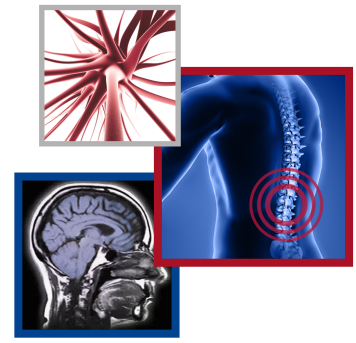
Device Evaluation

Pain Management



Application of the novel Nalu™ Neurostimulation System for peripheral nerve stimulation

Hemant Kalia[1], Scott Pritzlaff[2], Alice H Li[3], Einar Ottestad[3], Amitabh Gulati[4], James Makous[5] & Krishnan Chakravarthy*[,6,7]

[1]Rochester Regional Health System, Rochester, NY, USA
[2]Division of Anesthesiology and Pain Medicine, University of California Davis, Sacramento, CA, USA
[3]Department of Anesthesiology Perioperative and Pain Medicine, Stanford University, Stanford, CA, USA
[4]Memorial Sloan Kettering Cancer Center, New York, NY, USA
[5]Makous Research, LLC, Carlsbad, CA, USA
[6]Division of Pain Medicine, Department of Anesthesiology, University of California San Diego, La Jolla, CA, USA
[7]VA Department of Anesthesia, San Diego Health Care, San Diego, CA, USA
*Author for correspondence: kvchakravarthy@health.ucsd.edu

Practice points

- The Nalu™ Neurostimulation System is a potentially effective opioid-sparing treatment for chronic pain pathologies.
- Patient selection is the key to successful outcomes.
- Preoperative screening (e.g., antithrombotic/anticoagulation risk assessment) and surgical planning will help mitigate risks in patients with comorbidities.
- We recommend image guidance (ultrasound or fluoroscopy) to deploy percutaneous leads for both trial and permanent implant purposes.
- Appropriate societal guidelines should be followed to reduce severe neurological injury.
- We recommend a wear experience of the external components before trialing the system.
- Appropriate postoperative surgical care and restrictions should be followed.
- Regular follow-up will enhance therapy compliance.

Peripheral nerve stimulation is an established treatment modality for chronic neuropathic pain. Over the last decade, with the advent of innovative devices and delivery platforms, peripheral nerve stimulation has evolved from invasive open surgeries to image-guided, minimally invasive percutaneous procedures. The authors hereby present a novel device, the Nalu™ Neurostimulation System (Nalu Medical, CA, USA), which has established its advantages in providing predictable and reliable peripheral nerve stimulation therapy for chronic neuropathic pain management. This novel device is effective in treating chronic pain conditions such as post-herniorrhaphy pain syndrome, intercostal neuralgia, post-laminectomy syndrome, and complex regional pain syndrome and holds great promise for the treatment of peripheral neuropathic pain.

Plain language summary: Chronic nerve pain is a debilitating condition that can affect quality of life and functioning. The Nalu™ Neurostimulation System (Nalu Medical, CA, USA) provides long-term pain relief without medications. There are numerous devices currently available that can be utilized to block pain signals using small wires. This system is unique because the wires placed over affected nerves are powered by an external battery that does not require permanent surgical implantation. Pain after hernia surgery, back surgery, hip surgery and knee surgery, as well as nerve pain can be effectively managed by this system.

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Keywords: chronic pain • micro-IPG • miniaturized neuromodulation • neuromodulation • neuropathic pain • novel • peripheral nerve stimulation • peripheral neuralgia

Future Medicine

Background

Peripheral nerve stimulation (PNS) has enjoyed a renaissance in the last 5 years. Dedicated PNS devices have emerged as a viable technology to stimulate nerves for pain relief, reduce opioid use and maximize functional improvement [1,2]. Traditionally, PNS was an invasive surgical procedure that required the placement of leads on nerves via an open incision [3]. With the recent innovation in PNS technology, these new percutaneous systems can be placed via a minimally invasive approach using high-resolution ultrasound and, in some cases, fluoroscopy [4]. Instead of being employed as a last resort or later in the treatment continuum, PNS is now being used with increased frequency as an early intervention. Recent evidence has shown this therapy to be an effective option for neuropathic pain, postamputation pain, hemiplegic shoulder pain and postsurgical pain [5]. To advance the technology, novel strategies have involved precise placement of the contacts generating the electric field, designs that prevent dislodgement without damaging neural structures, advanced waveforms for sustainable pain relief and modular systems that include an implantable pulse generator (IPG) with a stable external power source [6,7].

