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## CME ARTICLE

### Update on Intradiscal Procedures and Future Approaches

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*Learning Objectives: After participating in this CME activity, the physician should be better able to:*

1. Evaluate the indications and contraindications to intradiscal electrothermal therapy.
2. Evaluate the indications and contraindications to baculoplasty.
3. Evaluate the indications and contraindications to percutaneous discoplasty.

As interventional pain medicine specialists have moved to more aggressive treatment of the disc, they have often been stymied by a lack of evidence-based therapy, which in turn has led refusals by insurance companies to cover these procedures. This article analyzes the current state of the evidence for and against these therapies and discusses other therapies that are on the horizon for discal intervention.

#### Annuloplasty

Intradiscal electrothermal therapy (IDET) was developed by Saal and Saal<sup>1,2</sup> to serve as an alternative to fusion for patients with chronic discogenic low back pain. The pathophysiology of

discogenic pain is complex but is thought to arise from nociceptive nerve receptors in the annulus, which increase when the disc degenerates, is injured, or is exposed to a variety of inflammatory substances. This increase in neural pain receptors causes increased and unremitting low back pain. IDET was developed to modify the collagen inside the disc, causing it to contract, while also destroying pain receptors.

#### IDET Procedure

IDET is performed with fluoroscopic guidance, while the patient is under conscious sedation, lying prone. As with many intradiscal procedures, discography—along with the pain provocation test—is integral in evaluation of the affected disc. A 17-gauge needle is inserted posterolaterally into the disc, generally from the patient's less-painful side. A 30-cm catheter with a flexible 5- to 6-cm heating tip is threaded circumferentially into the disc through the nucleus pulposus to the pathologic area of the annulus. After fluoroscopic confirmation, the catheter tip is heated to 90°C over a 13-minute period. Once at

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90°C, the temperature is maintained for an additional 4 minutes. The catheter and needle are then removed. The patient is then observed in a recovery area before being discharged home the same day.

Indications for IDET include long-term low back pain with failure of conservative therapy, a normal neurologic examination, negative straight-leg raise on physical examination, MRI confirmation of no neural compressive lesion, and positive pain provocation test. Exclusion criteria include inflammatory arthritis, nonspinal conditions that mimic lumbar pain, and any medical or metabolic condition that would interfere with proper follow-up.


There are no published studies of multiple-level IDET therapy. Much controversy<sup>3,4</sup> still centers on this technique, as there have been limited independent studies and few studies reporting long-term follow-up of patients undergoing IDET.

**IDET's Effect**

The presumed mechanism of collagen modification may lead to a reduction in the size of annular fissures and increase the stability of the disc. The long-term impact of this change has not been quantified, however, as no studies have demonstrated whether full biomechanical properties are restored, or to what extent and duration this approach works. IDET also thermocoagulates the nociceptors within the annular walls, thus destroying the ability to transmit nociceptive input and, in turn, relieve pain.

Reported complications include catheter breakage, nerve-root injuries, post-IDET disc herniation, cauda equina syndrome, infection, epidural abscess, and spinal cord damage. It is important to note that there are no frequency data available to indicate

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whether these are random operator errors or intrinsic to the procedure.

## **Evidence for the efficacy of IDET remains weak and has not passed the standard of scientific proof.**

In a systematic review of the literature in 2006, Appleby et al<sup>3</sup> concluded that there was compelling evidence for the relative efficacy and safety of IDET.

Freeman<sup>4</sup> performed a critical appraisal of the evidence of IDET and concluded that evidence for the efficacy of IDET remains weak and has not passed the standard of scientific proof. The present evidence includes 1 positive randomized trial, 1 negative randomized trial, 7 positive prospective evaluations, and 2 negative reports.

### **Radiofrequency Annuloplasty**

Radiofrequency (RF) annuloplasty (RFA) is a minimally invasive method of delivering RF thermal energy to the disc. An example of this approach is the discTRODE RF catheter electrode system, which uses heat to coagulate and decompress disc material. Ideal candidates for this procedure are patients with chronic low back pain as the result of an internally disrupted disc, but without radiculopathy.

## **There is supportive evidence for radiofrequency ablation for short-term improvement, but there are no published long-term follow-up data or head-to-head trial data.**

### **Catheter Electrode Procedure**

The catheter electrode procedure is typically performed with x-ray guidance, with a cannula inserted directly into an intervertebral disc. The catheter electrode is passed through the cannula into the outer disc tissue. RF current flows through the electrode, heating the tissue directly adjacent to the active tip of the electrode. An additional external temperature monitor allows the physician to observe temperature changes in surrounding tissue continuously throughout the procedure.

Documented complications are similar to those associated with IDET: catheter breakage, nerve root injuries, discitis, disc herniation, cauda equina syndrome, infection, epidural abscess, and spinal cord damage.<sup>5,6</sup> There are no published frequency data of these complications.

Finch et al<sup>7</sup> studied 31 patients by heating annular tears with a flexible RF electrode placed across the posterior annulus, and they compared the study group with 15 patients who underwent conservative management. Visual analog scale (VAS) scores in the

treatment group decreased significantly. Thus, there is supportive evidence for RFA for short-term improvement, but there are no published long-term follow-up data or head-to-head trial data.

