CADTH Horizon Scan

Vagus Nerve Stimulation for the Treatment of Post–COVID-19 Condition
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Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies; Health Technology Update articles typically focus on a single device or intervention. These technologies are identified through the CADTH Horizon Scanning Service as topics of potential interest to health care decision-makers in Canada.

- This Horizon Scan summarizes the available information regarding vagus nerve stimulation for the treatment of post–COVID-19 condition, also known as long COVID. In particular, the Horizon Scan discusses the Dolphin Neurostim, the first medical device to receive a Health Canada emergency authorization for expanded use in post–COVID-19 conditions.

- The emerging evidence from early findings of small pilot studies suggests that vagus nerve dysfunction may be implicated in some post–COVID-19 conditions and neurostimulation of the vagus nerve could help improve some symptoms. However, the evidence is limited because the studies were not powered to detect statistically significant differences in outcomes, and it is unclear if the reported findings were clinically meaningful.

- Due to the heterogeneity of post–COVID-19 condition and limited understanding of its pathophysiology, the extent of vagus nerve dysfunction's involvement in the condition is unclear. Where that dysfunction is implicated, electrical stimulation of the vagus nerve may be a potentially useful therapeutic option, likely complementary to other treatment options. Emerging evidence from ongoing and future research could help define the clinical effectiveness of the technology and guide its appropriate use.

Dolphin Neurostim for Treating Long-Haul Symptoms of COVID-19

The Dolphin vagal nerve stimulator (i.e., the Dolphin Neurostim) is the first medical device authorized by Health Canada to provide symptoms relief to people with post–COVID-19 condition. Post–COVID-19 condition, also known as long COVID (or long COVID syndrome due to its various symptoms), refers to ongoing physical or psychological symptoms that persist in some people for more than 3 months after acute COVID-19. The true prevalence of post–COVID-19 condition is uncertain and is reported to vary based on multiple factors and criteria used to assess the condition. For example, self-reported estimates indicate the prevalence may be between 4% and 10% and may vary based on the variant of infection. However, in up to 30% or 40% of people who acquire COVID-19, some common symptoms, such as fatigue and shortness of breath, can persist after the acute illness.

There is substantial uncertainty and limited knowledge about the pathophysiology, characterization, and clinical effectiveness of treatments for post–COVID-19 condition. However, vagal nerve stimulation may be a potential adjunct therapeutic option for some people.
How It Works

The vagus nerve is part of the body's autonomic nervous system and carries neurological signals from multiple organ systems to the brain, and vice versa. It has different functions in helping to regulate the digestive, cardiovascular, muscular, and respiratory processes of the body, and may relay certain sensory activation inputs from environmental signals, pro-inflammatory markers, or other signals to the brain and other organs. The nerve is also considered to play a role between the nervous and immune systems, modulating responses to inflammation. Due to its modulating role for many organ systems, the vagus nerve has been an active area of clinical research for more than 20 years.

Electrical stimulation of the vagus nerve has been studied for a variety of health conditions, most notably for epilepsy, depression, pain, and stroke rehabilitation. The nerve can be stimulated by electrical pulse delivered through a surgically implanted device or by a noninvasive device over a specified duration. Noninvasive stimulation may be delivered through electrodes placed on the skin surface in the neck or ear (targeting the auricular branch). The Dolphin Neurostim is a battery-operated noninvasive device that delivers electrical signals to the vagus nerve through its auricular branch by connecting a wire clip to a person's ear. People may use the device to self-administer stimulations multiple times a day, per their health care provider's guidance. Early evidence from similar devices suggests that noninvasive neurostimulation could help alleviate some symptoms related to the long-term effects of COVID-19.

Who Might Benefit?

The Dolphin Neurostim device is specifically intended for people experiencing long-term symptoms of COVID-19 and/or asthma-related shortness of breath. It is also intended for people for whom approved drug therapies are not tolerated or provide insufficient symptom relief, as assessed by their health care provider.

Availability in Canada

Health Canada provided emergency authorization for the expanded use of the Dolphin Neurostim device for long-term effects of COVID-19 (licence number 67326) in April 2022. Vagus nerve stimulation devices are available in Canada for other uses, such as epilepsy, and other neurostimulation devices are emerging in other countries for the treatment of acute or long-term COVID-19 symptoms.

What Does It Cost?

The Dolphin Neurostim kit, which includes the vagal stimulation accessories, is sold for $699 in Canada.
What Is the Evidence?

Early Hypotheses

Early during the COVID-19 pandemic in 2020, researchers hypothesized that stimulating the vagus nerve of people experiencing acute respiratory distress syndrome due to COVID-19 could increase their autonomic nervous system activity, leading to a heightened anti-inflammatory response. The anti-inflammatory response could alleviate some COVID-19 symptoms associated with inflammation of the lungs, such as difficulty breathing, shortness of breath, cough or chest tightness, pain and fatigue, and mental health distress. Until recently, there was little clinical research, beyond initial case reports, that assessed the involvement of vagus nerve dysfunction in the long-term effects of COVID-19 or whether vagus nerve stimulation could reduce or alleviate some of the associated symptoms.