Potential mechanism of action of PNS

Multiple theoretical mechanisms have been purported to explain the real-world clinical effect seen with PNS. The most widely accepted theory, known as gate control theory, promulgated in 1965 by Melzack and Wall, provided initial insight into the application of neurostimulation [8]. This theory was further substantiated in 1984 by Chung *et al.* in a primate model [9]. PNS may also reduce bio-inflammatory mediators such as prostaglandins and endorphins, which play an important role in peripheral sensitization of chronic pain [10]. In addition, there may be an antidromic effect, leading to modulation of spinal and/or central pathways, indirectly affecting chronic pain pathways [11,12].

Overview of the field

Multiple devices designed for stimulating a peripheral nerve exist across the world. Some devices possess large internal batteries, which ultimately limit the nerve stimulation targets owing to the size of the IPG [13]. Others are temporary and are after a predetermined stimulation period, on the order of a few months. Finally, external power generating devices must deliver consistent electrical energy to an implanted IPG or receiver, sometimes via a sophisticated telemetry protocol. Without robust communication between the implant and the external wearable device, a loss of therapy can ensue [14]. As this field evolves, advanced technologies designed while considering these constraints will become paramount for patients suffering from pain.

Introduction to the device

Regulatory affairs

The US FDA cleared the Nalu™ Neurostimulation System (Nalu Medical, CA, USA) for PNS on March 29, 2019 (510[k] no. K183579). The Nalu Neurostimulation System is indicated for pain management in adults with severe, intractable chronic pain of peripheral nerve origin (as the sole mitigating agent) or as an adjunct to other modes of therapy (used in a multidisciplinary approach). Like other commercially available PNS devices, this system is not intended for treating pain in the craniofacial area [15]. The FDA also cleared the Nalu Neurostimulation System for spinal cord stimulation (SCS) in March 2019 (510[k] no. K183047); however, the current article will focus primarily on PNS. The instructions for use can be found at https://nalumed.com/resources/physician-resources-content.

Device overview

The system utilizes an external source or therapy disc (TD) to power and control a micro-IPG (mIPG). The TD is a disc that overlies the impulse generator, powering the device and adjusting the IPG output in real time. The mIPG has a footprint approximately the size of a US dime and has a volume of approximately 1.5 cm^3. For comparison, traditional SCS IPGs have volumes ranging from 14 to 40 cm^3. This compact, small design allows for increased mIPG placement options and thus increases patient options for wearing their TD. Leads are placed percutaneously through an introducer needle and can be secured with anchors or a tined lead specifically designed for PNS applications. This system also offers a trial kit, which allows for percutaneous trials with one or two leads for up to 30 days.

Figure 1. Nalu™ Neurostimulation System therapy disc, adhesive clips and optional belt. (A) The therapy disc powers and controls the implantable pulse generator wirelessly using inductively coupled radiofrequency energy. **(B)** The therapy disc is held in place by an adhesive clip applied to the skin. Alternatively, it can be held in place by a belt/cuff worn over clothing; this is shown adjacent to the therapy disc in **(A)**.

Therapy Disc power source

The Nalu Therapy Disc (CA, USA) houses a rechargeable lithium-ion battery and electronics, including a microcontroller, which run software for therapy control. The TD is programmed via a clinician programming application (run on an Android tablet) that communicates over a secure Bluetooth® connection. The patient remote control application runs on both iOS and Android Bluetooth-enabled smartphones. It allows patients to select programs, manage alerts and turn the device on and off via the mobile device. The TD, used to power and command the IPG, does so wirelessly using inductively coupled radiofrequency energy. Although the TD sends power and instructions to the IPG, the actual stimulation pulses are generated inside the IPG, on the application-specific integrated circuit, in contrast to radiofrequency systems of the past where the stimulation impulses were generated outside of the body. The TD is held in place by an adhesive clip applied to the skin or a belt/cuff worn over clothing (Figure 1). This adhesive clip is unique to the PNS space, as it uses an ostomy-grade hydrocolloid adhesive attached to the area overlying the IPG. The adhesive has a low rate of skin reaction and can be easily removed via a medical-grade adhesive remover.

