumps and bruises. As demand for opioids began to increase, pill mills operated by unscrupulous clinicians cropped up and provided ready access to large amounts of highly addictive drugs in exchange for cash payments. In more recent years, reduced payments for clinical care and good payments for laboratory testing have created perverse financial incentives to prescribe opioids and conduct urine drug screening.

In addition, the problem has been exacerbated by a medical education system that failed to teach clinicians how to properly evaluate chronic pain, appropriately prescribe pain medications

Continued next page ›

or use nonopioid analgesic approaches effectively.

THE GREAT IRONY

We began to see physical and psychological dependence on these drugs and, ironically, not much improvement in

The U.S. has less than 5 percent of the world population, but uses about 80 percent of prescription opioids.

– *World Drug Report 2011, United Nations Office on Drugs and Crime*

pain control. Scientific evidence has now caught up with the expansion of opioid use, and we know that over the long term, opioids offer poor pain relief. On average, patients report a 20 to 30 percent reduction in pain — not 50 or 80 percent, and certainly not 100 percent. In my own career, I can think of only one person for whom I prescribed relatively high-dose opiates whose pain was significantly reduced and who was able to return to work. Only a small subset of patients tends to do really well on opioids for chronic noncancer pain, and they usually take small doses on an intermittent basis.

The result of all these factors was a meteoric rise in addiction, abuse and overdose, as well as other side effects of chronic opioid use — constipation, nausea, endocrine abnormalities, osteo-

porosis, sedation, depression, immunosuppression, opioid-induced hyperalgesia and death.

IS THERE HOPE THAT WE CAN TURN THIS AROUND?

There is hope, and now evidence, that the epidemic is starting to lessen. Public awareness about opioid abuse has increased. At the federal and state government levels, we see new pain-related legislation.

Ohio, one of the hotbeds of opioid abuse, has been among the most progressive states in terms of action. The Governor's Cabinet Opiate Action Team has published guidelines, and we have one of the country's best prescription drug monitoring programs. The state has closed down a number of bad actors and continues to investigate others. There has also been a marked increase in the amount of education available to address opioid issues in medical schools and for physician and nonphysician providers in practice to provide them with appropriate guidance for prescribing opioids for cancer and noncancer-related pain.

WHAT CLINICIANS CAN DO

The CDC has provided a rational and reasonable set of guidelines. The guidelines promote the use of opioids for short periods (for instance, a two- or three-day course versus a 30-day prescription for an ankle sprain), spell out appropriate indications, require checking online databases regarding patients' other prescriptions (especially benzodiazepines, other narcotics and pain medications) and recommend reduced dosages. The CDC's checklist for prescribing opioids for chronic pain is a helpful tool for primary care clinicians.

At Cleveland Clinic we recommend looking for a history of addiction, alcoholism

or suicide attempts prior to prescribing. If we decide to prescribe an opioid, we require the patient to sign a "consent for opioid management" form that outlines risks, spells out refill procedures, and explains urine drug screening requirements and more.

START LOW AND GO SLOW, AND DON'T BE AFRAID TO SAY 'NO'

I never expected to spend time on a daily basis explaining to people why I am not going to prescribe narcotic pain medication for them. I encourage colleagues, both primary care and specialists, who encounter patients requesting prescriptions for opioids to not be afraid to say no. Don't say yes when you want to say no.

The most common drugs involved in prescription opioid overdose deaths include²:

- *Methadone*
- *Oxycodone (such as OxyContin®)*
- *Hydrocodone (such as Vicodin®)*

On the other hand, patients in pain need help. To assess the impact of pain, I rarely ask the patient directly about his or her pain score. Instead I focus on function. I ask the patient if he is able to engage in activities of daily living, social activities or work. Is she getting up and moving? Is he able to do things with friends and family, or work around the house?

If a patient is not functioning well, we offer comprehensive evaluations to develop a clear diagnosis whenever possible, and

multimodality pain treatment programs that focus on improving function.

If there is evidence of dependency or addiction, we offer safe tapering and additional recovery approaches through Cleveland Clinic's Alcohol and Drug Rehabilitation Center. In addition, the Chronic Pain Rehabilitation Program is designed to reduce pain and chemical dependency and improve function. Alternative pain management strategies often involve physical therapy, psychological therapy, medical management and other approaches. The latter may include nerve blocks, injections, neuromodulation approaches such as high-frequency spinal cord or peripheral nerve stimulation, or alternative approaches such as acupuncture or osteopathic manipulation therapy.

Still, if someone with diabetic neuropathy is 150 pounds overweight and doing little to control their blood sugar, chances are slim that any medication or other strategy will effectively control this pain. For any pain management program to work, patients need to be engaged in their own health, and we need to work in tandem to achieve a good outcome.