### **Biacuplasty**

A relatively new annuloplasty procedure, intradiscal biacuplasty, involves a bipolar system that includes 2 cooled, RF electrodes placed on the posterolateral sides of the intervertebral annulus fibrosus, in similar placement to a discogram.

In their initial case report, Kapural and Mekhail<sup>8</sup> reported a young man with severe axial discogenic pain treated with this procedure. The 2 electrodes were placed fluoroscopically in a manner similar to that for a discogram twice. Two 17-gauge transdiscal introducers were placed in the posterior annulus using a posterolateral oblique approach. Then, RF probes were positioned through each of the introducers bilaterally to create a bipolar configuration. There was a gradual increase of the temperature of the electrodes to 55°C over 11 minutes. There were no intraoperative complications.

After the procedure, the patient was monitored for 45 minutes and then discharged home. The patient was observed for a 6-month follow-up period. Outcome assessment included a 36-item short form health survey (SF-36) and Oswestry questionnaires. VAS pain scores changed from 5 (baseline) to 2 at 30 days, and to 1 at 6-month follow-up. Oswestry scale improvement was noted from 14 points before the procedure to 11 points at 1-month follow-up, and 6 points at 6 months of follow-up.

Kapural<sup>9</sup> described the results of a 12-month follow-up of a pilot study, which presents excellent results. A head-to-head trial versus other discal therapies is necessary to demonstrate superiority, and this is underway.<sup>10</sup> From the prospective of possible complications, because there is no catheter to advance or coil, there are no catheter-related complications. The complications spectrum should be similar to performing a discogram or any RF procedure. Again, there are no large-scale studies that present complication frequency data.

## **As a small amount of nucleus pulposus is vaporized, intradiscal pressure decreases, in theory allowing the disc to return to its normal shape and state.**

### **Percutaneous Disc Decompression via Laser Discectomy**

Medical lasers have been used since the early 1960s. Choy<sup>11</sup> published their experiences with the use of a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser on the lumbar spine for nucleolysis. There are several types of lasers in use for the lumbar spine. The most common is the holmium:YAG (Ho:YAG) laser, and the others are potassium-titanyl-phosphate and the Nd:YAG laser. The Ho:YAG laser is most commonly

paired with the endoscope for disc ablation and removal capabilities. This laser-assisted technique combines 2 effective but limited approaches.

As the tissues absorb the laser, the light is converted to heat. At 100°C, the tissue vaporizes, and ablation takes place. As a small amount of nucleus pulposus is vaporized by the laser, intradiscal pressure decreases, in theory allowing the disc to return to its normal shape and state. If more disc material needs to be removed, endoscopic tools can be used to do so.

### **Laser Discectomy Procedure**

The patient is placed in a prone or lateral position under conscious sedation. An 18-gauge 7-inch needle is introduced just anterior to the superior articular process and superior to the transverse process via the “safe triangle.” Using fluoroscopy, the needle is placed 1 cm beyond the annulus into the nucleus pulposus just parallel to the disc axis, preferably halfway between the superior and inferior endplates.

If the procedure is endoscopically assisted, dilators are placed over the guide needle for visualization and the introduction of the endoscope. Irrigation with saline allows for better visualization of the spaces.

Depending on the type, the laser is fired either as a pulse or continuously. The Ho:YAG laser is pulse-fired. Newer laser models offer side-firing capabilities. This advancement helps to provide more control of laser placement and better observation, and it can help to reduce the risk of injury to several areas, especially those anterior to the spinal column. Larger fragments, which are more difficult to remove through the endoscope, can be ablated by laser. After firing the laser and removing or ablating an adequate amount of nucleus pulposus, the laser and dilators are removed. The incision can be closed with sutures or surgical adhesives. The patient is moved to recovery and sent home later in the day.

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**Indications for laser discectomy include back and leg pain with a confirmed disc herniation; a ruptured annulus and lateral recess stenosis are not contraindications.**

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### **Indications for Laser Discectomy**

Indications for laser discectomy include back and leg pain with a confirmed disc herniation; a ruptured annulus and lateral recess stenosis are not contraindications. Newer transforaminal procedures can treat those patients with fragments in the epidural space. In 2002, Tsou and Yeung<sup>12</sup> reported the 9-year retrospective results of their percutaneous transforaminal approach, with an 88.1% excellent-to-good result. Other authors<sup>13</sup> report success rates ranging from 78% to 85% in retrospective studies. There is a scarcity of prospective and randomized clinical trials of percutaneous laser treatment.

In contrast, a systematic review by Waddell et al<sup>14</sup> concluded: “there is no acceptable evidence for laser discectomy.” Relevant studies evaluating the effectiveness of laser disc decompression included 14 studies meeting inclusion criteria. There were no randomized trials. It is this poor clinical trial methodology that is hampering clear clinical evidence in support of this procedure.

### **RF Coblation (Plasma Discectomy)**

RF coblation (plasma discectomy) combines disc removal and thermal coagulation to decompress a contained herniated disc. With the patient in a prone or lateral position under sedation, a fluoroscopy-guided, posterolateral approach is made with a 17-gauge obturator stylet. A discogram is obtained at this time to confirm location and act as a positive provocation test. Taking care not to contact the anterior annulus, the practitioner first ablates the nucleus pulposus with RF waves while advancing the wand, causing molecular dissociation and converting the annular tissue into gas, which is then removed through the needle. As the wand is withdrawn, coagulation takes place, thermally treating the channel, which leads to a denaturing of nerve fibers adjacent to the channel within the nucleus pulposus. This process is repeated up to 6 times within an individual disc. The patient is then moved to recovery and sent home later the same day.

