



# Advances in Pain Medicine: a Review of New Technologies

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## Abstract

**Purpose of Review** This narrative review highlights the interventional musculoskeletal techniques that have evolved in recent years.

**Recent Findings** The recent progress in pain medicine technologies presented here represents the ideal treatment of the pain patient which is to provide personalized care. Advances in pain physiology research and pain management technologies support each other concurrently.

**Summary** As new technologies give rise to new perspectives and understanding of pain, new research inspires the development of new technologies

**Keywords** Pain medicine · Chronic pain · Neuromodulation · SI o

## Introduction

Chronic pain is one of the most common and debilitating illnesses. About 20% of adults in the USA live with chronic pain [1], and it is the leading cause of disability for this population [2]. The urgent need for effective therapy has led to a significant role for new technologies in pain medicine.

This review summarizes the new technologies that are evolving treatment strategies for patients with chronic pain.

Increased understanding of the electrical signals in the nervous system that cause chronic pain as well as the effect therapeutic stimulation causes on these signals informs novel neuromodulation approaches. These novel devices include peripheral and spinal stimulators that treat complex pain syndromes as well as axial back pain by sending electrical impulses that reverse pathologic neural processes. Clinical evidence supporting these modalities is growing, and continued device miniaturization and optimization are further extending utility. Interventional musculoskeletal techniques are also evolving to impact patient suffering. Sacroiliac (SI) joint fusion is a surgical technique used to treat back pain originating from SI joint dysfunction. Clinical evidence supports increased efficacy compared with alternative treatment, and new fusion technologies may provide further improvements with less invasive technique. Recent expansion of virtual telehealth technologies offers the opportunity to increase access to healthcare and optimize patients' ability to connect with their providers. Advancements in biotechnology are facilitating the development of novel pharmaceutical therapies for pain.

While some of these technologies already have proven efficacy, many remain investigational. The level of investment and growth in pain medicine therapeutics is an exciting

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and hopeful sign for pain medicine physicians and patients seeking relief.

## Neuromodulation

The field of neuromodulation, particularly spinal cord stimulation (SCS), has experienced renaissance in the past two decades with new expanding indications, including persistent spine pain syndrome (PSPS), complex regional pain syndrome (CRPS), refractory axial neck and low back pain and neuropathic limb pain, and, more recently, painful diabetic neuropathy [3•, 4–12]. In addition to indication expansion, technological improvements, specifically, standardization of surgical techniques, miniaturization of devices, innovations in waveforms, novel neural targets, and heightened understanding of novel mechanisms of action (MoA) contribute to increased safety and efficacy data supporting better patient outcomes, satisfaction, cost-effectiveness, and reduction of pain with improvement in function and quality of life (QoL) [3•, 4, 5, 13–24].

Early introduction of paresthesia-based, low-frequency tonic spinal cord stimulation leveraged the gate control theory. The deployment of innovative novel waveforms, particularly high-frequency 10 kHz (HF10), sub-perception physiological bursting (Burst), pulse stimulation pattern (PSP), differential target multiplex (DTM), and evoked compound action potential (ECAP) closed-loop stimulation optimize waveform delivery and the therapeutic window for pain modulation with precision and efficacy (Table 1) [6, 8, 13, 14, 17, 18, 25–38].

SCS is a particularly important treatment option in chronic pain, which is a highly prevalent condition in the USA, leading to disability, work-day loss, and decline in quality of life and function [1, 39]. Chronic spinal pain in particular is a complex pathological phenomenon, challenging to treat, and perhaps one of the most important global healthcare problems. As device technology and surgical technique evolved to become less invasive and understanding of the specific MoA heightened, the uptake and utilization of the therapy by interventional pain physicians also increased. For the past two decades, a commensurate increase in clinical research, specifically, level I evidence defining SCS as a safe and effective, critical treatment for treatment-refractory chronic pain, has occurred. Numerous high-quality clinical studies demonstrate long-term sustainability of improvement in pain, function, and QoL, with some studies demonstrating reduction in opioid utilization, increasing cost-effectiveness, and superiority over conservative care for numerous conditions, including PSPS, previously more commonly known as failed back surgery syndrome (FBSS); chronic neuropathic limb pain; CRPS; chronic intractable axial spinal pain; and painful diabetic neuropathy. Studies have shown that

healthcare resource utilization increases with longer time between pain onset and SCS implantation, so it is reasonable to consider SCS intervention earlier in the chronic pain treatment algorithm on a case-by-case basis [3•, 5, 7, 8, 10, 38, 40–43].