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1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. *MMWR Recomm Rep.* 2016; 65:1–49.
2. Ossiander EM, Using textual cause-of-death data to study drug poisoning deaths. *Am J Epidemiol.* 2014 Apr 1; 179(7):884–894.

HEALTH FORUM ON OPIOID ABUSE

In July, Richard W. Rosenquist, MD, Chairman of Cleveland Clinic's Department of Pain Management (pictured below at far right), was part of a panel discussion in Cleveland on "Public and Private Solutions to America's Opioid Crisis," hosted by JobsOhio and the 2016 Host Committee of the Republican National Convention. The panel pictured below (left to right) included Ohio Sen. Rob Portman, Ohio Department of Mental Health and Addiction Services Director Tracy Plouck, Anthem Blue Cross and Blue Shield of Ohio President Erin Hoeflinger, and Ohio Attorney General Mike DeWine (not pictured). During the discussion, it was reported that the Senate had voted to pass a bill that targets the nation's opioid epidemic (soon after signed into law by President Obama). The Comprehensive Addiction and Recovery Act (CARA) includes 18 provisions designed to combat opioid addiction across the country.

Pictured left to right Ohio Sen. Rob Portman, Tracy Plouck, Erin Hoeflinger and Richard W. Rosenquist, MD.



Pain Management physicians are often on the front lines of helping patients wean off opioids. See the story on p. 8 about a Cleveland Clinic patient who was able to stop using opioids with her physician's help.

Preventing Polypharmacy in the Pain Clinic

A clinical pharmacist suggests alternatives to opioids



// FEATURING ELIZABETH CASSERLY, PHARM.D, RPH, BCPS //

Drug interactions and polypharmacy play a large role in the opioid epidemic, says Elizabeth Casserly, PharmD, RPh, BCPS, a clinical pharmacist in Cleveland Clinic's Department of Pain Management.

"By themselves, and in low doses, opioids are typically safe," she says. "But when patients are on several opioids, at high doses, or in combination with benzodiazepines [anxiety drugs], they have a much higher risk of overdose and death."

Both opioids and benzodiazepines reduce respiratory rate and are addictive. Their potency multiplies when they're combined.

"It's not that physicians knowingly prescribe these drugs together," says Dr. Casserly. "It happens inadvertently — like when a patient fills a benzodiazepine prescription from their primary doctor and, maybe months later, fills an opioid prescription from their pain doctor. We really can't control what drugs patients already have at home."

HOW OPIOIDS BECAME THE GO-TO PAIN DRUG

Opioids are often prescribed for every type of pain, but they are not the most effective medication we have for every type of pain.

"They're like a shotgun," says Dr. Casserly. "They have a broad effect."

Other pain medications are less addictive and cause fewer interactions, but they work only on specific types of pain.

"For example, medication for nerve pain

won't work on inflammatory pain, and vice versa," says Dr. Casserly.

ALTERNATIVES TO OPIOIDS

Pain physicians can help prevent potentially deadly polypharmacy interactions by not prescribing opioids when possible, says Dr. Casserly. Here she lists opioid alternatives for treating the three primary types of pain.

1) For nerve pain. "We commonly prescribe tricyclic antidepressants (TCAs), such as amitriptyline, nortriptyline and desipramine," says Dr. Casserly. "Other options include serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, or anticonvulsants, such as gabapentin or pregabalin." Neuropathy is difficult to treat, and some medications can take weeks to have an effect. In the meantime, lidocaine cream or patches can give short-term relief, she says.

2) For inflammatory pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, ibuprofen, naproxen and meloxicam, can dull pain caused by in-

flammation. However, NSAIDs can cause complications for patients who have cardiovascular disease, kidney disease or gastrointestinal bleeding. For these patients, rubbing NSAID gels onto a painful joint may be safer than swallowing NSAIDs, says Dr. Casserly.

3) For musculoskeletal pain. Dr. Casserly recommends heat, stretching and physical therapy and possible use of short-term muscle relaxants.

PHYSICIANS AND PHARMACISTS WORKING TOGETHER

Staying apprised of pain medications and all their usage considerations may seem overwhelming. That's why more physicians are relying on pharmacists for ongoing guidance — and even collaboration on treatment decisions.

"Now with the opioid epidemic, more hospitals are looking to pharmacists for treatment alternatives," says Dr. Casserly. "It's good for all physicians to have a working relationship with a pharmacist for help with problem solving and exploring pharmaceutical options."

STAFF PHARMACIST ‘INVALUABLE’ TO THE CHRONIC PAIN CLINIC


She’s a first at Cleveland Clinic. Elizabeth Casserly, PharmD, RPh, BCPS, is a clinical pharmacist who works alongside physicians in Cleveland Clinic’s Department of Pain Management.

“I’m integrated into the Chronic Pain Clinic,” says Dr. Casserly. “I collaborate with physicians to determine the best treatment for each patient. If medication is needed, we discuss interactions and other considerations to identify the best drug.”