Indications for RF coblation include low back pain with or without radiculopathy, MRI confirmation of contained herniated disc, and failed conservative therapy. Patients who should be excluded from receiving this procedure include those with spinal stenosis, a loss of disc height of 50%, severe disc degeneration, spinal fracture, or tumor.

Derby et al<sup>15</sup> evaluated the “evidence-informed management” of chronic low back pain with minimally invasive nuclear decompression and concluded that nucleoplasty does not support the treatment of back pain alone, but the procedure is better suited for the improvement of referred extremity pain in patients with protrusion less than 4 to 6 mm, minimal stenosis, and relatively well-maintained disc height. There are no published data from large-scale studies regarding complication rates.

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**Percutaneous lumbar discectomy has been performed for more than 30 years with overall results ranging from disappointing to good.**

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### **Mechanical Disc Decompression**

Percutaneous lumbar discectomy (PLD) has been performed for more than 30 years with overall results ranging from disappointing to good. The techniques and equipment used for PLD vary widely and have fallen in and out of favor. The typical procedure uses a 3- to 5-mm cannula from the posterolateral approach; curettes; and time-consuming, manual removal of the nucleus pulposus with pituitary forceps. The theory was that reduction of intradiscal pressure would reduce irritation of the



nerve root and the nociceptive nerve receptors in the annulus. Few changes have been made in automated discectomy until recently, with innovations in automation.

The Dekompressor is a disposable, self-contained, battery-operated hand piece connected to a helical probe. The outer cannula measures 1.5 mm with an inner rotating probe. When activated, the probe rotates, creating suction to pull milled nucleus pulposus from the disc, up the cannula, and to a suction chamber at the base of the handheld unit. Approximately 0.5 to 2 mL of nucleus pulposus is removed. This efficient removal of disc material decreases surgical procedure times to approximately 30 minutes; with the probe used for not more than 10 minutes.

This procedure is performed under fluoroscopic guidance. The Dekompressor technique specifically has yet to be studied in a randomized prospective controlled clinical trial. In general, however, PLD has a reported rate of 60% to 87% good outcomes. Amoretti et al<sup>16</sup> reported results of clinical follow-up in 50 patients treated with PLD by use of the Dekompressor. Although the study was not a blinded, randomized study, data collection was thorough and precise. This study is the strongest evidence to date for use of the Dekompressor.

### **Automated Percutaneous Disc Decompression**

In a systematic review based on Cochrane Collaboration Review and meta-analysis of surgical interventions in the lumbar spine, Waddell et al<sup>14</sup> identified 3 trials comparing automated PLD (APLD) with other surgical techniques and concluded there was limited and contradictory evidence.

Randomized trials of APLD and microdiscectomy included studies by Chatterjee et al<sup>17</sup> and Haines et al.<sup>18</sup> Chatterjee et al<sup>17</sup> compared APLD with microdiscectomy in the treatment of contained lumbar disc herniation in a randomized study with blind assessment. The study included 71 patients with radicular pain as their dominant symptom after failure of conservative therapy for at least 6 weeks, and with MRI demonstration of contained disc herniation at a single level with a disc bulge less than 30% of the canal size.

The study excluded patients with dominant symptoms of low back pain, disc extrusion, sequestration, subarticular or foraminal stenosis, or multiple levels of herniation. The results showed satisfactory outcomes in 29% of the patients in the APLD group and in 80% of the microdiscectomy group. Chatterjee et al<sup>17</sup> concluded that APLD is ineffective as a method of treatment for small, contained lumbar disc herniations.

Haines et al<sup>18</sup> conducted a randomized study comparing APLD with conventional discectomy as a first-line treatment for herniated lumbar discs. The study measured outcomes with physical signs related to the severity of low back pain and sciatica, but it used a modified Roland Scale for disability assessment and the SF-36 for general health status.

The primary endpoint was patients' outcome ratings 12 months after surgery. The study included patients with unilateral leg pain or paresthesia with no history of lumbar spinal surgery, whereas exclusions included patients with moderate or advanced lumbar spondylosis, spondylolisthesis, lateral restenosis, herniated disc

fragment occupying more than 30% of the anteroposterior diameter of the spinal canal, herniated disc fragment migrating more than 1 mm above or below the disc space, calcified disc herniation, lateral disc herniation, or posterior disc space height less than 3 mm. The success rate for APLD was 41% compared with 40% for conventional discectomy. However, the authors<sup>18</sup> concluded that because of insufficient patient enrollment, the study was not powered to identify clinically important differences.

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## **Direct injection of growth factors or cytokine inhibitors has been unsuccessful because their effectiveness in the disc is too short-lived. Gene therapy is now under active investigation.**

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### **Future Approaches**

#### ***Glucosamine and Chondroitin***

Glucosamine and chondroitin sulfate enhance proteoglycan synthesis and have been used in multiple trials for peripheral joint osteoarthritis. There is evidence that glucosamine and chondroitin sulfate synergistically enhance the natural hypermetabolic repair response of chondrocytes and retard the enzymatic degradation of cartilage.