Innovative waveforms used with SCS technology may offer new methods for improving long pain outcomes, particularly with high-frequency and burst cycling optimization, pulsed stimulation patterns, and closed-loop ECAP. Precise anatomical targeting with glial cell modulation and differential target multiplex therapy may also be important factors. Offering significant promise is the capacity to optimize stimulation within an individual patient's therapeutic window, by the novel ability to monitor real-time spinal cord feedback and adjust the stimulation based on patient variables, such as impedance, posture, anatomy (scar tissue, implantable hardware, etc.) and patient position through a closed-loop feedback. Increasing sophistication of surgical techniques has led to reduced postoperative complications and less need for explantation; likewise, miniaturization of devices has led to increased patient comfort. Important technological advancements such as battery-free devices, accessibility of remote and external devices, microchips with upgradable programming, and newer waveform programming capabilities with real-time feedback are innovative clinical advantages that offer us the promising ability to modulate pain with precision and efficacy (Table 2).

## Dorsal Root Ganglion Stimulation

Dorsal root ganglion stimulation (DRGS) was approved a decade ago in Europe [44] and in 2016 in the USA [45]. The FDA approved DRGS for CRPS types I and II (causalgia). Providing focal and specific anatomic targeting therapy for up to four specific regions receiving, DRGS spared the patient the larger coverage zone of SCS and provided a higher margin of relief for more patients with CRPS than SCS [45]. In the years following the largest neurostimulation study of patients with CRPS, clinical application of DRGS expanded to include multiple chronic postsurgical pain syndromes including postthoracotomy, mastectomy, inguinal hernia repair, knee replacement, and phantom limb syndrome [46]. Other conditions such as chronic low back pain [47] and pelvic pain [48] are successfully treated with DRGS, but large prospective studies have not yet been published [49] on these expanded applications or postsurgical pain syndrome targets above the T10 level. While the FDA-approved levels are from T10 to S2 studies of off-label use showed that safe placement is possible as high as the C6 level [50], cervical-thoracic junctional levels were found to be helpful in managing hand and wrist pain [51].

The concept of DRGS came after careful anatomical and physiological studies showed that the ganglion is a structural

**Table 1** SCS waveforms, frequency, amplitude, pulse width, and proposed MoA, modified from Malinowski et al. [18]

Waveform stimulation setting	Frequency, amplitude, pulse width	Proposed MoA [references]
Tonic-conventional low-frequency continuous paresthesia-based stimulation	2–1200 Hz 2–8 mA 100–500 µs	Dorsal column stimulation Wide dynamic range (WDR) neurons inhibition Increase GABAergic neuron stimulation Reduction of glutamate [13, 14, 30, 31]
High-frequency (HF10) continuous paresthesia-free stimulation	10,000 Hz 1–5 mA 30 µs	Selectively activates inhibitory interneurons in the dorsal horn or the dorsal root entry zone, without activating dorsal column fibers Small-fiber recruitment, while blocking large axons leading to suppression of interneurons paresthesia-free Glial-neuronal interaction and induced temporal summation, which attenuates the WDR wind-up phenomenon [8, 13, 14, 28, 30, 109–111]
BurstDR electrical packets at 40 Hz with five intraburst spikes of 500 Hz non-continuous paresthesia-free stimulation with active recharge	200 Hz 0.25–1.6 mA 1000 µs	Multiple MOAs proposed, including modulation of lateral and medial pain pathways and the anterior cingulate cortex and facilitation of anti-nociceptive descending pathways BurstDR firing pattern mimic physiological stimulation dual-firing qualities of the thalamus, including sodium and calcium channels [29, 32, 33, 112, 113]
Differential targeted multiplex (DTM) three therapy options with four synchronous signals and six different amplitudes	20–1200 Hz Variable mA 500 µs max	Affects neural-glia interaction and modulates gene expression in the immune and inflammatory processes characteristic of neuropathic chronic pain modulating ion channels and synaptic signaling [15, 34]
Pulsed stimulation pattern (PSP)-layered pattern waveform	2–1500 Hz Up to 10.2 mA 12–1000 µs	Narrow pulses stimulation includes modulation of low threshold fiber, dorsal horn, dorsal root, and glial cells. High rate train (onset/offset) increases fiber recruitment, while long train (charge delivery) modulates high threshold fibers, dorsal column, lateral and medial pathways and low rate train (onset/offset) accommodation, and medial and lateral pathway [17]
Evoked compound action potential (ECAP) closed-loop stimulation	Variable based on ECAP	ECAP closed-loop stimulation measures the spinal cord nerve fibers' response to stimulation via ECAP and automatically adjusts stimulation within the therapeutic window to maintain ECAP at a consistent level. ECAP activation of the dorsal column fibers with antidromic and orthodromic inhibitory effects [35, 36, 114–116]

