2.2 Neurostimulators

Minimally invasive neurostimulators deliver low-level electric signals directly to selected nerve fibers. Stimulating these nerve fibers interrupts pain signals being sent to the brain, replacing the pain with a tingling sensation. The three types of neurostimulation are neuromuscular stimulation, peripheral nerve stimulation, and SCS. Neuromuscular stimulation is used on muscle groups to contract and re-educate muscles; this type of neurostimulation is useful in treating muscle atrophy, maintaining or increasing range of motion, and increasing blood flow to a targeted body area. Peripheral nerve stimulation involves stimulation of nerves outside the CNS. SCS involves placing electrodes in the epidural space to stimulate nerves in the spinal cord; SCS (also known as dorsal column stimulation) is used to treat chronic pain in the trunk or limbs.

Prescribed for carefully selected patients, neurostimulation is a reversible therapy that may result in a substantial reduction in neuropathic pain, an increased level of activity, fewer hospitalizations, reduced narcotic use, and an overall reduction in healthcare costs. Patients with pain in a single location are ideal candidates for neurostimulation, as are patients with chronic inflammation and scarring of the membranes surrounding the spinal cord, chronic migraine headache, complex regional pain syndrome, disorders of the spinal nerve root, and failed back syndrome.

A neurostimulation system consists of three implantable components (the extension, the lead, and the power source) and three external components (the control magnet, the programmer, and the screener). The extension is used to connect the lead to the power source. The lead is used to deliver electrical stimulation to the targeted nerves. There are two types of power sources used to provide electrical stimulation: an implantable pulse generator (IPG), consisting of a small, implantable, battery-containing metal container into which the leads are plugged; and a radiofrequency (RF) system, consisting of a small, implantable, antenna-containing receiver into which the leads are plugged, and an externally worn, pager-sized transmitter that contains the battery. The electrical energy used to run the neurostimulator is transmitted from the battery through the skin and into the receiver.

An advantage of an IPG power source is that it is more discreet and enables bathing or swimming while receiving stimulation due to the fact that it is fully implanted.
Disadvantages of an IPG power source include limitations in power output and frequency levels; fixed battery life (when the battery is depleted, the IPG must be replaced, which involves another operation); and added size and weight as a result of the battery, limiting possible implantation sites. Although IPG power sources have relatively low risks associated with their use, potential complications include allergic reactions, battery failure or leakage, bleeding, numbness, pain around the implant area, paralysis, post-surgical soreness, and scar formation leading to inadequate simulation.

An advantage of an RF power source is that the batteries are contained in the external transmitter, and when the battery is depleted it is easily replaced; batteries for the newer RF models are even rechargeable. Another advantage is that the higher electrical energy output of a renewable RF power source allows programming of specialized stimulation pulse patterns, which are required to achieve adequate pain relief for many pain conditions. In addition, the implantable receivers in RF systems are much smaller and lighter than IPG systems, allowing the physician greater flexibility in selecting an appropriate location on the patient’s body to place the device. Disadvantages of an RF power source include the fact that the external transmitter and antenna must be worn to allow stimulation and may not be worn in water. In addition, the skin underneath the antenna may become irritated, and interference in communication between the receiver and the transmitter may occur in obese patients.

2.2.1 Occipital nerve stimulation

In the US, the prevalence of migraine ranges between 11.7% and 22.7% in adults, with 26.1% of women between the ages of 18 and 44 reporting migraine or severe head pain (Smitherman et al., 2013). One European headache study, the Eurolight Project, estimates the overall percentage of migraine in Europe as high as 36.6%, with definite migraine accounting for 22.3% and probable migraine accounting for the remaining 14.3% (Steiner et al., 2014). Although the use of neurostimulation for the prevention of intractable migraines and headache pain is of great interest, and research in this area has been conducted over the past 15 years, neurostimulation therapies, including occipital nerve stimulation (ONS), are not yet approved by the FDA for the treatment of migraine or other headache disorders; however, these therapies may be prescribed off-label.
ONS devices deliver a small electrical charge to the occipital nerve to prevent migraines and headaches in patients who have not responded to medications. This therapy has emerged over the past decade as a promising potential treatment option for migraine pain sufferers; several clinical trials are currently under way.

Medtronic conducted an initial Phase I safety/efficacy clinical trial under an FDA-granted investigational device exemption (IDE), ONSTIM (ClinicalTrials.gov identifier: NCT00200109), which involved 66 patients at nine centers in Canada, the UK, and the US; patients were severely debilitated in that they had regularly experienced 15 or more headache days per month, and were not responsive to standard medical therapies. Results of this study will form the basis for a future pivotal trial that may pave the way to FDA approval, and future improvements in device and surgical techniques. The ONSTIM trial was designed to follow patients out to three years to evaluate longer-term safety and efficacy. Medtronic researchers, who announced results of the ONSTIM trial in September 2010, collected electronic diary data from the 66 patients at nine centers who were followed for a period of three months, and demonstrated that 39% (or 11 patients) of the patients who received adjustable stimulation (n=28) obtained at least a 50% decrease in the number of headache days per month, or at least a three-point decrease in overall pain intensity from baseline. Additionally, these patients experienced an average of 27% (+/-44.8%, standard deviation) fewer headache days per month compared to prior to treatment. In the study, the most common adverse device event was lead migration; however, this did not lead to long-term complications. At the time of study publication, long-term follow-up visits were still being completed. According to the researchers, the results of the ONSTIM trial demonstrated that ONS may be a promising therapy option for patients who have been unsuccessful with conventional medical therapy.