Derby et al<sup>19</sup> performed a pilot study using intradiscal injectable glucosamine and chondroitin sulfate with dimethylsulfoxide and hypertonic dextrose to promote a reparative response in the intervertebral disc. They hypothesized that the reduction in the pain and disability observed in patients treated with glucosamine and chondroitin mixtures results from favorable alteration in the biochemical milieu of the intervertebral disc. Clinical efficacy is similar to that of IDET procedures but with a much improved cost-benefit ratio. Placebo-controlled, randomized prospective comparative studies are needed to establish the efficacy of intradiscal glucosamine and chondroitin sulfate injections.

#### ***Cell-Based Therapies***

The aim of these therapies is to achieve cellular repair of the degenerated disc matrix. One approach has been to stimulate the disc cells to produce more matrix. Growth factors can increase rates of matrix synthesis by up to 500%. In contrast, cytokines lead to matrix loss because they inhibit matrix synthesis while stimulating production of agents that are involved in tissue breakdown. Thus, these proteins have provided targets for genetic engineering.

Direct injection of growth factors or cytokine inhibitors has been unsuccessful because their effectiveness in the disc is too short-lived. Gene therapy is now under active investigation; it has the potential to maintain high levels of the relevant growth factor or inhibitor in the tissue.

In gene therapy, the gene of interest (eg, one responsible for producing a growth factor such as transforming growth factor- $\beta$  or inhibiting interleukin-1) is introduced into target cells, which then continue to produce the relevant protein. This approach has

been shown to be technically feasible in the disc, with gene transfer increasing transforming growth factor- $\beta$  production by disc cells in a rabbit model by nearly 600%. However, this approach is limited by a lack of knowledge of the correct genes required to initiate repair within the disc. In addition, the cell density in normal human discs is low, and many of the cells in degenerate discs are already dead; stimulation of the few remaining cells may be insufficient to repair the matrix effectively.

### **Autologous disc cell transfer has been used clinically in small groups of patients, and initial reported results are positive.**

Cell implantation alone or in conjunction with gene therapy is an approach that may overcome the paucity of cells in a degenerated disc. The cells of the degenerated disc can be supplemented by adding new cells either on their own or together with an appropriate scaffold. This has been attempted with some success in animal discs. However, at present, no obvious source of clinically useful cells exists for the human disc, particularly for the nucleus, the region of most interest. Moreover, conditions in degenerate discs, especially if the nutritional pathway from the vasculature has been compromised, may not be favorable for survival of implanted cells. Nevertheless, autologous disc cell transfer<sup>20,21</sup> has been used clinically in small groups of patients, and initial reported results are positive.

#### **Augmentation of Nucleus Pulposus**

The objective of augmentation of the nucleus pulposus after disc removal is to prevent disc height loss and the associated biomechanical changes. Free-flowing materials may be injected via a small catheter, allowing minimally invasive access to the disc space. Fluids can fill the irregular surgical defects and bond physically to the adjacent tissue. Injectable biomaterials allow for incorporation and uniform dispersion of cells or therapeutic agents. Biomaterials are being developed that may act as a substitute for the nucleus pulposus.

A biomaterial for augmentation of the nucleus pulposus, NuCore Injectable Nucleus is composed of a solution of the protein polymer and a polyfunctional cross-linking agent. The material closely mimics the protein content, water content, pH, and complex modulus of the natural nucleus pulposus. Characterization studies indicate that the NuCore Injectable Nucleus is able to restore the biomechanics of the disc after microdiscectomy. The material is nontoxic and biocompatible. The mechanical properties of the material mimic those of the natural nucleus pulposus. Human clinical evaluation is under way in a multicenter clinical study<sup>22</sup> using the material as an adjunct to microdiscectomy.

#### **Conclusion**

The major difference between the pharmaceutical development industry and the medical device industry is the careful, incremental production of drug-related literature. The pharmaceutical industry engages medical communications and advertising agencies to plan

the launch of a product, including staging of various research studies that demonstrate efficacy and safety (as required by the FDA).

### **In contrast to the pharmaceutical development process, new medical device technologies are often introduced after a pilot study that is observational and not randomized.**

In contrast to the pharmaceutical development process, new medical device technologies are often introduced after a pilot study that is observational and not randomized. These repeated case series are often impressive, but from an evidence-based perspective, they constitute only weak evidence in support of the device. When subjected to a prospective, blinded, randomized trial, these devices and procedures (eg, vertebroplasty) do not live up to expectations. Under the Patient Protection and Affordable Care Act, also known as Obamacare colloquially by both supporters and detractors, we can look forward to more prospective head-to-head trials to clarify which technologies are critical advances and which are no better than placebo. The indications and contraindications of these interventional intradiscal approaches are clearly detailed, but from an evidence-based perspective, much work remains to demonstrate the superiority of one approach over another. ■

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## Reformulated Cancer Drug Seems to Prevent Morphine Tolerance

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The reformulation of a cancer drug, imatinib mesylate, could prevent opioid tolerance—or even reverse it—in patients who take opioids for chronic pain, according to research by Yan Wang, PhD, et al,<sup>1</sup> of the University of Texas MD Anderson Cancer Center.