**Table 2** Currently available SCS devices and MRI compatibility, modified from Clingan et al. [117]

SCS device	MRI compatibility
Abbott	Full-body conditional Conditional for head and extremity only ( <i>Prodigy System</i> )
Boston Scientific <i>Wave Writer</i> <i>Precision Montage</i> <i>Precision Novi</i>	Head only compatible ( <i>Wave Writer System</i> ) Full-body conditional ( <i>Precision Montage System</i> ) Not compatible ( <i>Precision Novi System</i> )
Medtronic	Full-body conditional
Nevro	Full-body conditional
Nalu	Full-body MRI conditional
Saluda	Unknown compatibility (considered unsafe at this time)

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gateway between the peripheral and central nervous system with the capacity to modulate painful stimuli [52]. When stimulated, the DRG sends action potentials from the DRG via the stem axon to the T-junction either enhancing or diminish afferent signals prior to their entering the dorsal zone at that specific spinal cord level [53]. The unique structure and function of the T-junction and the anatomy of the DRG create a novel approach and MoA compared to other forms of neuromodulation, as the DRG is close to bony structures in the foramen and surrounded by a limited amount of cerebrospinal fluid (CSF) allows for lower energy stimulation compared to SCS.

The implantation procedure for DRGS consists of implanting the four-contact lead across a specific ganglion (up to 4 levels) under x-ray with or without electrophysiological guidance [54]. This is achieved percutaneously through an epidural access using a 14-gauge needle, but open surgical approaches are described and in commercial development. Initially, anchoring was not recommended due to the risk of fracture, but a recent update in the literature now supports the use of anchoring in addition to an S-shape loop in the epidural space for strain relief. [55]

Success rate is high in majority of studies with one notable exception [56]. Patients demonstrated improved QOL and a decrease in consumption of analgesics including opioids [51]. Most studies also reported continuous improvement with time, a unique feature of DRGS which differs from other neuromodulation therapies.

### Peripheral Nerve Stimulation

Neuromodulation uses a low-level electrical current to stimulate a neurological target to alleviate pain and improve function in patients with chronic pain [57]. Neuromodulation has been used in both the central nervous system (CNS) and the peripheral nervous system for chronic pain treatment. Peripheral nerve stimulation (PNS) targets nerves in the peripheral nervous system and is used for chronic pain that fits the distribution of a known peripheral nerve.

Commonly, a peripheral nerve anesthetic block is performed before the implantation of a PNS system, to evaluate the potential efficacy of PNS to the intended nerve target. A PNS system contains a lead that delivers the electrical stimulation, attached to an external or implanted pulse generator (IPG) or battery. One of the first trials of PNS used leads surgically implanted in a “cuff-like” fashion around the nerve [58]. Newer, percutaneous techniques with the aid of ultrasound and fluoroscopic guidance have been developed for minimally invasive lead placement. PNS is used to treat many chronic pain syndromes, including facial pain, chest wall pain, headaches, phantom limb pain, peripheral nerve pain after trauma, and pelvic/urogenital pain as well as back pain [59–61]. Though complications are rare, the most common complications of PNS include lead migration, implant/IPG site pain, and infection [62].

