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Devices Expand Treatment Options for **MIGRAINE**



Migraine has historically been managed medically, but in the last three years, four device companies have entered the market. They hope to become first-line therapies for a two- to four- million patient slice of the multibillion-dollar migraine market. Part 2 of a 2-part article on devices for migraine.

▶ MARY STUART

While the COVID-19 pandemic has derailed the plans of many companies in 2020, the emerging device market for the treatment of migraine has reported much good news.

This year brought FDA clearances for **electroCore Inc.**, **Cefaly Technology SPRL**, and **Theranica Bio-Electronics Ltd.**; FDA's Breakthrough Device Designation for **Salvia BioElectronics BV**; and hefty Series A investments for Salvia and **ShiraTronics Inc.**

These announcements have focused attention on unmet medical needs that exist for millions of migraine sufferers (36-40 million in the US alone) many of whom aren't adequately helped by many choices of drugs constituting a \$1.3 billion market that is growing by more than 13% (according to a January 2020 report published by research firm Reports and Data).

Unlike many chronic diseases, migraine strikes the young as well as the old, and sadly, can affect an entire life trajectory. Coping with the symptoms of onset, the painful throbbing headaches themselves, (which might be accompanied by nausea and light sensitivity), and the aftermath, consumes much of patients' lives, impacting social activities, family lives, careers, and emotional well-being.

The triggers of migraine are numerous and often mysterious, and many patients are anxious, always aware that the next attack could come at any minute. Some migraineurs say they feel misunderstood, seen as making too much of what others perceive as just a headache; others feel eternally guilty for being the cause of cancelled family vacations or other plans. While the disease is described in terms of episodes—how many headache days patients experience in a month (with 14 or fewer categorized as episodic and 15 or more constituting chronic migraine, for example) it's an entire way of life for a migraine sufferer.

There is an economic side as well, since migraine patients use many healthcare resources, including increased visits to providers, emergency visits, and diagnostic testing, and it's the third-leading cause of disability in people under the age of 50.

Drugs fall short because they don't control pain adequately, stop working for many patients, or bring such

side effects as sedation, dizziness, nausea, inability to concentrate, constipation, and weight gain, among others. According to various studies, the adherence to oral migraine medications is low; 80% of patients have discontinued their prescribed drugs within one year, because of modest efficacy and side effects.

Humanitarian Need and a Large Market

As noted, there has been a crescendo of activity in the device market for migraine recently (see *Figure 1*). Many have entered with noninvasive neuromodulation therapies that work on peripheral or central pain pathways, with devices targeting the vagus, occipital, trigeminal, or other nerves to interrupt pain transmission in progress (the acute migraine indication) or to reduce the number of headache days patients experience (the prevention label).

While several devices have overcome clinical and technical challenges to get to market, a couple of challenges remain, most notably, scant reimbursement for these mobile, home use devices, and unclear payment models. These types of mobile device therapies don't fall into neat reimbursement categories; they're not pharmaceuticals, and they're not conventional durable medical equipment (DME). Last month, *MedTech Strategist* spoke with electroCore to find out how it is handling this challenge. (See "*electroCore Tackles its Biggest Headache*," *MedTech Strategist*, October 21, 2020). Here we investigate the strategies of Theranica, which is selling a noninvasive device in the US and Europe, and Salvia BioElectronics, the outlier with an implantable device for the most severe chronic migraine patients. (See also "*Salvia BioElectronics: A Neurostimulation Platform for Migraine*," *MedTech Strategist*, March 13, 2019.)

Today, many migraine device companies make the argument that with efficacy that's comparable to drugs but a better safety profile and almost no side effects, they're well positioned to become first-line therapies. But a longer-term challenge remains from the pharmaceutical industry. In the last three years, a new class of migraine drugs targeting the CGRP (calcitonin gene-related peptides) pathway has come to market, and these largely injectable drugs have shown both improved efficacy and fewer side effects. We don't

know how these drugs will fare in the long run, but with superior efficacy, they could change the positioning or attractiveness of device therapies.

For now, the device market for migraine is large enough to hold many comers, particularly since the pathophysiology of migraine is still unknown and it can take many forms: episodic and

chronic with different levels of severity, with and without aura. The population is heterogeneous too, since people perceive pain differently, have various co-morbidities, different levels of acceptance for drugs or devices, and preferences for the timing and form-factor of their therapies. This argues for the need for many different choices in the migraine market, and lots of room for innovative device therapies.