The research, published under “Brief Communications” in *Nature Medicine*, showed that a reformulated version of imatinib mesylate (Gleevec, Novartis Pharmaceuticals Corporation, East Hanover, NJ) was able to prevent and reverse tolerance to morphine in animal studies.

If translational studies establish that the drug reverses analgesic tolerance with a favorable therapeutic index, it could benefit patients who are experiencing chronic pain but becoming increasingly tolerant to opioids.

“For chronic intractable pain, there’s nothing else that works as well as the opiates. For decades, people have been trying to figure out ways to reverse tolerance because it’s a huge problem,” said Howard Gutstein, MD, an author of the study and professor of anesthesiology at University of Texas MD Anderson Cancer Center.

“If [imatinib] works in people, as it does in animals, it really is a game changer, because there’s nothing else out there,” Gutstein said.

**Although other, previously published studies had also shown that opioids activated receptor tyrosine kinases, including PDGFR, the physiologic significance of the relationship was not well understood.**

The drug they reformulated is imatinib, an inhibitor of platelet-derived growth factor receptor- $\beta$  (PDGFR- $\beta$ ). Imatinib is a cancer drug currently approved by the FDA to treat leukemia and specific gastrointestinal tumors.

Gutstein and colleagues showed that PDGFR- $\beta$ -mediated signaling plays a key role in morphine tolerance. PDGFR- $\beta$  inhibition, they determined, selectively eliminated morphine tolerance in rats. If a PDGFR- $\beta$  inhibitor can do the same in clinical trials, it could ease suffering in patients with intractable pain who face a dilemma as they develop tolerance to morphine’s analgesic effects.

In the studies, the authors determined that morphine induces tolerance via the  $\mu$ -opioid receptor, which transactivated PDGFR- $\beta$ , a receptor tyrosine kinase. Experiments with fentanyl showed similar activation of PDGFR.

Although other, previously published studies had also shown that opioids activated receptor tyrosine kinases, including PDGFR, the physiologic significance of the relationship was not well understood.

Other methods used to attenuate morphine tolerance, such as N-methyl-D-aspartate receptor (NMDAR) antagonists, have yielded little practical gain because the NMDARs have proven to be either ineffective or neurotoxic.

Gutstein said he and his colleagues chose to study PDGFRs because the receptor is localized in pain-processing regions of the central nervous system (the dorsal root ganglion and spinal cord dorsal horn).

“When we started these studies, imatinib was the only available compound,” he said.



Gutstein and his colleagues formulated imatinib, a receptor tyrosine kinase inhibitor, with the commonly used carrier molecule Captisol (Ligand Pharmaceuticals, La Jolla, CA), a modified cyclodextrin. This formulation optimized the ability of imatinib to cross the blood-brain barrier.

In a series of experiments on rats, the researchers were able to see that intrathecal administration of imatinib in conjunction with morphine completely eliminated morphine tolerance without altering morphine's analgesic potency. Imatinib also completely reversed tolerance in animals that already were tolerant to high morphine doses.

"We think it's a mechanism that's common to other opioids as well, but morphine is the most widely used opioid," said Gutstein.

An animated illustration can be viewed on MD Anderson Cancer Center's YouTube channel at [http://www.youtube.com/watch?v=nrB\\_maaAlTg](http://www.youtube.com/watch?v=nrB_maaAlTg) or at <http://tinyurl.com/78rmz2q>.

The results of these experiments show promise for patients with chronic pain who find relief only from morphine therapy but face dose escalation as they develop tolerance.

"If human studies show that imatinib or other similar agents can reduce, reverse, or avoid opioid tolerance, then practitioners may begin to consider whether using these agents could be helpful for patients being treated chronically with opioids to manage their pain," said David S. Craig, PharmD, BCPS, clinical pharmacy specialist at H. Lee Moffitt Cancer Center & Research Institute in Tampa, Florida.

Gutstein and his colleagues were highly motivated to pursue their work—one of them was suffering from cancer pain, in fact.

"Our research was inspired by a research colleague and one of the authors of the study, Bing Mo, a postdoctoral student, who died of liver cancer and suffered from a lot of pain during our study," said Gutstein. "We hope that with continued study of imatinib we can provide something useful to patients."

## Further Study Needed

There is a paucity of research on opioid tolerance and the optimal ways to attenuate tolerance, particularly in patients on long-term opioid therapy. The clinical significance of using imatinib for this purpose remains to be seen. Although the US FDA has approved imatinib for human use, its safety and efficacy in preventing and reversing morphine tolerance in humans requires further study.

In addition, because the reformulated drug more efficiently crosses the blood-brain barrier, Gutstein and colleagues will undertake additional safety and efficacy trials in animals and neurotoxicology studies to ensure the drug is not harmful. According to the official website for Gleevec, almost all people who take it at the doses approved for leukemia and gastrointestinal tumors experience adverse effects, which include fluid retention, hematologic toxicity, severe congestive heart failure and left ventricular dysfunction, hepatotoxicity, hemorrhage, gastrointestinal disorders, and dermatologic toxicities.

"Tolerance to the effects of opioids in humans is very complex, but clinical observations suggest that tolerance may compromise therapeutic outcomes in some patients, and for this subgroup, the

potential utility of this class of drugs is of interest," said Russell Portenoy, MD, chairman and Gerald J. Friedman chair in pain medicine and palliative care at Beth Israel Medical Center and professor of neurology and anesthesiology at Albert Einstein College of Medicine.