Prior to embarking on a PNS trial or permanent implant, it is strongly recommended that the patient undergo an ergonomic 'wear experience'. A wear experience typically lasts 5 days, during which the patient wears the adhesive clip and an inactive TD. The wear experience is critical because it ensures that patients are comfortable using the adhesive clip and TD, have no skin reaction to the clip adhesive and can identify a site for future IPG placement that is accessible and comfortable. A preliminary study of 50 patients showed favorable long-term wearability and comfort (see later discussion) [25]. In cases where the proposed IPG site will not allow for the use of a clip, a fabric belt or limb cuff may be used in lieu of the clip.

IPG & leads

The Nalu mIPG is a 'ported' system in which separately implanted leads are attached via connector ports and is available in single- or dual-lead configurations. The hermetic mIPG housing includes a ceramic enclosure and a feedthrough connected internally to a printed circuit board assembly. Because of this battery-free design, the mIPG has an expanded label from the FDA for an expected service life of 18 years [16]. The mIPG can accommodate single- and dual-lead configurations, including four-contact (tined) and eight-contact (non-tined) leads (Figure 2). The mIPG pocket is created with a custom pocket tunneler supplied by Nalu Medical (Figure 3). This tool ensures that the created pocket is tight-fitting and at the appropriate depth, thereby minimizing mIPG movement and

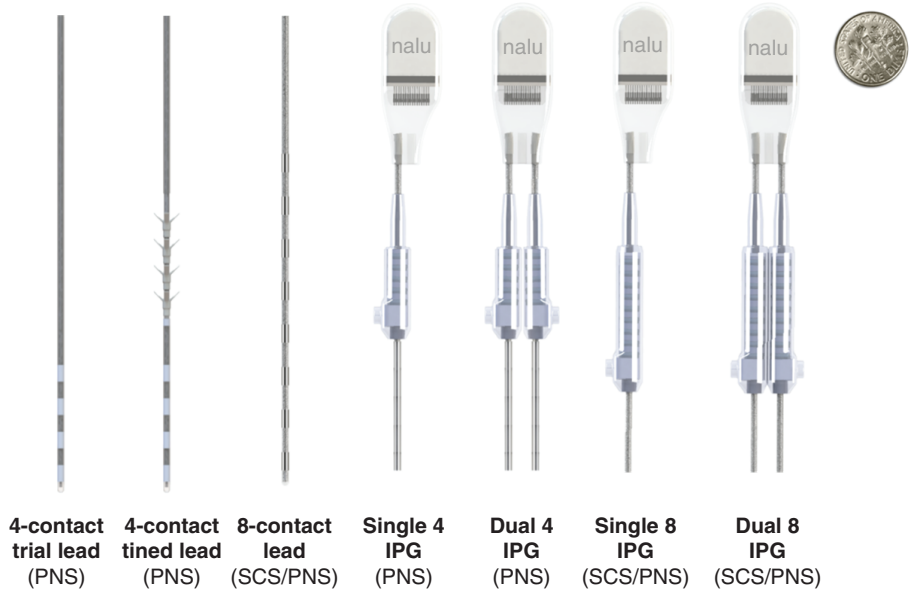

Figure 2. Peripheral nerve stimulation lead and implantable pulse generator configurations for the Nalu™ Neurostimulation System. Lead and IPG configurations for the PNS system. Tined four-contact or non-tined eight-contact leads may be used for the PNS system. The eight-contact leads can be secured with an SCS-style torque anchor. IPGs can accommodate either four- or eight-contact leads (single or dual).
IPG: Implantable pulse generator; PNS: Peripheral nerve stimulation; SCS: Spinal cord stimulation.

Figure 3. Nalu™ Neurostimulation System pocket tunneler. The pocket tunneler tool helps ensure that the implantable pulse generator can be placed below the skin at a consistent depth (<1 cm) and approximately parallel to the skin. The marks on the top portion of the tool are spaced 1 cm apart and can be used to measure the distance from the incision site to the end of the pocket site.

ensuring strong connectivity. Leads are connected to the mIPG ports in a manner similar to other SCS devices and secured with a setscrew by tightening with a torque wrench.

Figure 4. Nalu™ Neurostimulation System trial setup. Trial peripheral nerve stimulation setup. Leads connect to the external interface cable via two access ports on the side of the lid. The external interface cable is then passed outside of the sterile field and connected to the trial therapy disc for paresthesia testing.