Figure 1
Medical Devices for Migraine

Founding Year, Company, Location	Description/ Funding
(2004) Cefaly Technology SPRL (Liège, Belgium)	<i>CEFALY DUAL Migraine Device</i> , an external trigeminal nerve (specifically the supraorbital branch) stimulator, combines two different stimulation paradigms in one device for acute or prevention. Cleared in October 2020 as the first product for the acute treatment and prevention of migraine in adults available over-the-counter; Previously cleared for both indications only by prescription. Private equity firm DW Healthcare Partners holds a majority interest.
(2011) CoolTech LLC (Baltimore, MD)	<i>CoolStat</i> is targeted temperature management approach, which blows ambient air into a single-use nasal mask worn by the patient; migraine is only one of many potential indications. \$6 million in equity and \$4 million NIH grants have brought it to the clinical trial phase in neurogenic fever.
(2005) electroCore Inc. (Basking Ridge, NJ)	Publicly-traded on NASDAQ. Noninvasive handheld <i>gammaCore</i> , placed on the side of the neck, is vagus nerve stimulator cleared for both prevention and the acute treatment of migraines, and is the only device therapy cleared for cluster headaches.
(2002) eNeura Inc. [founded as Neuralieve] (San Jose, CA)	<i>sTMS</i> is home use noninvasive transcranial magnetic stimulation device targeting the occipital nerve with online migraine diary and ability for remote prescription update. Company filed for Bankruptcy in August 2020; no updates on the fate of the products.
(2014) Nocira LLC (Tempe, AZ)	Noninvasive device creates subtle pressure changes in the ear to stimulate multiple sensory nerve impulses into the central pain cortex of the brain. Private equity from AZ Crown Investments LLC and other private accredited investors.
(2017) Salvia BioElectronics BV (Eindhoven, the Netherlands)	Thin foil technology allows for an implantable device that can stimulate branches of the occipital and trigeminal nerves without the drawbacks of the conventional neurostimulators that are now used off-label in chronic migraine patients. Preclinical stage. €3.1 million seed round in 2018 from Brabant Development Agency, Thuja Capital Seed Fund II, Netherlands Enterprise Agency, Brabant StartUp Fund, and €26 million Series A led by Panakès Partners, INKEF Capital, SHS Gesellschaft für Beteiligungsmanagement with participation from BOM Brabant Ventures, Thuja Capital and Dolby Family Ventures.
(2018) ShiraTronics Inc. (Brooklyn, MN)	Spun out of accelerator NuXcel to develop a neuromodulation therapy for migraine, rumored to be implantable. \$36 million Series A round completed in March 2020 from Breakout Ventures, USVP, Amzak Health, Strategic Healthcare Investment Partners, Aperture Ventures, LivaNova PLC and a leading academic institution.
(2016) Theranica Bio-Electronics Ltd. (Montclair, NJ and Netanya, Israel)	<i>Nervio</i> is wearable, smartphone-controlled arm band that works on mechanism of conditioned pain modulation. Cleared for acute migraine—FDA <i>de novo</i> clearance gained in May 2019, CE mark granted Sept. 2020; future indications include migraine prevention, and adolescent labelling. \$42.5 million raised to date up through Series B round; investors include LightSpeed Venture Partners, aMoon, Omron Venture Partners, LionBird, Corundum Open Innovation, and Takoa.

Source: MedTech Strategist

Theranica: Targeting a Central Pain Mechanism in Migraine with a Wearable

Theranica Bio-Electronics (Netanya, Israel) was founded by electrical engineer and CEO Alon Ironi, and Ronen Jashek, software engineer and COO, his partner from a previous start-up, which developed integrated silicon receiver chips for the mobile digital TV industry, along with Slava Barabash and serial medtech entrepreneur Shimon Eckhouse, PhD.

After more than 20 years in the telecommunications and digital electronic consumer industries, Ironi wanted to dedicate his experience to something more personally meaningful, and his inspiration was right in front of him. His daughter suffered from migraine.

Ironi, Jashek, and their partners teamed up with David Yarnitsky, MD, a leading neurologist, pain researcher and director of the Department of Neurology at Rambam Health Care Campus (Haifa, Israel) who also heads the Laboratory of Clinical Neurophysiology at the Rappaport Faculty of Medicine of the Technion-Israel Institute of Technology. Their goal was to create a safe, effective, low side-effect home-use device therapy for people who suffer from migraines.