Boston Scientific is researching the use of ONS utilizing the Precision ONS System for the treatment of chronic migraine when used in conjunction with anti-migraine medications. The company is recruiting patients for a pivotal, randomized, double-blind trial, OPTIMISE (ClinicalTrials.gov identifier: NCT01775735), which was initiated in May 2013. The trial, expected to enroll 180 patients and complete by June 2017, will use the ONS technique, which involves implantation of electrical leads in the subcutaneous space, with the leads transversing to the occipital nerve in the back of the head, under X-ray guidance. The leads are implanted under the skin to an IPG in the chest wall or abdomen.
2.2.2 Neuromuscular stimulators

One of the oldest types of neuromuscular stimulation devices is the high-voltage pulsed galvanic (HVPG) stimulator. Galvanic stimulation increases blood flow, and reduces edema and inflammation for patients suffering from soft tissue trauma. Compared to conventional TENS, HVPG stimulation has a significantly wider spectrum of applications, including increasing localized blood circulation and range of motion; muscle spasm relaxation; prevention of atrophy due to disuse; reduction of edema following acute injuries, sprains, and strains; and wound and tissue healing by increased collagen formation.

Two major uses for HVPG devices are for the pain associated with carpal tunnel syndrome and diabetic foot. Devices in this class are characterized by a unique twin-peak monophasic waveform with very short pulse duration (microseconds) and a therapeutic voltage of greater than 100 volts. This combination, along with a low total current per second (microcurrent), allows relatively comfortable stimulation. In addition, the combination provides an efficient means of exciting sensory, motor, and pain-conducting nerve fibers.

2.2.3 Spinal cord stimulators

SCS systems are devices that transmit electrical signals to the spinal cord for pain relief. Although traditionally recommended by neurosurgeons, SCS systems increasingly are being used by anesthesiologists, orthopedic surgeons, and physiatrists. Pain management continues to be the most widespread application of SCS, with sophisticated advancements allowing the technology to address difficult-to-treat pain associated with arachnoiditis, complex regional pain syndrome, failed back syndrome, and peripheral neuropathies; however, pain associated with other disorders such as angina pectoris, pancreatitis, peripheral vascular disease, occipital neuralgia, and urinary incontinence, also may be amenable to treatment with SCS.

With the complexity of implantable SCS devices, those devices that incorporate computer interactive programming have gained in popularity. In addition, the capability of SCS to independently stimulate multiple channels as well as multiple arrays of electrodes has increased the efficacy, reliability, and safety of the modality, which may play an increasingly important role in the medical management of chronic conditions affecting the nervous system.
2.2.4 Market forecast

The use of SCS has proven successful and cost-effective for relieving chronic pain, depression, epileptic seizures, neuropathic pain, and pelvic pain, among others. The aging of the population and the increasing prevalence of chronic pain could result in substantial market growth through 2021; new product introduction also offers growth potential in this market.

Growth in the US SCS market flattened in 2014 after the CMS instituted a new physician reimbursement policy on 1 January 2014 for trialing SCS in the office setting, which effectively reduced payments by more than 70%. Subsequently, SCS trial volumes fell dramatically as physicians adapted to the new reimbursement requirements and moved their SCS trials to an alternate setting, such as an ambulatory surgery center or a hospital. However, this was a temporary disruption in the market, with SCS volumes recovering and returning to mid-single-digit growth in 2015.

Future growth in this market will be driven by strong demand due to an increasing prevalence of chronic pain among the growing elderly and obese populations. Another driver of global sales of SCS systems is the cost-conscious boost in sales of lightweight, portable, and rechargeable implantable spine stimulators with prolonged battery life. Next-generation devices offering diagnostic tools and customization for improved efficacy and treatment are also expected to accelerate sustainable market growth over the forecast period covered by this analysis.

2.2.6 Emerging technologies

2.2.6.1 electroCore

According to Medtech Insight’s October 2016 article, electroCore Stimulates More Promise With Migraine Therapy, research has demonstrated the potential of electroCore’s non-invasive vagal nerve stimulation therapy, called gammaCore, for reducing menstrual migraine attacks by more than a third. The handheld gammaCore device works by stimulating the cervical branch of the vagus nerve; treatment is self-administered using a conductive gel and a stimulation time of two minutes. The study, which assessed the efficacy of gammaCore in treating menstrual migraine, monitored 56 patients for a 12-week baseline period, then 51 patients for a 12-week treatment period using the gammaCore device. Patients using the device reported a 35% decrease in the average number of migraine days,
reduced pain intensity in the migraines that did occur, and a 37% decrease in the use of analgesics for migraine treatment. The product was CE marked in 2011 and is available in Germany and the UK; gammaCore is not yet approved in the US.