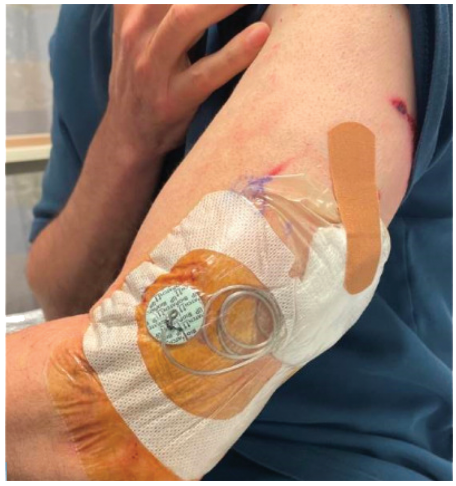

Figure 5. Nalu™ Neurostimulation System peripheral nerve stimulation trial of the radial nerve at spiral groove. Trial peripheral nerve stimulation lead placed on the radial nerve at the spiral groove. Excess lead is coiled and the external interface cable is covered with gauze and an occlusive dressing.

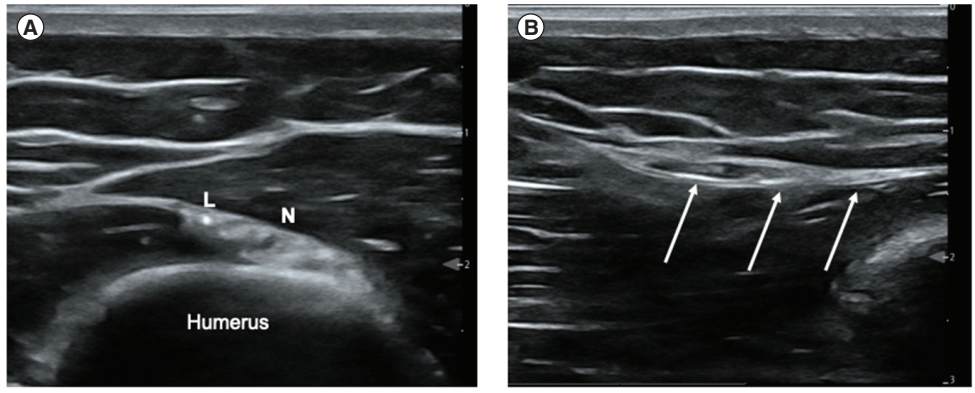

Figure 6. Ultrasound placement of Nalu™ Neurostimulation System peripheral nerve stimulation lead on the radial nerve in the upper arm. (A) Short-axis view of the nerve and peripheral nerve stimulation lead at the spiral groove of the humerus (left). **(B)** Long-axis view of the peripheral nerve stimulation lead and visible electrode contacts (arrows) in the same location.
L: Lead; N: Nerve.

PNS trial

Similar to SCS trials, the Nalu PNS system allows for percutaneous trials of up to 30 days. An external interface cable is used to connect leads to a trial TD controlled by the patient (Figures 4 & 5). Trial leads are four-contact (tined) or eight-contact (non-tined) leads.

Lead placement

In many cases, ultrasound is employed to facilitate accurate and comfortable lead placement. Additionally, ultrasound allows for clear visualization of vascular structures, which often run in close proximity to nerves. Because of the design of the leads, parallel placement (in relation to the nerve) is preferred to maximize programming capabilities and mitigate loss of stimulation if migration occurs (Figure 6). In some cases, fluoroscopy may be utilized with ultrasound, especially in cases where a patient has challenging anatomy (Figure 7). Saving a fluoroscopy image at