"It is important to avoid leaping from preclinical models to humans when issues involving tolerance are discussed," Portenoy said. "Most experienced clinicians believe that tolerance alone—at least as it is inferred because of declining analgesia in the absence of a progressive lesion—is actually a very uncommon driving force for dose escalation."

However, Gutstein noted that "pure" tolerance as described by Portenoy is rare in the cancer population, but not as unusual in the nonmalignant chronic pain population.

"It is also fairly common in cancer survivors left with chronic pain as a consequence of treatments [such as] chemotherapy and radiation," Gutstein wrote via e-mail in a follow-up correspondence with *Topics in Pain Management*. "It is likely [that] in pain directly caused by cancer, disease progression and tolerance development could both contribute to escalating morphine doses."

## Could Reduction of Tolerance Pose a Risk?

Although these findings are a big step forward, there is a possibility that removing the natural mechanism of tolerance could have unforeseen consequences.

"Any drug that reversed tolerance to opioid side effects at the same time as reversing analgesic tolerance may not produce any benefit whatsoever, and actually could be risky," Portenoy said. "In humans, we rely on tolerance to side effects, like respiratory depression, to increase the safety of opioid drugs. Any preclinical work focused on the reversal of analgesic tolerance will need to be followed by both preclinical and clinical studies to evaluate outcomes related to non-analgesic effects."

In response, Gutstein noted that, "the reasons people overdose on narcotics, in pain treatment or drug abuse, is that they develop tolerance to the analgesic (or euphoric) effects of the drugs far more rapidly than the respiratory depressive effects. That is why addicts show up in emergency rooms not breathing, and patient disasters occur at home or in hospital wards. If in fact imatinib did reverse tolerance to opioid-induced respiratory depression, we would have expected to see many of our animals that were rendered tolerant to high doses of morphine die when imatinib was given. We did not observe any mortality. The underlying assumption that Dr. Portenoy makes is that tolerance to all effects of morphine are mediated via the same mechanism. Given that tolerance to opioids develops at different rates for different effects (and in the case of effects like constipation, tolerance unfortunately does not develop), it seems unlikely that this is the case."

"In fact," Gutstein said, "reducing the dose of morphine required to provide analgesia for a patient should improve the safety index of morphine." ■

## Reference

1. Wang Y, Barker K, Shi S, et al. Blockade of PDGFR- $\beta$  activation eliminates morphine analgesic tolerance. *Nat Med*. 2012;18(3):385-387.



## First Class-Wide Risk Evaluation and Mitigation Strategy Targets Extended-Release Formulations

The FDA approved a risk evaluation and mitigation strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications on July 9, 2012.<sup>1,2</sup>

The release of the REMS is designed to alert health care professionals and patients about the proper prescribing and the safe and proper use of ER/LA opioid analgesic medications. Manufacturers are responsible for making educational materials available to prescribers and patients. The FDA officials expect the first continuing education activities under the new REMS will be offered to prescribers by March 1, 2013.

The FDA also approved a patient-counseling document that prescribers can begin using any time now to discuss the risks and benefits of these products with their patients.

Key components of the REMS are:

**Training for prescribers:** Educational programs will be available in the spring of 2013.

**Updated medication guide and patient counseling document:** These are intended to be consumer-friendly information on the safe use, storage, and disposal of ER/LA opioid analgesics. They will address changing doses and emergency contact instructions.

**Assessment and auditing:** The FDA will require drug companies that manufacture the opioids on the list to train prescribers, and to achieve certain goals for the percentage of prescribers of ER/LA opioids who complete the training. The assessments will also address whether the REMS is adversely affecting patient access to necessary analgesics. Manufacturers will be required to also reporting on whether patient access is restricted.

A few days after the announcement, the American Pain Society (APS) issued a statement supporting the REMS and saying that it is consistent with the APS's policy. However, the APS statement expressed disappointment that the REMS applied only to ER/LA opioids.

"Despite our appreciation for the ER/LA REMS as announced, APS continues to disagree with FDA's decision to limit REMS to extended-release, long-acting opioids only. All opioids must be used, stored, and disposed of in similar ways for maximum safety," the statement said in conclusion. (Full text of the statement appears below.)

### Second-Generation REMS

In this second-generation REMS approach, one set of strategies applies to a whole class of opioids. Until now, the FDA required each manufacturer to submit a strategy to the FDA for its particular drug, leading in some cases to disparities between drugs that were manufactured by different companies, but which had the same risks.

Opioids are not the only class of drugs that require REMS, and not all opioids require them—only extended-release and long-acting opioids, including methadone. Some immediate-release opioids also have had to submit REMS to the FDA and follow them, requiring education and documentation on the part of physicians, as well as patients who take the drugs.

The ER/LA class of opioids consists of highly potent drugs that are approved to treat moderate to severe persistent pain for serious and chronic conditions (Table 1).<sup>3</sup>

## American Pain Society Response to REMS Announcement

*The following statement was issued by the American Pain Society in response to the July 9 announcement by the FDA of its extended-release, long-acting opioid REMS decision.*

The FDA's Risk Evaluation and Mitigation Strategies (REMS) for extended release/long-acting (ER/LA) opioids, announced on July 9, is consistent with the American Pain Society's strong belief that competency-based educational programs will benefit both primary care and specialty prescribers of ER/LA opioids and ultimately improve patient safety and decrease diversion while still assuring access to these medications for patients who need them.