### 2.2.6.2 Mainstay Medical International

Mainstay Medical International developed the ReActiv8 implantable neurostimulation device, which includes two leads implanted near the L3 vertebra, a battery-powered implantable pulse generator that delivers electrical pulses, and an external wireless programmer/activator. According to Medtech Insight’s September 2016 article, *Starts & Stops: Back Pain Neurostim Device, Prostatic Stent Move Into Pivotal Trials*, Mainstay Medical International has initiated a 128-patient, US pivotal study of its ReActiv8 neurostimulation device for patients with chronic low back pain. Unlike SCS, the main approach for this indication, ReActiv8 works by reactivating the neural drive of the lumbar multifidus muscles that stabilize and support the spine. In 2016, the device was CE marked for sale in Europe, where the company is conducting a long-term post-market study. In February 2017, Mainstay Medical International announced the sale and implantation of the first ReActiv8 device in Germany (Mainstay Medical International, 2017). According to Medtech Insight’s May 2016 article, *Mainstay Set To Launch ReActiv8 Neurostimulator In Germany*, the company’s direct sales force will focus on German hospitals that treat a large back-pain patient population with a multidisciplinary approach, and will expand sales and marketing to additional customers and countries as it gains experience and momentum.

### 2.2.6.3 Stimwave

With a next-generation SCS technology that is unlike anything else on the market, start-up Stimwave Technologies could be a serious competitor in neuromodulation in the years ahead. In January 2015, the company initiated the US launch of its Freedom-4 Spinal Cord Stimulation System, a tiny, injectable, wireless, neurostimulation platform that is less invasive, less costly, and 95% smaller than conventional SCS devices. The Freedom-4 SCS System received 510(k) clearance in October 2014 and is indicated for relief of chronic back and leg pain.

The company leveraged nanotechnology and high RF energy transmission to develop the system, which includes an implantable device so small it can be injected percutaneously and threaded into the epidural space via a 14-gauge Tuohy needle.
Unlike traditional SCS systems, the Freedom-4 does not utilize wires to connect the electrodes to an IPG. Instead, it utilizes an external RF transmitter (worn on a belt or attached to clothing) and a state-of-the-art microchip to power and wirelessly send commands to the implanted device using a smartphone platform to control and program the stimulation. This wireless approach dramatically reduces some of the potential complications seen with traditional SCS, including lead migration and infections associated with external and implantable pulse generators.

In June 2015, Stimwave received FDA IDE approval to launch an 80-patient clinical trial to evaluate its next-generation Freedom-8 SCS System in the treatment of chronic back and leg pain. In addition to having eight electrodes, the Freedom-8 is approximately one centimeter longer than the Freedom-4, and has more advanced programming features, including Stim Surge, which allows for intermittent burst stimulation and has the capability to operate at high frequencies up to 10 kHz. In October 2016, a Phase III multicenter, prospective, randomized, controlled clinical trial of the Freedom-8 was initiated (ClinicalTrials.gov identifier: NCT02514590), with a primary completion date in the second half of 2017. Stimwave’s Freedom systems obtained CE mark approval for sale in Europe in December 2015.

According to Stimwave, the newer product line provides greater flexibility in terms of designing more consumer-friendly configurations for the body-worn transmitter, and allows the technology to be worn more discreetly with devices as light as three to four ounces. For example, the company has developed a soft, fabric-like antenna woven in a washable T-shirt with a small wire that goes down through the clothing to a very simple button-type controller. Other product forms recently released or in development include a wrist band, a brassiere, a Bluetooth headset, an insertable clothing patch, a room-based transmitter, and a wireless bed antenna that patients may use while sleeping. Other features include adaptive stimulation as well as a full-body MRI compatibility feature similar to that of the Freedom-4, allowing for MRI scans at 1.5T and 3T, a feature unique to Stimwave.

In an interview with Medtech Insight, Stimwave revealed that the Freedom platform technology can offer any kind of combination of waveforms and frequencies, and may be placed in a much wider array of target locations than traditional SCS, including at peripheral nerves and the DRG. The company estimates that approximately 25% of physicians are currently using SCS products off-label for peripheral nerve stimulation (Stimwave, 2015).
The potential applications for peripheral nerve stimulation are broad, and include the treatment of chronic intractable groin pain, knee pain, and shoulder pain. Like other players in this segment, Stimwave is currently evaluating advanced programming options for the system, including high-frequency stimulation at 10 kHz. The company notes that high-frequency stimulation using Stimwave’s platform is very different from Nevro’s H10 therapy.

Stimwave is leveraging its micro-sized neurostimulation technology for use in other applications as well, and has potential products in the pipeline for headache, facial pain, peripheral neuropathy, joint and groin pain, and a multitude of other indications.