Yarnitsky has deeply researched and often published on a pain inhibition mechanism known as conditioned pain modulation (CPM). This is the notion that in certain diseases including migraine, patients have dysfunctional pain processing; a harmless stimulus is perceived by the brain as noxious and the patients experience pain. CPM may be triggered by a non-painful but felt peripheral stimulus resulting in the release of certain neurotransmitters in the brain stem, which shuts down the pain.

Theranica's device for treating migraine, *Nervio*, is thus very different from those of other migraine device companies in

terms of its mechanism of action and the body site where it is placed. While several other migraine devices are applied to the head or neck to target occipital and trigeminal nerves, *Nervio* is a wearable armband placed on the upper arm, a spot that was chosen for several reasons. First, in order to trigger CPM, the therapeutic stimulus needs to be delivered far from the site of pain (thus the company terms its stimulation paradigm "Remote Electrical Neuromodulation" or REN).

Second, sites on the body where there are layers of fat or muscle weren't a good option because such barriers would attenuate the signal targeting the nerves. In addition, placing the remote stimulation near a concentration of motor neurons wasn't a viable solution. For example, while the wrist-worn device is a popular form-factor in wearables, the company had to avoid that design because of the large concentration of motor neurons on the wrist such that a stimulus in that location might have caused involuntary muscle contractions. Finally, the armband is easy for patients to place (see *Figure 2*).

Nervio is cleared for the acute treatment of both episodic and chronic migraine with and without aura (it received FDA *de novo* clearance in May 2019 and a CE mark in September 2020). According to the Migraine Research Foundation, there are more than four million chronic migraine patients in the US, and each year, about 2.5 million people diagnosed with episodic migraine transition into chronic migraine.

In its approved migraine indications, *Nervio* has achieved efficacy similar to that of the triptan class of migraine drugs, achieving, at two hours, pain relief of about 67% and 37% freedom from pain, which the company demonstrated in a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 252 patients with a frequency of migraine days of 2-8 per month. Real-world experience has backed-up those efficacy levels, according to a post-marketing study (by Stewart Teppler, *et al*) that published in *Pain Medicine* in September 2020.

A Side-Effect Free, Drug-Free, and Convenient Therapy

Migraine patients who treat themselves with *Nervio* will keep it with them at all times, so they'll be



Figure 2
Wearing *Nervio*

Source: Theranica

In its approved migraine indications, *Nerivio* has achieved efficacy similar to that of the triptan class of migraine drugs.

ready to apply the treatment no matter where they are, as soon as they feel the symptoms that signal the onset of a migraine attack. As soon as they do, and Ironi notes that most patients are very good at recognizing their early symptoms, they place the armband, turn the device on, and start a treatment. Using a simple app on their smartphone, they can adjust the stimulation intensity to a level where they can feel it but it's not painful. Patients' pain thresholds vary, and different patients may tune the intensity to deliver the higher or lower levels of energy, Ironi says, just as long as they can feel the stimulus on the arm, but it's not painful.

Theranica's patent-protected stimulation paradigm delivers a dual-phasic waveform with a sequence of frequency transitions that repeat over the 45-minute treatment interval. At the end of the 45-minute treatment session, the user removes the armband and puts it back in its carry-on bag.

If they choose to, patients can use the migraine diary in the app to register their symptoms and treatments, and they can easily share this information with family members. "Physicians always want to know whether the therapy they prescribed works or not, and this is a more accurate record than the patients' recollection of past treatments," says Ironi.

Working out the Business Model

In the US, *Nerivio* is sold by prescription and since October is eligible for coverage by major commercial medical benefit insurance programs. Depending on each individual program, patients may pay as little as \$0 out of pocket for one unit of *Nerivio*, which delivers 12 treatments. The app indicates how many treatments are left, so when it's time to replace the device,

patients can do so easily from the app, which sends a refill request to the specialty pharmacy that distributes *Nerivio*. When a device has been used up, the patient disposes of it (or sends it free of charge for electronic recycling to California Electronic Asset Recovery [CEAR]).

Nerivio became available in the US in October 2019, at the time, largely on a self-pay basis, and by now many patients have refilled numerous times, Ironi notes. (The frequency of refill depends on the number of migraine episodes patients treat with the device, since, as noted, each device contains 12 treatments.)

According to Ironi, the company successfully began adjudicating *Nerivio* prescriptions in October (2020) while it negotiates reimbursement agreements with health insurance companies. As noted, migraine patients can be expensive users of healthcare resources, and a therapy like *Nerivio* can potentially help them avoid trips to the emergency room and might even cut down on drug costs and all the back and forth that goes into determining the right drug for a particular patient.