More medical centers have begun adding pharmacists to their clinical teams, she notes.

Pain Management Department Chairman Richard W. Rosenquist, MD, stresses the importance of Dr. Casserly’s role, saying, “I have been working with a clinical pharmacist in my pain practice for 22 years and have found them to be invaluable members of the team.”

Dr. Casserly can be reached at cassere@ccf.org or 216.212.2426.



Pharmacist Elizabeth Casserly works with Pain Management physicians to address polypharmacy concerns. Here she is reviewing a patient chart with Robert Bolash, MD.



AFTER TWO DECADES ON OPIOIDS, PATIENT GETS HER LIFE BACK

In 1990, Ms. Smith (a pseudonym to protect confidentiality) was injured when a medical cart fell on her left side. The accident led to a series of surgeries and setbacks, and in 1997 she was diagnosed with complex regional pain syndrome (CRPS). She soon began many years of opioid drug use that led to serious health problems. By 2005, the CRPS had spread to her right side and she was taking more opioids for the pain and had to go on long-term disability from her job.

“Narcotics were ruining my life,” Ms. Smith says. “I knew something had to change.” In 2008, after years of being on several opioid prescriptions, she began seeing Cleveland Clinic Pain Management Specialist Bruce Vrooman, MD.

Of her long list of prescriptions, she remembers taking fentanyl, OxyContin®, Ativan®, ketamine, Robaxin® and morphine, some as many as four times a day. In the beginning she says they made her antisocial. They eventually made her feel like she was in a stupor and she began losing her memory. Over time, the meds ravaged her body, leading to hair loss, tooth loss, bowel blockage and extreme weight loss. She went from her normal weight of 115 pounds to 80 pounds.

By building a rapport with Dr. Vrooman and talking to a pain psychologist, Ms. Smith says she found new ways to cope with and manage her pain.

“Frequently, patients are taking relatively high doses of opioid medications when they are referred to our office,” says Dr. Vrooman. “Rarely are they doing well, as these medications are pro-inflammatory and contribute to endocrine dysfunction and immunosuppression. And besides the risk of addiction, they may lead to worsening pain, or hyperalgesia. My first goal is to help patients learn to help themselves by decreasing destructive behavior and gaining insight into their pain condition. Ms. Smith showed a willingness to change.”

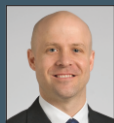
Today, Ms. Smith has pain every day, but she keeps busy. She swims, volunteers at church, spends time with her husband and is training her puppy as a service dog. “With help, I learned how to avoid dwelling on the pain and to stay positive. Exercise makes all the difference,” she says.

Now in her 50s, she takes a medication called low-dose naltrexone (LDN), which is shown to be a safe, effective and inexpensive medication for certain pain patients. She says people tell her she looks a lot younger than she did. Her memory is clear, and she has her sense of humor back.

“Today Ms. Smith is goal-directed, has energy and good mobility,” says Dr. Vrooman. “Her mood affect is bright, and she has developed excellent coping and wellness skills. After we were able to titrate her opioid medications downward, we started her on LDN, and this has led to dramatic changes in her life.”

He says low-dose naltrexone is an opiate antagonist that increases endorphin production and acts as a glial attenuator. It calms the body’s autoimmune system, and she tolerates it well. Ms. Smith is also taking an antidepressant, vitamin D and magnesium, and she uses lidocaine ointment for pain as needed. With a positive attitude and a strong support network, Dr. Vrooman says she will continue to do well.

LDN is currently being used in an off-label manner, but has been shown in clinical studies at Stanford University among other institutions to be safe and effective in treating conditions such as CRPS, fibromyalgia, multiple sclerosis and Crohn disease. The future is bright for this promising alternative to opioid medications.



Dr. Vrooman can be reached at vroomab@ccf.org or 216.445.9641.

Dorsal Root Ganglion Stimulation Offered for CRPS in Lower Extremities



// FEATURING NAGY MEKHAIL, MD, PHD, AND SAMUEL SAMUEL, MD //

In February, the U.S. Food and Drug Administration approved a novel treatment for patients with complex regional pain syndrome (CRPS I and II) in the lower extremities. Dorsal root ganglion (DRG) stimulation is an outpatient neuromodulation therapy, similar to traditional spinal cord stimulation (SCS). Rather than being placed over the posterior aspect of the spinal cord as in SCS, leads are implanted on the dorsal root ganglion, a cluster of neurons in the posterior root of spinal nerves.

“The dorsal root ganglion represents the sensory gate of the spinal cord,” says Nagy Mekhail, MD, PhD, of Cleveland Clinic’s Department of Pain Management. “Every sensory perception entering the spinal cord must pass through the dorsal root ganglion.” The DRG neurons are capable of modulating all sensations before processing to the spinal cord and other areas of the central nervous system. That makes DRG stimulation a particularly effective therapeutic approach for patients with chronic intractable pain.