The action of PNS is hypothesized to utilize both central and peripheral mechanisms. The gate theory introduced by Wall and Melzack suggests that PNS inhibits afferent transmission of pain signals to higher central nervous centers [26]. Some studies suggest that PNS activates the dorsolateral prefrontal cortex, anterior cingulate gyrus, parahippocampal areas, and the somatosensory cortex [63]. Other CNS structures implicated in pain reduction from PNS include reduction in the firing of wide dynamic range (WDR) neurons in the spinal cord and effects on the central NMDA pathways as well as endogenous neurotransmitters of pain in the peripheral nervous system [63].

Neuromodulation manufacturers have developed multiple ways to implement PNS. Systems may be temporarily or permanently implanted, with the decision to use a temporary versus permanent implant depending on the patient’s goals and preferences. The Nalu, StimQ, StimRouter, Mainstay Medical, and Moventis systems are permanent implants with the ability to trial the device before implantation. The SPRINT system is unique as it can be implanted for 60 days and subsequently removed, with pain relief continuing after removal. Low-frequency tonic stimulation waveforms are

used most frequently, though other programs such as high frequency and burst stimulation have been trialed [64].

## SI Joint Fusion

The sacroiliac joint (SIJ) is a diarthrodial joint that connects sacrum and the ilium. It acts as a shock absorber and aids in redistribution of forces from the spine to lower extremities and vice versa while standing, walking, or changing posture [65, 66]. SIJ dysfunction has been identified as a common, yet underdiagnosed cause of acute and chronic low back pain [67–69]. Over the last decade, SIJ fusion techniques have gained popularity owing to recent advances in the minimally invasive surgical techniques [70] and have been seen as an alternative to opioid medications for pain management [71]. SIJ fusion procedures have increased in tandem with approval of these devices by the FDA. Over the last decade, almost 24 devices have been granted FDA approval for SIJ fusion, while another 9 devices are awaiting FDA 510(k) substantial equivalence determination [72].

Table 3 lists these devices along with the favored surgical approach and their compatibility with the grafts [72]. SIJ fusion is most commonly achieved through the lateral approach [72] by placing the device through the ilium into sacrum, thus bridging the joint [71]. This approach has been associated with a more stable fusion, minimal complications, and statistically significant improvements in patient reported outcomes [72–74]. The less common posterolateral approach involves accessing the sacroiliac joint from the posterior inferior iliac spine in an anteroinferior direction [72], while the posterior allograft approach involves placing the allograft bone products or devices into the ligamentous component of sacroiliac joint. This allografting technique involves minimal soft tissue destruction and requires only half a day of hospitalization [71].

The first reported SIJ fusion was performed by Smith-Peterson in 1921 using an open approach [75]. Despite the adverse effects of the open approach, minimally invasive techniques gained traction only after 2008 when the iFuse Implant System (SI bone) was granted US FDA approval [76•]. The iFuse implant includes triangular titanium implants (with a 3D-printed option) and is one of the most commonly used SIJ fusion devices [72]. Polly et al. reported statistically significant improvement in quality of life and pain reduction with the use of iFuse implants in a randomized controlled trial of patients with SIJ dysfunction [74]. Subsequent authors have also reported improvement in patient reported outcomes, shorter duration of hospital stay, and reduced opioid prescription use with triangular titanium implants for the treatment of SIJ pain [77–80]. The incidence of complications (non-union [81], deep wound infection, nerve root impingement [82], back pain, hematoma)

associated with the use of triangular titanium implants has been reported to be less than the incidence of similar complications with the open approach surgery [76•].

The second most commonly used device for SIJ fusion are cannulated screws [71, 72]. These facilitate true bony fusion and arthrodesis across the sacroiliac joint and are available in various sizes; screw selection depends upon the anatomical variations of SIJ in patients and the preferences of surgeon [71]. Spain and Holt [83] conducted a retrospective analysis using Kaplan–Meier survival analysis on patients who underwent SIJ fusion or fixation between 2003 and 2015; the authors concluded that SIJ fixation done with screws had a 4-year cumulative revision rate of 30.8%, while fusion done with titanium triangular implants had a revision rate of 5.7%.