To this end, the company recruited a subset of the patients enrolled in the randomized controlled trial mentioned above to participate in an eight-week open-label extension looking at *Nerivio*'s impact on medication usage. The patients could treat their migraine attacks with *Nerivio* and/or their customary medications.

The study analysis, which was published in *Frontiers in Neurology* in April 2020, was performed on 117 patients who had treated at least one migraine attack with *Nerivio* for which pain intensity at 2 hours post-treatment was reported. Of that subset, 89.7% used only *Nerivio* to treat all of their attacks (that's to say, they completely avoided drugs). There was no deterioration in pain relief and pain-free results associated with the incorporation of remote electronic modulation into usual care, compared to using only drugs in the run-in phase of the study. More than 57% of the patients in the analysis achieved pain relief at two hours post-treatment in at least 50% of their treatments and over 30% of the participants achieved a pain-free outcome at two hours post-treatment in at least 50% of their treatments.

This study suggest that there might be cost advantages to *Nerivio* and the potential to sparingly use migraine drugs that cause medication overuse headaches, good data with which to approach commercial insurers. In May, the company hired two executives to spearhead that process, Ironi says. On its website, Theranica describes its product as a "prescribed digital therapeutic," which might pave the way to digital therapeutic formularies increasingly being created by pharmacy benefit managers.

In the meantime, an additional market access strategy revolves around agreements with two telemedicine companies that

make it easier for patients to get the prescription-only device. In February, Theranica partnered with Cove, a migraine-focused telemedicine service of **Thirty Madison Inc.**, which offers patients medical consultations for a small fee. If the independent provider prescribes *Nerivio*, Cove sends the device directly to the patient. In April, the company forged a similar collaboration with **UpScript Health**, a direct-to-consumer telemedicine platform for pharmaceutical companies and medical devices requiring a prescription.

Next steps for the company include launching, early next year, new clinical studies in migraine prevention and in the treatment of post-traumatic headache. In the near term, the company is working on publication of a study on migraine in which *Nerivio* was used to treat adolescents (ages 12-17). Those results have already been submitted for FDA review in the hope of expanding the indications to include patients as young as 12. The adolescent study results are of great interest, says Ironi, since that is a population for which both parents and physicians are typically more reluctant to prescribe drugs.

As noted, Ironi himself is the parent of a daughter with migraine. "Our goal is to make this device a first-line treatment for as many people across the world as possible," he says. Many people suffering from migraine aren't happy with their therapies. "Sometimes their prescribed drugs don't work for them or they suffer from side effects. Our dream is to make this device accessible to them at an affordable price, such that they can manage their migraine in a way that is safe and drug free."

Salvia BioElectronics: The Benefits of Implantable Neurostimulation

In the roster of medical device companies addressing migraine, Salvia BioElectronics is the only one that has publicly disclosed an implantable neuromodulation approach for chronic migraine. The FDA recently recognized both the unmet clinical need and the company's approach, granting Salvia a Breakthrough Device Designation in early November, which promises access to FDA experts and prioritized review. With its late September Series A financing, which brought in \$31 million, the company is well equipped to move its therapy out of the preclinical stage and into clinical development.

The company was founded in 2017 by the team that created Sapiens Steering Brain Stimulation, which developed an

advanced lead technology for deep brain stimulation.

Medtronic plc acquired the start-up for \$200 million only three years after its founding.

This time, the team (consisting of Hubert Martens, PhD, CEO, Daniël Schobben, chief operating officer, and Wim Pollet, MD, chief medical officer) identified severe, chronic migraine as an underserved medical need in which their neuromodulation expertise could make a difference.

Severe migraine consumes so much of a patient's life, between the symptoms of onset—irritability, fatigue, food cravings, sensitivity to light, muscle stiffness, nausea, and more—days ahead of a debilitating migraine attack that might last from four to 72 hours. When it's over, the patient often feels like they have a hangover. In those suffering from chronic migraine, defined as at least 15 headache episodes (22 headache days on average) that last for four hours or more per month, eight of them due to migraine, it rules their lives.

In interviewing physicians and patients, Salvia's founders heard that migraine "determines whether one goes to a party or not, takes a family vacation, or whether they're going to build up their career or work at home," Martens says. Most striking to Martens: "We have spoken to young women in their 30s who said they gave up on the idea of having a family because of their disease, which is extremely difficult to imagine. It has enormous impact on their lives." In fact, migraines affect women disproportionately; in the US, women represent 70% of the 40 million people who suffer from migraine.