ADVANTAGES OF DRG STIMULATION

DRG stimulation features two surgically implanted components: a pulse generator, which is placed beneath the skin in the buttocks or abdomen, and up to four leads. The leads are attached to the pulse generator and the tissue near the target treatment area. When activated, the leads send very small electrical

impulses to the dorsal root ganglion, thereby blocking the pain stimulant.

Patients first undergo a trial for one week to ensure the therapy is effective. Then, one week to 10 days later, surgeons implant the system under the skin, much like they would a pacemaker. The implant procedure takes approximately 60 to 90 minutes.

Dr. Mekhail cites four distinct advantages of targeting the dorsal root ganglion for pain relief:

- **Directed anatomical targeting** — DRG stimulation offers a highly directed stimulation field, which can limit stimulation to the pain area. In the clinical trial of DRG stimulation for chronic lower limb pain — the ACCURATE study — 94.5 percent of patients received targeted stimulation in the area of pain without extraneous paresthesia compared with 61.2 percent of patients in the SCS control group.
- **Low energy requirements** — The dorsal root ganglion is surrounded by a very thin layer of spinal fluid. Because the layer between the stimulator and the dorsal root ganglion cells is so narrow, DRG stimulation uses only about 10 percent of the energy required for traditional SCS. That, in turn, leads to longer-lasting batteries.

- **Marginal risk of lead migration** — The dorsal root ganglion is tucked in a very small space, reducing the chances of lead migration. Stimulation leads reported less than a 1 percent migration rate in the ACCURATE Study. Traditional SCS reports a 14 percent migration rate. (*Washburn et al., Industry Wide Incidence Rate of SCS Related Complications, NANS 2010.*)
- **Minimal postural effects** — Because the dorsal root ganglion is located in such a small space, the spinal fluid in between does not vary with the patient’s body position. Therefore, the pattern of stimulation for DRG is constant regardless of any changes in body position. The patient receives the same stimulation — and pain relief — whether lying, standing, sitting or walking. Conversely, the pattern of stimulation varies with position among SCS patients.

CLINICAL INDICATIONS

Dr. Mekhail is one of two pain management physicians at Cleveland Clinic trained to perform the DRG stimulation procedure. Dr. Mekhail functioned as the medical monitor of the FDA-sponsored multicenter ACCURATE study. The other is Samuel Samuel, MD, Director of the Pain Management Clinic at Cleveland Clinic Marymount Hospital, who participated as investigator in the ACCURATE



study that led to FDA approval of the St. Jude Medical Axium™ Neurostimulator System for CRPS.

“The results I’ve seen so far are very encouraging, and I am really excited about this procedure,” says Dr. Samuel. During the clinical trial, which ran from September 2014 to July 2015, he handled the first two cases done at Cleveland Clinic. One patient had CRPS II following foot surgery and a subsequent infection. She couldn’t walk and experienced severe pain if someone touched her foot.

“The minute we turned on the DRG stimulation, her pain was 100 percent gone,” says Dr. Samuel. “We could touch and squeeze her foot with her feeling absolutely no pain.” The patient received the implant one week after her trial and has remained pain-free ever since. She’s back to her normal life – wearing shoes,

walking and working, adds Dr. Samuel.

The FDA has approved DRG stimulation for lower extremity CRPS, which could include neuropathic pain conditions and chronic pain following foot, knee, groin and other surgeries. DRG stimulation is not a replacement for SCS, but rather an alternative in the right clinical scenario. “Certain areas are tough to capture with spinal cord stimulation – the foot, the front of the knee, the groin,” says Dr. Samuel. “DRG stimulation is a new treatment for conditions that are inadequately treated with conventional SCS.”

Dr. Mekhail says one of the best future indications for DRG stimulation is diabetic neuropathy. Over time, high blood sugar can damage the peripheral nerves, particularly in the legs and feet. Patient pain is often managed with medication, which can be costly and may cause mul-

multiple side effects. “Using DRG stimulation at the L5 ganglia, we can target both feet and relieve the intractable pain of diabetic neuropathy,” he says.

He also recommends the procedure for patients with CRPS who have had limited or no success with conservative treatment, including physical therapy, medications and sympathetic nerve blocks. “If these treatments have not worked within three to six months, move on,” says Dr. Mekhail. “DRG stimulation can pay for itself over time by saving healthcare costs, and it can provide patients much-needed relief.”

DRG STIMULATION STUDY RESULTS

Traditional spinal cord stimulation (SCS) has been utilized since 1967, and although the technology has evolved, it's not a panacea for chronic pain patients. "I call it the 50/50 club: All the studies so far indicate that 50 percent of patients get relief [with SCS] and 50 percent don't, which is really quite dismal," says Nagy Mekhail, MD, PhD, of Cleveland Clinic's Department of Pain Management.