The posterolateral approach involves stabilization of SIJ by either placing 1–3 surgical screws across the joint or 1–2 percutaneous cortical allografts along the joint and is favored by interventional pain physicians due to the minimally invasive nature of these techniques [76•]. General anesthesia with endotracheal intubation may be necessary in select patients as the posterior approach presents some challenges with respect to access to the airway due to prone positioning [71]. Rialto SI fusion system uses a posterior approach while utilizing intraoperative stereotactic navigation, but clinical data regarding its efficacy is still lacking. A retrospective comparative study by Claus et al. between Rialto and iFuse system reported no significant difference in procedure length or the improvement in patient reported outcomes at 6-month or 1-year follow-up [84]. Though multiple studies have reported favorable outcomes with the use of Rialto SI fusion system, clear consensus regarding its efficacy is lacking [85–88].

CornerLoc is a posterior approach allograft-based device in which two biological implants made from demineralized bone matrix are placed in an orthogonal direction for SIJ fusion [71]. This implant is devoid of any metal, and the entire procedure can be performed with local anesthesia in less than an hour [71, 89]. Another emerging device that can be implanted percutaneously is LinQ, which contains a cavity in the center filled with demineralized bone matrix [71].

SIJ fusion devices have shown promising results for the treatment of SIJ dysfunction and low back pain. Though studies have advocated their use over other traditional methods for the treatment of pain originating from SIJ, more robust clinical trials are warranted to formulate evidence-based clinical guidelines for their use [71, 73, 90].

## Telemedicine Technology for Pain Medicine

Virtual health and mobile applications have been designed to provide treatment and to improve communication between patients and provider, and the efficacy of these applications

**Table 3** List of devices along with the favored surgical approach and their compatibility with the grafts

Company	Device	Temporary/ permanent	Mechanism of action	Waveform	Ability to trial	MRI compatibility	IPG battery life	External/internal battery
SPR Therapeutics	SPRINT	Temporary	Electrical stimulation applied through temporary implanted microlead electrode	Identical stimulus, monopolar stimulation	N/A	External components and lead contraindicated, retained lead remnant is MRI conditional	N/A	External
Bioness	StimRouter	Permanent	Active electrical stimulation is applied transdermally to a targeted peripheral nerve	Symmetric or asymmetric	N/A	Conditional (external components are contraindicated)	8 h for EPT (external pulse transmitter)	External
Nalu Medical Inc	Nalu PNS	Permanent	Pulsed electrical current used to target spinal cord and peripheral nerves	Charge balanced (delayed) biphasic asymmetric	Yes	1.5 T	18 years	External (re-chargeable therapy disc lasts 55 h at nominal settings)
Stimwave	StimQ	Permanent	Pulsed electrical currents creating an energy field to target specific peripheral nerves	Charge balanced (delayed) Biphasic asymmetric	Yes	1.5 T	IPG-free	External
Moventis	Moventis PNS	Permanent	Pulsed electrical currents creating an energy field to target specific peripheral nerves	Charge balanced (delayed) Biphasic asymmetric	N/A	No	N/A	External
Mainstay Medical	Reactiv8	Permanent	Implantable electrical neurostimulation system that stimulates the dorsal ramus of the lumbar medial branch at L2 that innervate the lumbar multifidus muscles for the treatment of multifidus dysfunction etiology	N/A	No	No	> 5 years	Internal

is emerging in the literature. Automated text messaging has been shown to be a promising method of monitoring opioid utilization after surgery [91]. The use of online support forums, phone-based telehealth, and automated symptom check-in was correlated with reduced pain and depression symptoms among cancer patients [92, 93]. Mobile and electronic applications designed for pain therapy have been shown to be effective in reducing short- and medium-term chronic pain symptoms [94], while participation in a recent online program reduced pain-related distress in comparison with the standard of care alone [95].