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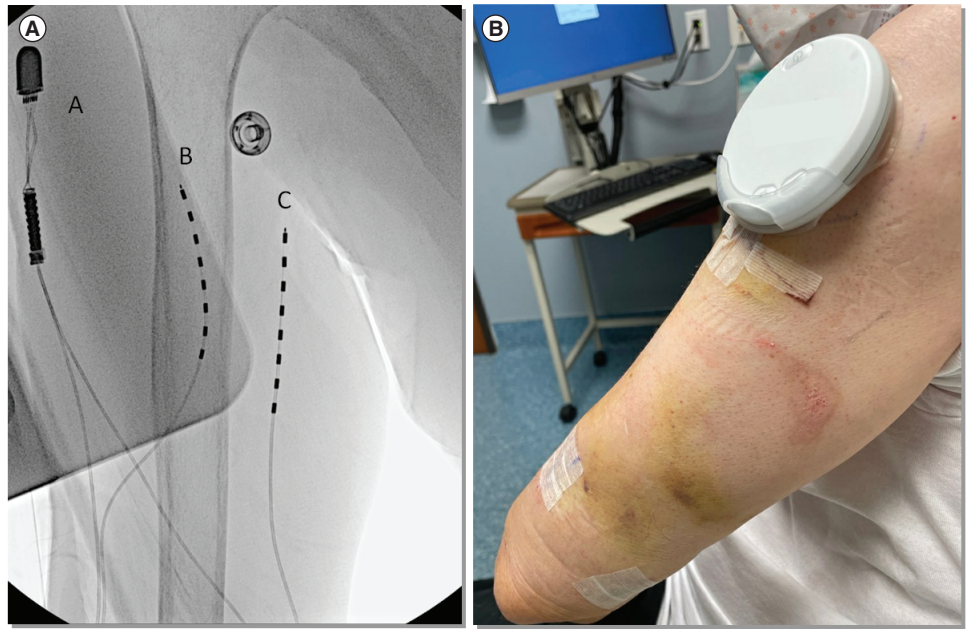

Figure 7. Permanent placement of Nalu™ Neurostimulation System peripheral nerve stimulation leads. Placement of the micro-implantable pulse generator at the deltoid area (A) with eight-contact leads running parallel to the radial (B) and ulnar (C) nerves. **(A)** Leads were placed with ultrasound and final placement was visualized with fluoroscopy. **(B)** The therapy disc contains a rechargeable lithium-ion battery and electronics for powering and running the micro-implantable pulse generator.

the end of the case (especially with permanent implants) can serve as an imaging baseline for each patient and can be used for reference in the future if there is a concern about lead migration.

Clinical efficacy

Preliminary data for the Nalu Neurostimulation System consist of two SCS clinical trials and a series of SCS and PNS case reports. In a 2019 prospective, multicenter, randomized controlled trial, Levy *et al.* delivered a pulsed stimulation pattern (PSP) with the Nalu system and found that anatomical SCS lead placement was superior to physiological lead placement in achieving pain relief [17]. Methodologically, 20 patients were randomized to receive either anatomically placed leads delivering PSP (n = 10) or physiologically placed leads (paresthesia-based) delivering PSP (n = 10) for 10 days followed by 3 days of tonic stimulation and return to standard medical practice. The group that received anatomical PSP demonstrated greater pain relief than the group that received physiological PSP for both low back pain ($p < 0.05$) and leg pain ($p < 0.05$). Notably, cathode placement at T9 was associated with the highest response (defined as ≥50% pain relief), whereas T8 placement yielded only 11% response and T10 placement yielded only 16% response. T9 placement yielded 100% response among anatomically placed leads and 74% response among all leads.

In 2021, Verrills *et al.* presented their 3-month data on the Nalu system from the Australian nPower study, an ongoing 12-month prospective open-label clinical trial for SCS treatment of intractable chronic leg pain and/or back pain [18]. During the trial, patients were provided with multiple stimulation paradigms. Patients who passed an SCS trial continued on to the long-term implant phase of the study, with planned follow-up at 30-, 90-, 185- and 365-day intervals after device activation. Of the 27 patients who were enrolled in the study at the 3-month time point, 24 had completed their 3-month follow-up visit. In these 24 patients, the average reduction in leg pain was 79% (n = 24; $p < 0.0001$), and the average reduction in back pain was 73% (n = 23; $p < 0.0001$). A therapeutic response (defined as ≥50% pain relief in this study as well) was seen in 83% (20 of 24) of patients with leg pain and 78% (18 of 23) of patients with back pain. Of note, the researchers successfully treated both leg and back pain, as all patients, except for two, suffered from both leg and back pain. Seventeen patients reported a total of 23 adverse events, which is typical of other SCS systems [19]. The most common adverse events were mild

skin irritation and unpleasant stimulation, both of which were resolved. There were no reports of pocket pain at the Nalu mIPG site.

In a 2021 case report, the Nalu SCS system was used to treat complex regional pain syndrome in a 30-year-old female with chronic low back and thigh pain from a car accident 3 years earlier [20]. Without an anatomical explanation for her pain, she had been trialed on multiple lines of therapy, including pain medication, four femoral nerve blocks and pulsed femoral nerve radiofrequency ablation. For the Nalu system, the SCS trial phase consisted of two eight-contact leads that were placed at the superior aspect of T8 and T9, during which the patient's Numeric Pain Rating Scale scores dropped from 8 to 0.5 (94% pain relief). Five months post-permanent implant, the patient reported 100% relief with 100% coverage of her pain area. In addition to these pain measures, her quality of life improved, with a considerable drop in pain medication requirement; an average of 8 h of uninterrupted sleep a night compared with 1 h prior to SCS implant; and an improved exercise, social and work schedule.