The recently approved dorsal root ganglion (DRG) stimulation therapy offers hope for improved relief. Dr. Mekhail cites several promising results from the safety and effectiveness trial of DRG stimulation:

- Three months after the implant, 70 percent of participants who received DRG stimulation had more than 80 percent pain relief, compared with 52 percent of the control group who underwent SCS.
- One year after the implant, 67.3 percent of DRG subjects had more than 80 percent pain relief, compared with 54 percent of SCS subjects.
- 94.5 percent of DRG subjects received targeted stimulation in the area of pain without extraneous paresthesia, compared with 61.2 percent of SCS subjects.



At left: Dr. Mekhail placing a stimulator at the dorsal root ganglion in a patient's spine. The procedure lasted just an hour and a half and completely eliminated the patient's back pain.

Below: The lightweight battery pack that fuels the stimulator fits in the palm of the hand.



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Dr. Samuel can be reached at samuels@ccf.org or 216.444.8621.

Stem Cell Therapy for Neuropathic Pain: New Findings Show Promise

// FEATURING JIANGUO CHENG, MD, PHD //

Stem cell research at Cleveland Clinic could pave the way for an entirely new approach to chronic pain treatment that reduces medicine's current reliance on opioid therapy for intractable pain. The modality also shows promise as a tool for reversing opioid tolerance (OT) and opioid-induced hyperalgesia (OIH), particularly problematic side effects of opioid therapy. Jianguo Cheng, MD, PhD, and his colleagues at Cleveland Clinic have developed patented methods of attenuating opioid tolerance.

Animal studies by Dr. Cheng and colleagues have demonstrated the effectiveness of mesenchymal stem cell (MSC) transplantation in reducing hyperalgesia due to nerve injury. The group's work has shown MSC transplantation's effectiveness in reducing pain induced by sciatic nerve injury in rats and mice. MSC transplantation significantly reduced pain

sensitivity evaluated by foot withdrawal thresholds in animals in response to thermal or mechanical stimulation. These cells produced immune modulatory and anti-inflammatory effects, promoted sensory nerve repair, and showed strong analgesic properties that could provide a safer and more effective alternative to current treatment modalities in the management of neuropathic pain, says Dr. Cheng, Professor of Anesthesiology and Director of Cleveland Clinic's Multidisciplinary Pain Medicine Fellowship Program.

Pain medicine researchers are searching for an alternative to opioid therapy because neuropathic pain often does not respond to morphine and other opioids. Opioid analgesics can also lead to a variety of complications, ranging from itching and constipation to dependence, addiction, respiratory depression and death.

About 30 percent of neuropathy cases are caused by nerve damage associated with diabetes. However, hundreds of diseases are linked to neuropathic pain. Sources of neuropathic pain include alcoholism, amputation (which can result in phantom pain), some chemotherapy drugs (for example, cisplatin, paclitaxel, vincristine), radiation therapy, complex regional pain syndrome II, trigeminal neuralgia, shingles, spinal stenosis, and central nervous system disorders such as Parkinson disease and multiple sclerosis.

Recent research by Dr. Cheng and his group has yielded new discoveries that bode well for MSC transplantation as a potential treatment modality. One investigation compared the analgesic effects of MSCs derived from bone marrow with MSCs derived from adipose tissue. Adipose-derived cells were found to be as efficacious as bone marrow-derived cells

in reducing neuropathic pain in rats. The finding suggests that stem cell therapy could offer a practical option because stem cells from adipose tissue are relatively easy to obtain.

Recent investigations by Dr. Cheng and his colleagues comparing the analgesic effectiveness of intrathecal versus intravenous methods of MSC transplantation show both methods to be equally effective. The finding has important implications because intravenous transplantation of MSCs could offer a safer and more expeditious route of delivery than intrathecal transplantation.

“We originally thought that stem cells would have to be introduced intrathecally

in order to reduce pain, and that stem cells introduced intravenously would pass through the lungs and fail to produce analgesia,” says Dr. Cheng. “The finding that intravenous transplantation is as effective as intrathecal transplantation is encouraging.”

