The Impact of Pain

Bioelectronic medicine has the potential to provide more effective solutions for managing pain, in particular through non-invasive vagus nerve stimulation. Fortunately, the attention to bioelectronic medicine is growing, so a new treatment may not be far away.

As patients and healthcare providers can attest, living with pain can not only have a pervasive and devastating effect on patients' lives, but also has massive implications on society at large. Chronic pain alone is the cause of billions of dollars in lost productivity each year. For example:

- The loss of productivity due to chronic pain in Sweden has been estimated to constitute 91% of the socioeconomic cost of £7.37 billion (1)
- More than 50% of workplace absence due to disability in the UK stems from a health condition with general chronic pain symptoms (1)

While pharmacologic therapies are commonly prescribed for pain management and may be effective in certain instances, both physician over-prescription of and patient dependence on these medications continues to grow, creating substantial hurdles to long-term treatment (2).

Opioid dependence has become a growing epidemic around the world, specifically in the US:

- Opioid overdoses accounted for more than 42,000 deaths in 2016, more than any previous year on record. An estimated 40% of opioid overdose deaths in the US alone involved a prescription opioid (3)
- On average, 115 Americans die every day from an opioid overdose (4)
- Approximately 11.5 million adults misuse prescription pain relievers; the most common reason for the misuse was to relieve physical pain (63.4%) (5)
- In 2017, the US Department of Health and Human Services declared opioid dependence a public health emergency

With the prevalence of opioid dependence rapidly increasing worldwide, a critical need for innovative treatments exists (6). Now more than ever, solutions are needed that are less addictive to assist in reducing the burden pain has on patients, their families, and the system.

Emergence of Bioelectronic Medicine for Pain Management

As the prevalence of the opioid epidemic grows, researchers have begun to examine options beyond pharmacologic treatments. One of these alternatives is known as bioelectronic medicine. A relatively new approach to treat disease, bioelectronic medicine uses technology to moderate electrical activity within the body's nervous system. It can be delivered to the patient in a way that is safer and different to a traditional pharmaceutical pathway. While it has historically been used for the treatment of chronic pain and movement disorders, bioelectronic medicine is now being explored in various forms that are non-invasive and avoid a high risk surgical approach (7).

Non-Invasive Vagus Nerve Stimulation

Non-invasive vagus nerve stimulation (nVNS) is a type of bioelectronic medicine that has emerged as a therapy to alleviate pain associated with cluster headache and migraine. Migraine and cluster headache leave patients crippled with pain, and the symptoms of these conditions often impact the individuals' ability to manage daily life. nVNS offers patients the option to receive a mild electrical stimulation to the vagus nerve through the skin, allowing the body's biochemistry to modify pain signals and normalise physiological function, resulting in the reduction of pain. As a non-opioid, non-dependent, and self-limiting treatment, nVNS offers patients a safe and proven therapy for two debilitating neurological conditions.

Success in Treating Migraine and Cluster Headache Pain

Physicians often encounter patients for whom the standard of care, traditional treatment through over-the-counter or prescription drugs, has failed.
The impact of pain to prevent pain during their migraine and cluster headache attacks. Due to the debilitating nature of migraine and cluster headache, and the difficulty with finding treatment options that are both effective and with low-to-no side effects, the discovery of nVNS as an effective therapy is an encouraging development.

nVNS has started to revolutionise the pain treatment landscape, as evidenced by several clinical trials showing patient benefit and the approval of a self-administered nVNS device. Provided later is an overview of three clinical trials, which demonstrate these positive effects in patients with pain caused by migraine and episodic cluster headache.

Non-Invasive Nerve Stimulation for Migraine

One clinical trial examined the effect of an nVNS therapy for the acute treatment of pain associated with migraine (8):

- Adults aged 18-75 years diagnosed with migraine were included
- A total of 243 patients with migraine were randomised to receive either nVNS (N=120) or sham (N=123)
- 12.7% of patients who used an nVNS therapy within 30 minutes after an attack experienced pain freedom and 21% of patients who used an nVNS therapy within 60 minutes after an attack experienced pain freedom, in comparison to sham where only 4.2% of patients experienced pain freedom within 30 minutes of an attack and 10% of patients experienced pain freedom within 60 minutes of an attack

Non-Invasive Nerve Stimulation for Episodic Cluster Headache

Two additional clinical trials explored the effect of an nVNS therapy for the acute treatment of pain associated with cluster headache in adult patients. In the first trial (9):

- Adults aged 18-75 years diagnosed with cluster headache who experienced at least five attacks lasting 15-180 minutes were included
- A total of 150 patients with episodic cluster headaches (eCH) or chronic cluster headaches (cCH) (101 eCH, 49 cCH) were randomised to receive either nVNS or sham
- 34.2% of eCH patients who used nVNS therapy were successfully able to treat more than 50% of cluster headache attacks compared to 14.9% who used a sham

Figure 1: nVNS stimulation protocol in acute treatment of migraine with/without an aura

In the second trial (9):