Emerging Evidence

The emerging evidence to date is based on findings from pilot studies with limited sample sizes. Results from a pilot study in Spain reported that in a prospective cohort of 348 patients with post–COVID-19 condition (described as “long COVID”), functional tests suggested that 228 (66%) had symptoms indicative of vagus nerve dysfunction. However, the study is ongoing. Monitoring the final results will be important to examine the association between vagus nerve dysfunction and post–COVID-19 condition, and potentially inform treatment or future research. Another study, from Greece, also reported early results suggesting that people affected by post–COVID-19 condition may have autonomic nervous system disruption. However, it was a case-control study with a small sample size (11 cases of post–COVID-19 condition) and limited clinical assessment.

Other studies investigating vagus nerve stimulation as a possible therapeutic intervention for post–COVID-19 condition are emerging. However, these studies used devices that were not authorized for treating post–COVID-19 condition in Canada at the time of this Horizon Scan report. A preprint paper from the US reported results from a study where people with at least 1 symptom associated with post–COVID-19 condition self-administered noninvasive vagus nerve stimulation (using a device similar to the Dolphin Neurostim) at home. In total, 24 people were assigned to either a sham or active treatment group for a 4-week study period, with each group having 12 participants. The study reported that the participants confidently administered the therapy without assistance after 3 days of guided virtual sessions. The results suggested that after 4 weeks, people in the active treatment group may have experienced greater symptoms reduction than those in the sham group; however, the study was not powered to compare results between the study groups.

A pilot study in France used semipermanent needles to the ear to administer vagus nerve stimulation or a sham treatment to patients admitted into hospital with severe cases of acute infection of COVID-19. No differences in clinical outcomes were observed between the 2 groups over a 14-day study period. However, the study was not powered to detect clinically meaningful differences. A randomized control trial from Spain compared noninvasive vagus nerve stimulation (using a gammaCore device) to standard of care in a total of 97 patients (47 of whom received vagus nerve stimulation) admitted to hospital for COVID-19. Electric stimulation was delivered 3 times a day for up to 15 days for the treatment group, while the control group received standard of care. Results showed that levels of inflammation markers had decreased significantly among participants who received vagal nerve stimulation.
compared to those who received standard care. No statistical differences in clinical outcomes were reported. As both of these studies enrolled patients admitted to the hospital who had acute COVID-19 illness (but not post–COVID-19 condition), it is unclear how the results may translate to people experiencing the long-term effects of COVID-19.

Clinical trials examining other noninvasive stimulation devices, such as the Tens Eco (NCT05205577) and Parasym (NCT05225220), for the treatment of post–COVID-19 condition are ongoing. Neither this report nor a recent review of different neurostimulation devices identified any publicly available studies investigating the Dolphin Neurostim device for post–COVID-19 condition or COVID-19. The authors of the review, however, did report that several studies are ongoing to assess neurostimulation devices for conditions unrelated to COVID-19, but which may have similar mechanisms of action.

Safety

No safety concerns were reported in the identified studies on using neurostimulation as a potential therapy for post–COVID-19 condition or by Health Canada’s listing of the Dolphin device. Stimulation that requires surgical implants may have a higher risk of adverse events than noninvasive devices.

Issues to Consider

Due to the heterogeneity observed among people with post–COVID-19 condition, vagus nerve dysfunction may not explain all cases or be implicated in all people with the condition. In cases where nerve stimulation may be a feasible and potentially useful therapeutic option, it will likely be complementary to other health interventions. Health care providers would need to be appropriately trained and may require more fulsome clinical evidence before recommending the therapy to patients. Moreover, research to understand the exact parameters of neurostimulation (e.g., duration, frequency, intensity) that can produce a safe and clinically meaningful effect on symptoms is needed to help inform treatment design.

Looking Ahead

As research continues to investigate and understand the pathophysiology of post–COVID-19 condition, emerging therapy options, such as vagus nerve stimulation, may be considered to complement care. Based on the available literature and Health Canada’s approval, the Dolphin Neurostim device and other similar devices could be a suitable therapy for some people with post–COVID-19 condition. Monitoring the emerging evidence from larger clinical trials will help understand the role of vagus nerve dysfunction in post–COVID-19 condition and determine the place in therapy of vagus nerve stimulation to treat long-term effects of COVID-19. If the device were to be widely offered as a treatment option, issues related to cost and coverage would need to be addressed to ensure the therapy is equitably accessible to people who could benefit from it.
References