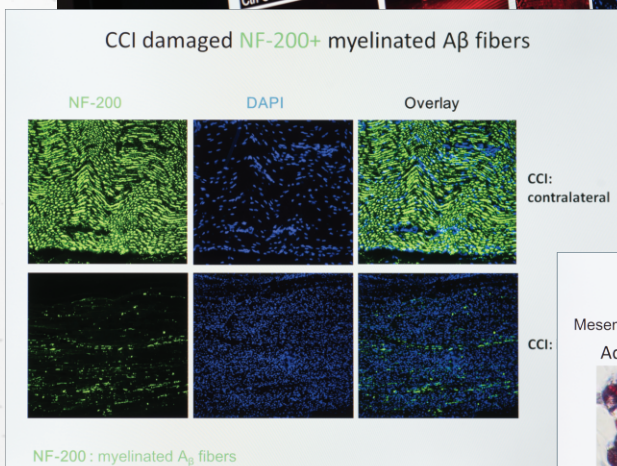
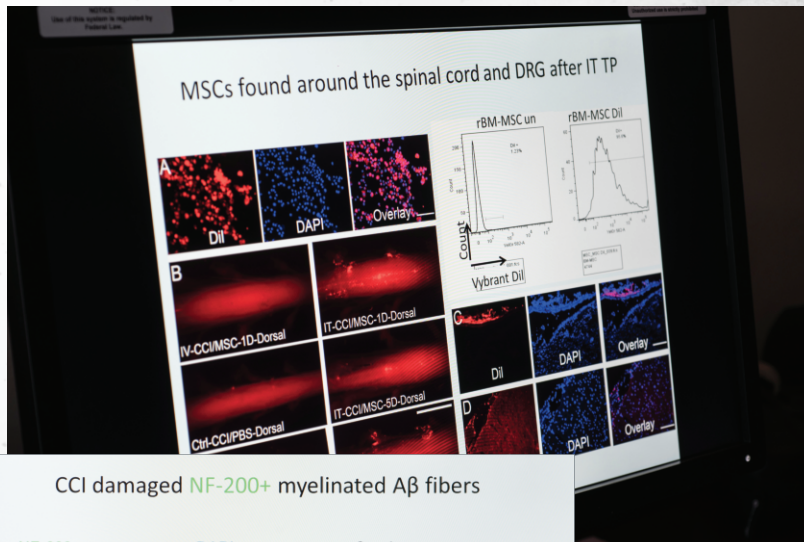
Dr. Cheng’s group has also discovered that MSCs can be found in the area surrounding the injured nerve following intravenous MSC transplantation. “For reasons we do not yet fully understand, these cells have the ability to migrate to the injury site to promote repair of the injured nerve fibers,” Dr. Cheng says. “The cells can sense the injury’s location and travel to it.”

Although many questions must be answered before it can be known whether stem cell therapy is safe and effective for humans, some small patient studies show potential, Dr. Cheng says. According to one observational study in Australia, MSC transplantation reduced pain in patients suffering from trigeminal neuralgia, a particularly difficult condition to treat. “Though the findings are preliminary, the study provides some evidence that what we have learned in the laboratory can be translated to clinical use,” Dr. Cheng says.

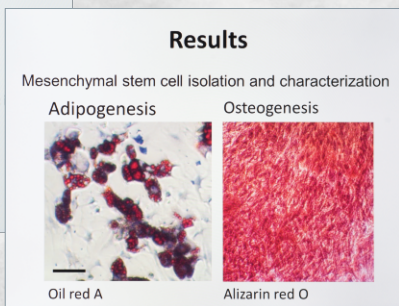
Dr. Cheng’s team has achieved analgesia with MSC transplantation from rats to mice, providing early evidence that stem cells’ anti-inflammatory and immunomodulatory properties can be transferred between species. An important pre-clinical study will be to see whether the transplantation of human stem cells to animals also can produce analgesic and anti-tolerance effects, Dr. Cheng says.

Dr. Cheng’s team presented research at the 2016 annual meeting of the American Academy of Pain Medicine showing MSCs’ potential to reverse opioid tolerance and opioid-induced hyperalgesia, problems that can compromise the safety and efficacy of opioid therapy. Intravenous transplantation of bone marrow-derived MSCs significantly attenuated OT and OIH in animals whether the transplantation was performed seven days before or 14 days after the initiation of daily morphine injections. These data demonstrate that MSC transplantation can not only prevent the development of OT and OIH but can also reverse these conditions.

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Stem cells, generated from the bone marrow and fat tissues, were transplanted either intrathecally or intravenously to treat neuropathic pain and opioid tolerance.



Using OMT as a Complementary Pain Treatment



// FEATURING WILLIAM WELCHES, DO, PHD //

While many patients feel better with conventional pain management treatment and/or procedures, others continue to struggle to live their normal lives. In this latter circumstance, complementary or alternative therapies can help. It can be useful to combine mainstream therapies with alternative therapies for which we have scientific evidence of safety and effectiveness.

Research has shown that osteopathic manipulation therapy (OMT), or the therapeutic application of manual pressure, can help relieve low back pain, neck pain, sports injuries, repetitive stress injuries and some types of headaches. According to the National Institutes of Health, looking at six studies, OMT treatment significantly reduces low back pain. The *Annals of Internal Medicine* also recommends considering the use of spinal manipulation for treatment of acute and subacute low back pain. Recently, John C. Licciardone, DO, and co-workers at the University of Texas Medical School have shown that OMT is clinically effective for chronic low back pain.