Salvia set out to help the people most in need; those who experience chronic migraine and who have not responded well to other therapies, which include oral drugs, injectable drugs such as sumatriptan and Botox, and noninvasive neurostimulation devices. Martens describes the company's addressable market as "several million patients in the Western world that have this severe condition, don't respond adequately to existing solutions, and don't have contraindications to neurostimulation. We are talking about many millions of patients worldwide."

A Therapy that Doesn't Rule Patients' Lives

As noted earlier, there are several companies selling noninvasive 510(k)-cleared migraine devices, but many are struggling to find the best business models to get paid for devices that patients use in their own homes, and none yet have the depth of clinical efficacy data that helps clinicians to prescribe them, which is a challenge. However, they play a valuable role in the continuum of care, since there is a wide spectrum of disease and just as with pharmaceuticals, some will work for some people better than others.

Patients feel like they're weighing one bad option against another. The tradeoff, Martens says, "Should I suffer through the migraine or take an injection that makes me nauseous?"

On the other hand, there is a history of efficacy, in intractable chronic migraine patients, of implantable neurostimulation devices targeting the occipital nerve (in the back of the neck) or the supraorbital nerve (a branch of the trigeminal nerve above the eye), or both. These are off-label therapies that use devices developed for other parts of the body, and have a form-factor that's not ideal for this indication. Adverse events that result in device explantations and repeat surgeries include lead migration or breakage, infection, and skin erosion.

Martens notes that despite these drawbacks, patients have posted testimonials on the Internet describing how the therapy has changed their lives for the better, even when they've had to undergo multiple surgeries. So dire is the problem of intractable migraine that approximately 1,000 of these procedures are done in the US each year, Martens estimates, and there is an existing pathway to reimbursement for them.

Salvia's founding team thus started off with a scientific proof-of-principle and a reimbursement pathway for peripheral nerve stimulation, reducing some of the clinical and market risk, and went to the white board to design the product that would best fit the market's requirements.

First and foremost is the corollary to the desire that migraine not rule patients' lives. "They don't want the therapy to rule their lives either," Martens notes, adding that he's spoken with patients who feel they're weighing one bad option against another. The tradeoff, he says, "Should I suffer through the migraine or take an injection that makes me feel nauseous?"

For all of those reasons, the company knew its therapy would need to prevent migraines—to shorten the number of headache days per month—rather than abort a migraine in progress. "If you try to abort 22 headaches a month, the physiological

process has already started, and it wears you out. What is really needed is to prevent the headache from occurring at all. That is where we can really make a difference."

Meeting Both Clinical and Market Requirements


Salvia BioElectronics has developed thin and conforming bioelectronics foils that adapt to the anatomy of the head, to replace the conventional leads that are the cause of so many adverse events. A small external device activates the foils, which will be placed on branches of both the occipital and trigeminal nerves. These are validated targets in migraine, and earlier studies suggest that stimulating both nerves simultaneously appears to result in greater efficacy.

To prevent migraines, a patient would undergo therapy for several hours a day with the neuromodulatory effect of reducing the reactivity of the headache circuits in the brain that trigger migraine attacks. Martens notes that the nervous system of chronic migraineurs becomes so jittery that small triggers initiate migraine attacks. "This is not a cure, but if we can reduce 22 headache days by half or even less than half, we will deliver an enormous improvement in a patient's quality of life."

Salvia's recent financing will help it complete development of its device so it can initiate clinical studies. "We are detailing our clinical study program as we speak, and thanks to our Breakthrough Device Designation, we are enjoying an open communication with the FDA so we can align our plans and strategies with them," Martens notes.

As to the future market, Martens points out that there are nascent referral patterns, from headache specialists to interventional pain clinicians who implant neurostimulation devices in migraine patients on an off-label basis, and reimbursement available (after lots of boxes are checked).

Martens notes, "It is important that physicians get paid for the service of implanting the devices, and these CPT codes established for peripheral nerve stimulation were based on the older technology, so it is pretty well reimbursed." He notes that Salvia's solution is less invasive and less cumbersome to implant. "We believe that ultimately this could be a relatively short outpatient procedure and that today's available codes are sufficient."

But scaling towards the future, if it begins to reach many patients in need, "We want the solution to be sustainable for the physicians that perform the procedure and for payors. We have tried to optimize our technology to create that balance." 

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