Professional and consumer education programs can achieve significant benefits for improving awareness and reducing behaviors that contribute to opioid abuse. For example, the FDA's mandate that simplified medication guides and information sheets for ER/LA opioids be made available for patients will hopefully lead to improved knowledge concerning proper use, storage and disposal of these drugs and result in less intentional and unintentional diversion of these medicines.

The educational opportunities for prescribers and dispensers mandated by the REMS should be offered through a variety of channels. APS and other professional societies can play a vital role in helping to develop educational modules as part of the REMS programs implemented by FDA and drug manufacturers. Clinician training programs should be evidence-based, and designed to develop and improve clinical skills such as patient assessment, communication, and recognition of risks for abuse as the basis for developing integrated treatment plans, revising treatment plans, and making referrals to pain specialists as necessary.

Despite our appreciation for the ER/LA REMS as announced, APS continues to disagree with FDA's decision to limit REMS to extended-release, long-acting opioids only. All opioids must be used, stored and disposed of in similar ways for maximum safety. (See American Pain Society, <http://www.ampainsoc.org/press/2012/remstatement.html>.)

**Table 1. Extended-Release and Long-Acting Opioid Products Required to Have an Opioid REMS**

<b>Brand-Name Drugs</b>	<b>Generic Name</b>	<b>Sponsor(s)</b>
Avinza	Morphine sulfate extended-release capsules	Pfizer
Butrans	Buprenorphine transdermal system	Purdue Pharma
Dolophine	Methadone hydrochloride tablets	Roxane
Duragesic	Fentanyl transdermal system	Janssen Pharmaceuticals
Embeda*	Morphine sulfate and naltrexone extended-release capsules	Pfizer
Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt
Kadian	Morphine sulfate extended-release capsules	Actavis
MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
Nucynta ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals
Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals
OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
Palladone†	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma
<b>Generic Drugs</b>		
Fentanyl	Fentanyl extended-release transdermal system	Actavis, Lavipharm Labs, Mallinckrodt Mylan Technologies, Noven, Aveva, Watson
Methadone hydrochloride	Methadone hydrochloride concentrate	Roxane
	Methadone hydrochloride tablets	The Pharamanetwork, Mallinckrodt, Sandoz, Vistapharm
	Methadone hydrochloride oral solution	Roxane
Morphine sulfate	Morphine sulfate extended-release capsules	Watson
	Morphine sulfate extended-release tablets	Endo, Mallinckrodt, Mylan, Neshier, Ranbaxy, Rhodes, Watson Labs
Oxymorphone hydrochloride	Oxymorphone hydrochloride extended-release tablets	Impax, Actavis

\*Not currently available or marketed due to a voluntary recall but still approved. †No longer being marketed but still approved.  
REMS, risk evaluation and mitigation strategy.

On a frequently asked questions page on the FDA website,<sup>3</sup> to the question as to why the FDA is requiring REMS only for extended-release and long-acting opioids, the FDA responds:

“FDA is requiring a REMS for ER/LA opioid analgesics because FDA has concluded that there is a disproportionate safety problem associated with these products that must be addressed.”

In releasing the class-wide REMS, the FDA press release described it as “part of a multi-agency Federal effort to address the growing problem of prescription drug abuse and misuse. The

REMS introduces new safety measures to reduce risks and improve safe use of ER/LA opioids while continuing to provide access to these medications for patients in pain.”

“Misprescribing, misuse, and abuse of extended-release and long-acting opioids are a critical and growing public health challenge,” said Margaret A. Hamburg, MD, FDA commissioner. “The FDA’s goal with this REMS approval is to ensure that health care

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## Topics in Pain Management CME Quiz

To earn CME credit, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **August 31, 2013**. Only two entries will be considered for credit.

**Online quiz instructions:** To take the quiz online, **log on to your account at <http://www.topicsinpainmanagement.com>**, and click on the “CME” tab at the top of the page. Then click on “Access the CME activity for this newsletter,” which will take you to the log-in page for [CME.lwwnewsletters.com](http://CME.lwwnewsletters.com). Enter your *username and password for this screen as follows*: Your *CME username* will be the letters LWW (case sensitive) followed by the 12-digit account number above your name on the paper answer form mailed with your issue. Your *CME password* will be 1234; this password *may not* be changed. Follow the instructions on the site. You may print your official certificate *immediately*. Please note: Lippincott CME Institute, Inc., *will not* mail certificates to online participants. **Online quizzes expire at 11:59 pm Pacific Standard Time on the due date.**