In Cleveland Clinic's Department of Pain Management, William Welches, DO, PhD, is an osteopathic physician who has expertise in OMT. "I use osteopathic manipulation, along with several programs, including diet therapy and acupuncture, to help patients with their pain," says Dr. Welches. "My techniques and programs are integrated with those of my colleagues in Pain Management to provide patients with comprehensive treatment."

Dr. Welches says OMT is a whole system of evaluation and treatment designed to achieve and maintain health by restoring normal body function.

"It is critical that we bring the full range of therapies to bear on the treatment of chronic pain if we are going to improve function and overall success rates," says Richard W. Rosenquist, MD, Chairman of Cleveland Clinic's Department of Pain Management.

Dr. Welches can be reached at welchew@ccf.org or 216.295.1010.

STIMWAVE TRIAL FOR BACK AND LEG PAIN AFTER SPINE SURGERY

A multicenter randomized trial of wireless spinal cord stimulation is underway to demonstrate the efficacy of various stimulation frequencies. This technology is now available without an implantable battery.

The key inclusion criteria for patients:

- Chronic back pain or back and leg pain
- Previous spine surgery
- Pain unrelieved by medical treatments

A spinal cord stimulator is placed within the epidural space to deliver electrical signals to diminish pain. No implantable battery is required. Study-related procedures will be paid by the sponsor, Stimwave LLC.

For more information, please contact Robert Bolash, MD, Clinical Site Investigator, at bolashr@ccf.org, or Natalie Mansour, MD, Clinical Study Coordinator, at mansoun@ccf.org.



Pain Management Trials Now Enrolling Patients

Cleveland Clinic’s Department of Pain Management is enrolling patients in a range of ongoing clinical studies, including those outlined below.

SELECTED CLINICAL TRIALS IN THE DEPARTMENT OF PAIN MANAGEMENT

Study Name	Site PI and Contact	Description/Objective	Patient Population/Key Inclusion Criteria	Sponsor
WHISPER: A Randomized Controlled Study to Evaluate the Effectiveness of the Precision Spinal Cord Stimulator System at Sub-Perception Amplitude	PI: Nagy Mekhail, MD, PhD Contact: Meera Kumari, MD 216.444.1292	Randomized, controlled trial to evaluate the Boston Scientific Precision SCS System, programmed with commercially approved settings but without providing tingling sensations in subjects who have chronic low back and/or limb pain.	Patients 22 years or older implanted with the Precision SCS System for at least 6 months prior to informed consent. Interested in SCS-induced pain relief without paresthesia. Willing to comply with protocol requirements.	Boston Scientific
Axsome: Treatment of CRPS with Disodium Zoledronate Tetrahydrate pill	PI: Nagy Mekhail, MD, PhD (national PI) Contact: Tariq Niazi, MD, 216.445.8270 Meera Kumari, MD 216.444.1292	Randomized, double-blind trial to assess the efficacy and safety of AXS-02 (Disodium zoledronate tetrahydrate) administered orally to subjects with chronic regional pain syndrome type I (CRPS-I).	Patients 18 years or older with confirmed diagnosis of CRPS-I in upper or lower limb within past 6 months.	Axsome Therapeutics Inc.
Mesoblast Study: A Prospective, Multicenter, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Injection of rexlémestrocel-L Alone or Combined with Hyaluronic Acid (HA) in Subjects with Chronic Diskogenic Lumbar Back Pain Through 12 Months	PI: Nagy Mekhail, MD, PhD Contact: Meera Kumari, MD, 216.444.1292 Tariq Niazi, MD 216.445.8270	Treatment of chronic diskogenic lumbar back pain (> 6 months’ duration) associated with moderate degenerative disk disease (DDD) not adequately controlled by conservative measures.	Male and female subjects, at least 18 years of age, inclusive, and skeletally mature, in the opinion of the investigator. Documented diagnosis of moderate DDD from L1 to S1, with one symptomatic disc, in the opinion of the investigator. Baseline of at least 40 mm and less than 90 mm of 100 mm on low back pain VAS (average pain over 24 hours).	Mesoblast Ltd.
Intrathecal pump: Study of Hydromorphone HCl by Intrathecal Administration Using a Programmable Implantable Pump	PI: Nagy Mekhail, MD, PhD Contact: Tariq Niazi, MD 216.445.8270	Controlled, two-arm, parallel-group, randomized withdrawal study to determine the safety and efficacy of hydromorphone HCl by intrathecal administration using a programmable implantable pump.	Patients 18 to 75 with a clinical diagnosis of chronic pain for at least 6 months who are presently on intrathecal pain medication and have (or are eligible for) SynchroMed® II pump implantation.	CNS Therapeutics
Neuros: High-Frequency Nerve Block for Post-Amputation Pain	PI: Nagy Mekhail, MD, PhD Contact: Tariq Niazi, MD, 216.445.8270 Meera Kumari, MD 216.444.1292	High-frequency nerve block for post-amputation pain.	Male and female subjects, at least 18 years of age, inclusive. Subjects shall have had a unilateral amputated lower limb for no less than 12 months.	Neuros Medical Inc.