- Adults 18 years and older diagnosed with episodic cluster headache or chronic cluster headache were included
- A total of 102 patients with episodic or chronic

Figure 2: Percentage of patients who were pain-free from the first migraine

Repeated-measures analysis

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>nVNS</th>
<th>Sham</th>
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<tr>
<td>30 min</td>
<td>12.7% (n=120)</td>
<td>4.2% (n=123)</td>
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<tr>
<td>60 min</td>
<td>21.0% (n=120)</td>
<td>10.0% (n=123)</td>
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<tr>
<td>120 min</td>
<td>30.4% (n=120)</td>
<td>19.7% (n=123)</td>
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Table 1: Percentage of patients who were pain-free from the first migraine

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cluster headaches (30 eCH, 72 cCH) were randomised to receive either nVNS or sham
- 64.3% of eCH patients who used nVNS therapy (complete resolution of the headache with no use of rescue medications) were successfully able to treat more than 50% of cluster headache attacks compared to 15.4% who used a sham

**Pain Management Innovation**

While bioelectronic medicine has emerged as an effective treatment option for pain management, pharmacologic treatments are still heavily relied upon. In the UK alone, nearly 24 million opioids are prescribed annually (11). As the impact of pain on patients and society grows, the medical community has a responsibility to not only evaluate alternate treatments for pain, but also advocate for the development and commercialisation of additional treatments that are both safe and effective.

**nVNS Stimulation Protocol**

Figure 3a: nVNS stimulation protocol in first clinical trial for acute treatment of cluster headache (eCH and cCH)

Treatment: Three consecutive stimulations

- Stimulation 1: 2 minutes
- Stimulation 2: 6 minutes
- Stimulation 3: 9 minutes

Initial assessment of pain intensity

- 15 minutes

Figure 3b: Episodic cluster headache patients successfully treated ≥50% of attacks

<table>
<thead>
<tr>
<th>% of patients</th>
<th>nVNS</th>
<th>Sham</th>
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<tbody>
<tr>
<td>10%</td>
<td>14.9% (n=47)</td>
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<td>20%</td>
<td>34.2%† (n=38)</td>
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*Response defined as ‘no pain’ or ‘mild pain’ at 15 minutes

Over 2x greater response

nVNS §P=0.01

Figure 4a: nVNS stimulation protocol in second clinical trial for acute treatment of cluster headache (eCH and cCH)

Figure 4b: Episodic cluster headache patients successfully treated ≥50% of attacks

<table>
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<th>% of patients</th>
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<tbody>
<tr>
<td>10%</td>
<td></td>
<td>15.4% (n=13)</td>
</tr>
<tr>
<td>20%</td>
<td>64.3% § (n=14)</td>
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</tbody>
</table>

*Response defined as ‘no pain’ or ‘mild pain’ at 15 minutes

Over 4x greater response

nVNS §P=0.01

Figure 4a: nVNS stimulation protocol in second clinical trial for acute treatment of cluster headache (eCH and cCH)

Figure 4b: Episodic cluster headache patients successfully treated ≥50% of attacks
About Migraine

- Migraine is the third most prevalent and sixth most disabling illness in the world, impacting nearly one billion people worldwide (10).
- Treating acute migraine is challenging due to substantial nonresponse rates among medication users and difficulty in predicting an individual's response to a specific agent or dose. At initial onset of a mild-to-moderate migraine, physicians are likely to recommend nonprescription nonsteroidal anti-inflammatory drugs and combination analgesics containing aspirin, caffeine, and even opioids.
- Abortive therapy is typically suggested as early as possible after the onset of symptoms. Despite significant advancements in the medical management of this challenging disorder, clinical data have revealed a proportion of patients – approximately 40% – do not adequately respond to pharmacologic or surgical intervention and remain symptomatic.

References

4. Centers for Disease Control and Prevention, Wide-ranging online data for epidemiologic research (WONDER), CDC, National Center for Health Statistics: 2017
7. Vitale F and Litt B, Bioelectronics: The promise of leveraging the body’s circuitry to treat disease, Bioelectronics in Medicine 1(1): pp3-7, 2017
8. Tassorelli C et al, Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study, Neurology 91(4): e364-e373, 2018
10. Visit: migraineresearchfoundation.org/about-migraine/migraine-facts

About Cluster Headache

- Cluster headache is a rare but extremely painful primary headache disorder characterised by recurring unilateral attacks. Frequently called ‘suicide headache’ due to the severity of pain associated with its occurrence, cluster headache bouts occur rapidly with variable frequency, but often at the same time each year or day and are often more frequent at night.
- Diagnosis of cluster headache may be delayed significantly due to patients and physicians mistaking the end of a bout for resolution of a separate, standalone condition. Very few viable therapies are available, making prevention and treatment strategies a challenge and highlighting a critical unmet need. Cluster headaches are typically treated with a combination of high flow oxygen and injectable drugs, as well as surgically invasive neuro-stimulation and/or nerve blocks with acute treatment often used to try and stop the pain once it has started, which can be difficult and frustrating for patients as the pain can become incredibly intense very quickly.