Preliminary results have shown that performing neurofeedback therapy for pain management remotely, using EEG headsets and a mobile app, may be an effective way to increase access to this treatment for individuals in rural areas [96]. Virtual reality headsets may be more convenient and effective for symptoms of phantom limb pain when compared with mirror therapy or psychotherapy [97]. High-frequency transcranial magnetic stimulation, commonly used in the treatment of depression, may have increased efficacy when compared to sham treatment for treating chronic pain, although results are mixed [98]. The most recent study found symptoms improved in the short term but returned to baseline by 2 weeks [99]. A newer technology, transcranial direct current stimulation, induces a low-current flow through deep brain structures to hyperpolarize and inhibit targeted areas. In a small randomized trial, inhibition of the dorsal anterior cingulate cortex using this technique reduced pain and anxiety symptoms among individuals with chronic low back pain [100].

With the rapid expansion of telehealth visits during the COVID-19 pandemic, there is significant opportunity for growth and significant need to identify ways to best utilize new communication methods to improve patient outcomes. For example, the use of mobile apps to help with pain management among elderly populations has been found to be complicated by that population's lower levels of technology literacy [101]. Numerous technologies and advances in portable form factors have been applied in creative ways to address pain symptoms, and while they show promise, most need further validation.

## Biotechnology and Pharmaceuticals

Advances in biotechnology have encouraged the exploration of new modalities for pharmaceutical therapies. Gold nanorods conjugated with TNF siRNA were shown to reduce thermal pain in rats [102]. Tramadol hydrochloride attached to nanoparticles with endogenous ligands has been found to have improved pharmaceutical properties, including a longer release time and increased uptake when compared with tramadol alone [103]. Another method being explored is magnetofection: intrathecal injection of gold-iron nanoparticles

with magnetic properties, which can be conjugated with antibodies for specific targets, and steered to precise locations using magnetic fields [104]. Voltage-controlled microfluidic devices could provide precise, remote temporal control of medication release, enabling personalized treatment protocols for chronic pain [105]. Automated patch clamping (APM) is a technology of particular relevance to pain research and can record ion channel potentials with much greater throughput than traditional manual methods. The maturation of this technology over the past 20 years has benefitted the development of new small molecule analgesic candidates [106]. Many of these advances are years away from clinical application, but present promising new avenues of future research and development.

## Conclusions

Chronic pain is a complex issue. Even among patients with the same diagnosis, the specific pain features, symptoms, overall health status, biopsychosocial factors, and socioeconomic status of each patient may differ greatly. All these factors play a large role in the experience and management of the individual's pain. On a systems level, access to healthcare, access to pain specialists, access to health insurance, transportation, disability, and governmental support services all factor into the treatment options a patient may or may not be able to pursue.

Chronic pain is the leading cause of disability among US adults. An estimated 50–100 million US adults live with chronic pain, costing an estimated \$560–630 billion each year in medical costs, disability programs, and lost productivity [107]. An estimated 40–70% of chronic pain patients do not receive “proper medical treatment,” either being over- or under-treated for their pain [108]. Currently, the global SARS-CoV-2 pandemic makes access more uncertain as healthcare systems are strained, creating more barriers to care for individuals who already struggle to access the treatment they need.

The combination of treatment modalities needed to manage a patient's pain is unique to each patient, and with the growing trend toward personalized medicine, this will only become more important to future clinical practice. The recent progress in pain medicine technologies presented here represents the future of this ideal. Advances in pain physiology research and pain management technologies support each other concurrently. As new technologies give rise to new perspectives and understanding of pain, new research inspires the development of new technologies. Similarly, the SARS-CoV-2 pandemic is simultaneously impeding access to traditional healthcare while expanding access through emerging telehealth technologies and sparking innovations through necessity.

As we increase our understanding of the multifaceted nature of pain, the technologies and modalities which enable us to put that understanding into practice emerge in parallel. Armed with numerous options, pain medicine physicians of the future will be able to precisely target each patient's pain through internal and external technology, pharmacotherapeutics, and emerging surgical and percutaneous technologies and techniques. With the ability to treat patients in a precise and targeted way, physicians will be able to help ease the burden of chronic pain on patients, their families, and the healthcare system at large.

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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