VAS = visual analog scale

The Department of Pain Management

WHO WE ARE

25 Physicians with board certification in pain medicine

104 Employees (physicians + all caregivers)

8 Research staff (physician + PhD researchers)

WHO WE TREAT – AND HOW (2015 NUMBERS)

 **83,797** Patient visits
64,482 Outpatient visits | 19,315 Inpatient visits

 **23** Number of countries from which patients came

 **38,969** Procedures

 **8,666** Imaging studies sent to Cleveland Clinic Imaging Institute

OUR OTHER MISSIONS

 **8** Active research projects

 **\$208,929** External funding for research

 **24** Residents for the year

 **10** Fellows for the year

 **203** Attendees at our 18th Annual Pain Management Symposium in February

OTHER KEY ACCOMPLISHMENTS OF 2015-2016

- Successful rollout of the care team model across all pain care locations to promote greater collaboration between physicians and midlevel providers
- Initiated 9 multicentered, sponsored trials that include 50 patients
- Received an unrestricted \$100,000 donation to the Pain Management Department
- Construction underway on \$550,000 in renovations for the medical offices at Cleveland Clinic Lutheran Hospital



Department of Pain Management Staff

Our specialists are available at multiple locations across Northeast Ohio.



Richard W. Rosenquist, MD
 Department Chair
 216.442.5728 | rosenqr@ccf.org
 Cleveland Clinic main campus
Specialties: Postsurgical pain syndromes, neuropathic pain, neck pain, low back pain, pain in athletes



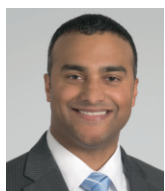
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 Lutheran Hospital, Westlake Medical Campus Building A
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 Fairview Hospital, Lorain Family Health and Surgery Center
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 Strongsville Family Health and Surgery Center, Lakewood Hospital
Specialties: Interventional pain management, back pain, neck pain, arachnoiditis, neuropathic pain, myofascial pain

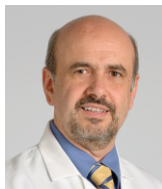


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ment, diskogenic back pain, herniated disks,
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**William Welches, DO, PhD**

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ic back and neck pain, musculoskeletal pain,
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pain, cancer pain

New Staff**Crawford Barnett, MD**

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South Pointe Hospital

Specialties: Back and neck pain, facial pain,
neuropathic pain, abdominal pain, musculo-
skeletal pain, CRPS, pelvic pain

Congratulations



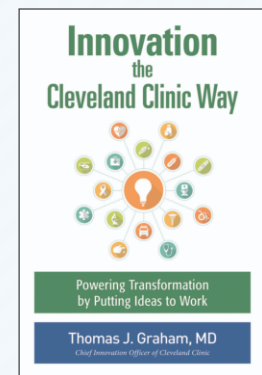
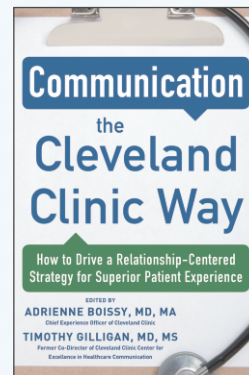
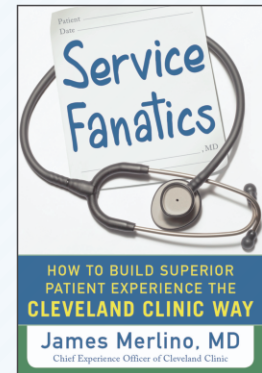
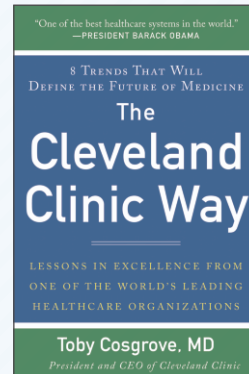
Richard W. Rosenquist, MD, Chairman of Cleveland Clinic's Department of Pain Management, was presented with the **2015 American Society of Regional Anesthesia and Pain Medicine**

John J. Bonica Award. This award recognizes an individual for his or her outstanding contributions to the development, teaching and practice of pain management in the tradition of John J. Bonica, MD. Dr. Rosenquist received the award at the 14th Annual Pain Medicine Meeting in Miami, where, as part of the honor, he presented a lecture titled "At the Table or On the Menu: The Value of Engagement in Pain Medicine."



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About Cleveland Clinic

Cleveland Clinic is an integrated healthcare delivery system with local, national and international reach. At Cleveland Clinic, more than 3,400 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 18 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2016, Cleveland Clinic ranked No. 2 in *U.S. News & World Report's* "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 22nd consecutive year).



Physician Directory

View our staff online at clevelandclinic.org/staff.

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