With regard to PNS case reports, the Nalu PNS system was used for unilateral intercostal neuralgia pain in a 65-year-old female with chronic left-sided mid-back and rib cage pain [21]. Prior to receiving the device, this patient had already received another SCS implant and pain pump for chronic low back and cervical pain. During the PNS trial, in which two leads were implanted to target the left intercostal nerves at T8 and T9, the patient reported 78% relief of her mid-back and rib cage pain. At 10 months post-permanent implant, she reported 70% pain relief and 100% coverage of the pain area. In another case report, the Nalu PNS system was used to treat chronic ilioinguinal neuralgia pain in a 53-year-old male with groin pain after hernia surgery [22]. Prior unsuccessful pain therapies had included pain medication, nerve blocks and radiofrequency ablation. After a successful PNS trial targeting the ilioinguinal nerve, the patient opted for permanent implant of the Nalu system. At 6 months after permanent implant, the patient reported Numeric Pain Rating Scale scores of 2, a drop from 9 preimplant, representing 78% pain relief with 95% coverage. Finally, the Nalu PNS system was also used to treat cancer pain in a 53-year-old male with severe bilateral low abdominal wall pain [23]. After a diagnosis of HIV and anal carcinoma, this patient had undergone multiple surgeries, including anal resection, colostomy placement in the right lower abdominal quadrant, cystectomy and left ureteral ileal conduit in the left lower abdominal quadrant. Despite taking numerous medications including multiple opioids, antidepressants, anticonvulsants, tramadol and tizanidine, his Numeric Pain Rating Scale score remained at 10 of 10. He also required multiple hospitalizations for intravenous hydromorphone through a patient-controlled analgesia pump for his uncontrolled abdominal pain. In addition, multiple local anesthetic and corticosteroid blocks in the transversus abdominis plane granted only transient (3- to 7-day periods) relief. This was followed by a trial with the Nalu multi-contact PNS lead system, which was placed in the transversus abdominis plane under ultrasound guidance, specifically targeting the intercostal nerve branches of T9–11 and the ilioinguinal and iliohypogastric nerves. A reported pain reduction of 90% from this trial led to a permanent Nalu system implant. At 8 months post-implant, the patient reported stable pain relief of 88% (from a baseline Numeric Pain Rating Scale score of 9 to 1) with 100% coverage of the pain area. Since implant, the patient has no longer required hospitalization for uncontrolled abdominal pain. Although the case reports referenced here are not yet published in peer-reviewed literature, they have been accepted as podium and poster presentations at national and international conferences, which further adds to the body of evidence in support of the Nalu Neurostimulation System.

Safety & tolerability

A review of the Manufacturer and User Facility Device Experience database shows a low overall medical device reports rate of <4% for commercial Nalu Neurostimulation System PNS patients, and the events are consistent with other implanted neuromodulation systems [19]. Users contraindicated for the Nalu Neurostimulation System are those who are unable to operate the system, have failed trial stimulation by failing to receive effective pain relief, are poor surgical risks or are pregnant. Shortwave, microwave or ultrasound diathermy should not be used within the vicinity of a patient implanted with a Nalu Neurostimulation System or when wearing a TD. The energy from diathermy can be transferred through the stimulator and cause tissue damage, resulting in severe injury. Patients who regularly work in environments with elevated levels of nonionizing radiation should not be implanted with the device. The energy in high-level areas can be transferred through the device and cause tissue damage, resulting in severe injury. Patients who have implanted cardiac or other neurostimulation systems should not use the Nalu Neurostimulation System. Electrical pulses from the Nalu Neurostimulation System may interact with the sensing operation of an implanted cardiac or neurostimulation system, causing the system to respond inappropriately.

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Although most of the commercially available peripheral nerve stimulator systems have established a safety profile, there is a dearth of literature regarding their long-term efficacy. In 2016, Deer *et al.* conducted a prospective, randomized, double-blind, multicenter partial crossover study to evaluate the safety and efficacy of a peripheral nerve stimulator (Bioness, CA, USA) and reported no significant adverse events [1]. Ninety-four patients with primarily neuropathic pain of the trunk or extremities were randomized into a treatment (n = 45) or control (n = 49) arm. The treatment arm had statistically significant improved pain at the end of 3 months with successful translation into improved quality of life.