1. **Indications for IDET include long-term low back pain with failure of conservative therapy and all of the following except**
  - A. normal neurologic examination
  - B. negative straight-leg raise on physical examination
  - C. an ependyoma at an adjacent level
  - D. an MRI scan that does not show compression or effacement of the disc upon a spinal nerve
2. **Exclusion criteria for IDET include all of the following except**
  - A. inflammatory arthritis
  - B. pancreatitis with radiation to upper lumbar area
  - C. radial tear in the annulus
  - D. vertebral fracture with loss of disc height
3. **Complications that have been reported with IDET include all of the following except**
  - A. catheter breakage
  - B. nerve root injuries
  - C. discitis
  - D. retroperitoneal hematoma
4. **Reported complications with RFA using the discTRODE RF catheter electrode system include all of the following except**
  - A. catheter breakage
  - B. nerve root injuries
  - C. discitis
  - D. transverse myelitis
5. **The Dekompressor technique specifically has yet to be studied in a randomized prospective controlled clinical trial.**
  - A. True
  - B. False
6. **Derby et al evaluated minimally invasive nuclear decompression and concluded that nucleoplasty does not support the treatment of back pain alone, but the procedure is better suited for the improvement of referred extremity pain in patients with protrusion less than 4 to 6 mm, minimal stenosis, and relatively well-maintained disc height.**
  - A. True
  - B. False
7. **A systematic review by Waddell et al concluded: “there is no acceptable evidence for laser discectomy.”**
  - A. True
  - B. False
8. **APLD is effective as a method of treatment for patients with small, contained lumbar disc herniations.**
  - A. True
  - B. False
9. **Glucosamine and chondroitin sulfate synergistically enhance the natural hypermetabolic repair response of chondrocytes and retard the enzymatic degradation of cartilage.**
  - A. True
  - B. False
10. **NuCore Injectable Nucleus comprises a solution of the protein polymer and a polyfunctional cross-linking agent that mimics the protein content, water content, pH, and complex modulus of the natural nucleus pulposus.**
  - A. True
  - B. False



## NEWS IN BRIEF

### Red Flag Raised on Aspirin's Effect in Migraineurs

Results of an exploratory study published in *Headache* suggest that migraineurs have a higher prevalence of high on-aspirin platelet reactivity (HAPR) than do healthy volunteers. The migraineurs also seemed to have a higher prevalence of HAPR than patients with coronary artery disease who were taking 325 mg of aspirin.

If migraineurs have a greater risk of platelet inhibition from aspirin, this could also mean a higher risk of stroke and myocardial infarction (MI). Clinical implications could involve a potential need for antiplatelet therapy in this population.

The authors used a single-group, pretest/posttest design, with 50 migraineurs who did not have history of stroke or MI. Of the 50 patients, 44 were women whose average age was 43. They were prospectively treated for 14 to 21 consecutive days with 325 mg generic enteric-coated aspirin, after undergoing a 14-day aspirin washout.

The authors measured platelet reactivity after aspirin washout and after aspirin treatment. (See Jesurum JT, et al. Aspirin's effect on platelet inhibition in migraineurs. *Headache*. 2012, Apr 5. doi: 10.1111/j.1526-4610.2012.02143.x [epub ahead of print].)

### TENS Shown Effective for Low Back Pain in Pregnancy

A prospective study by Keskin et al, at Fatih University's medical school in Ankara, Turkey, found that transcutaneous electrical nerve stimulation (TENS) was a safe treatment for low back pain during pregnancy, and that it was more effective than either exercise or acetaminophen.

The authors assessed 79 participants in the study, who were each at 32 or more weeks of gestation, and who reported low back pain with a score of 5 or more on a visual analog scale (VAS).

Subjects were randomly assigned to a control group or to 1 of 3 treatment groups: 19 patients used exercise as treatment; 19 used acetaminophen; and 20 received TENS.

More than half (57%) of patients in the control group reported pain intensity increasing. In all 3 treatment groups, patients reported that pain had decreased in intensity: all of the patients in the TENS and acetaminophen groups reported a decrease in pain, whereas 95% of those in the exercise group reported a decrease. VAS and Roland-Morris disability questionnaire scores indicated a significantly greater degree of pain relief in the TENS group than in the exercise and acetaminophen groups. (See Keskin EA, et al. Transcutaneous electrical nerve stimulation improves low back pain during pregnancy. *Gynecol Obstet Invest*. 2012;74(1):76-83.)

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professionals are educated on how to safely prescribe opioids and that patients know how to safely use these drugs.”

The administration's statements said officials do not believe the new regulations will result in pain patients not getting their medications.

While it is required of companies to provide the training, the FDA press release said, “There is no mandatory requirement that prescribers take the training and no precondition to prescribing ER/LA opioids to patients. However, the Obama Administration endorsed a mandatory training program on responsible opioid prescribing practices in April 2011 as part of its comprehensive plan to address the epidemic of prescription drug abuse. The program, which would be linked to DEA registration by providers, would require legislative changes that are being pursued by the Administration.”

The press release continued, “The FDA continues to support this approach, but absent the needed legislation, intends to exercise its authority to require mandatory elements for companies and voluntary elements for prescribers—all of which are impor-

tant and necessary steps to help curb the misuse and abuse of ER/LA opioid analgesics, without being overly burdensome.”

#### References

1. U.S. Food and Drug Administration. FDA introduces new safety measures for extended-release and long-acting opioid medications [press release]. July 9, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310870.htm>.
2. U.S. Food and Drug Administration. Risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids. <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm>.
3. U.S. Food and Drug Administration. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251735.htm>.

#### Coming Soon:

- Pain Management After Thoracic Surgery
- More on Risk Evaluation and Mitigation Strategies