In 2011, Verrills *et al.* reported their results from a prospective observational study consisting of 100 patients who underwent peripheral nerve stimulator implantation (St. Jude Medical, TX, USA and Boston Scientific, CA, USA) for chronic craniofacial, thorax, lumbosacral, abdominal, pelvic and groin pain syndromes [24]. The average follow-up period was 8.1 ± 4.7 months (range: 1–23), and patients reported no long-term complications and demonstrated an average pain reduction of 4.2 ± 2.5 on an 11-point pain scale, with 72% of patients using less analgesics post-implantation.

In 2019, Staats *et al.* evaluated patient comfort levels during the wearability tests of the TD and adhesive clips of the Nalu Neurostimulation System [25]. A total of 50 patients wore the TD in the lumbar recess for 30 days. On a 1–10 Likert comfort scale (1 = intolerable to 10 = comfortable), the average score after the first day of use was 8.2, which increased to 9.3 after 30 days. By contrast, ease of removal (1 = difficult to 10 = easy) of the adhesive clips was initially rated at an average score of 8.9, which increased to 9.6 after 30 days. On average, adhesive clips lasted 3–5 days before needing to be replaced. Overall, 98% of the patients studied found the clips usable. The researchers concluded that patients were very comfortable wearing the TD and the adhesive clips through 30 days of activities of daily living.

Additional studies with the Nalu system have looked at different environments, patient-reported skin types and three different adhesive clip hydrocolloid formulations. A 14-day study of 15 patients in Chicago involved an average winter temperature of 36°F and relative humidity of 64% [26]. A 14-day study of 18 patients in New Orleans involved an average summer temperature of 84°F and relative humidity of 70%. The patients recruited for these two human factors studies reported sensitive/dry skin (33%), high perspiration (33%) and pool/sauna usage (28%). Results for comfort, ease of use and time of wear were similar to the 30-day study results [25]. Comfort scores showed a noticeable improvement around the third day of wear, indicating an accommodation period [26]. These two studies also asked patients to rate their overall awareness of the adhesive clip and TD. On a scale of 0–10 (0 = not at all aware to 10 = always aware), awareness scores on the first day were 3.5 and dropped to 1 by day 14.

In addition, a smaller Nalu study was conducted in which 15 patients wore the TD in seven PNS locations: infraclavicular, forearm, abdomen, thigh, calf, shoulder and ribs. Each location was evaluated with a clip and/or belt, and the results were similar to the lower back location [25] for both comfort and ease of use (unpublished observations). Additional postmarket prospective registries will help ascertain the safety profile of this novel device.

Conclusion

Although the Nalu Neurostimulation System appears to have clinical benefits in both SCS and PNS applications, additional data are required to determine its generalizability, durability and impact on quality of life. The safety profile of this novel system also appears to be similar to other commercially available systems in the US. The device also provides a platform for delivering and subsequently studying novel neurostimulation waveforms in the chronic pain population. Ideally, future work would involve sham-controlled crossover studies that quantify patients' long-term pain response and opioid requirements as well as the effect of the device on quality of life.

Author contributions

All authors contributed to study conception, design, administration and reporting as well as the analysis and interpretation of data.

Financial & competing interests disclosure

H Kalia is a consultant for Abbott and Omnia Medical. S Pritzlaff is a consultant for SPR Therapeutics, EBT Medical and Nalu Medical. E Ottestad is a consultant for SPR Therapeutics, Nalu Medical, Coloplast, Invicta Medical and Reflex Medical. A Gulati is a consultant for Medtronic, Flowonix, SPR Therapeutics, Nalu Medical and Tremeau Pharmaceuticals and an adviser for AIS Healthcare and Spark Biomedical. J Makous is a paid consultant for and shareholder of Nalu Medical. K Chakravarthy is a consultant for Medtronic, Biotronik, Mainstay Medical, SI-BONE, Bioness, PainTEQ, Vivex Biologics and Vertos Medical. He also has stock options in Nalu Medical, Mainstay Medical, Higgs Boson Health, UMEHEAL, Oska Wellness, Aya Biosciences, Rune Labs and Yantra Biomed. In

addition, he is a founder of Newrom Biomedical, AccuFix Medical and Douleur Therapeutics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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