

CADTH Horizon Scan

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

**Authors:** Sinwan Basharat, Quenby Mahood

**ISSN:** 2563-6596

**Note:** Manufacturer input was sought to review an earlier version of this report, but none was obtained.

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up to date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

**Funding:** CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to [Requests@CADTH.ca](mailto:Requests@CADTH.ca).

## Table of Contents

---

<b>Key Messages</b> .....	<b>4</b>
<b>Dolphin Neurostim for Treating Long-Haul Symptoms of COVID-19</b> .....	<b>4</b>
<b>How It Works</b> .....	<b>5</b>
<b>Who Might Benefit?</b> .....	<b>5</b>
<b>Availability in Canada</b> .....	<b>5</b>
<b>What Does It Cost?</b> .....	<b>5</b>
<b>What Is the Evidence?</b> .....	<b>6</b>
Early Hypotheses.....	6
Emerging Evidence.....	6
<b>Safety</b> .....	<b>7</b>
<b>Issues to Consider</b> .....	<b>7</b>
<b>Looking Ahead</b> .....	<b>7</b>
<b>References</b> .....	<b>8</b>

## 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.<sup>1,2</sup> 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.<sup>3</sup> 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.<sup>4</sup> For example, self-reported estimates indicate the prevalence may be between 4% and 10% and may vary based on the variant of infection.<sup>5</sup> 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.<sup>3,6</sup>

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.<sup>7</sup>

## 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.<sup>8</sup> 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.<sup>8,9</sup> The nerve is also considered to play a role between the nervous and immune systems, modulating responses to inflammation.<sup>8</sup> 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.<sup>9</sup>

Electrical stimulation of the vagus nerve has been studied for a variety of health conditions, most notably for epilepsy, depression, pain, and stroke rehabilitation.<sup>10</sup> The nerve can be stimulated by electrical pulse delivered through a surgically implanted device or by a noninvasive device over a specified duration.<sup>11</sup> Noninvasive stimulation may be delivered through electrodes placed on the skin surface in the neck or ear (targeting the auricular branch).<sup>12</sup> 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.<sup>1</sup> People may use the device to self-administer stimulations multiple times a day, per their health care provider's guidance.<sup>1</sup> Early evidence from similar devices suggests that noninvasive neurostimulation could help alleviate some symptoms related to the long-term effects of COVID-19.<sup>13,14</sup>

## 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.<sup>2</sup> 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.<sup>2</sup>

## 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.<sup>2</sup> 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.<sup>15,16</sup>

## What Does It Cost?

The Dolphin Neurostim kit, which includes the vagal stimulation accessories, is sold for \$699 in Canada.<sup>1</sup>

## 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.<sup>17</sup> 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,<sup>17</sup> pain and fatigue, and mental health distress.<sup>17,18</sup> 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.<sup>19</sup>

### 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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>13</sup> 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.<sup>13</sup>

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.<sup>22</sup> 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.<sup>22</sup> 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.<sup>14</sup> 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.<sup>14</sup> No statistical differences in clinical outcomes were reported.<sup>14</sup> 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)<sup>23</sup> and [Parasym](#) (NCT05225220),<sup>24</sup> 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.<sup>25</sup>

## 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.<sup>11</sup>

## 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.<sup>7</sup> In cases where nerve stimulation may be a feasible and potentially useful therapeutic option, it will likely be complementary to other health interventions.<sup>7</sup> 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.<sup>9,26</sup>

## 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

1. Center for Pain and Stress Research. Dolphin Neurostim: integrating neuromodulation science into pain management. 2022; <https://www.dolphinmpps.com/>. Accessed 2022 Jul 28.
2. Health Canada. Authorized medical devices for uses related to COVID-19: list of medical devices for expanded use. 2022; <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/medical-devices/authorized/expanded-use.html>. Accessed 2022 Jul 28.
3. Public Health Agency of Canada. Post COVID-19 condition (long COVID). 2022; <https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms/post-covid-19-condition.html>. Accessed 2022 Jul 28.
4. Ledford H. How common is long COVID? Why studies give different answers. *Nature*. 2022;606(7916):852-853. [PubMed](#)
5. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*. 2022;399(10343):2263-2264. [PubMed](#)
6. Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022;28(5):657-666. [PubMed](#)
7. Azabou E, Bao G, Bounab R, Heming N, Annane D. Vagus nerve stimulation: a potential adjunct therapy for COVID-19. *Front Med (Lausanne)*. 2021;8:625836. [PubMed](#)
8. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. *Front Psychiatry*. 2018;9:44. [PubMed](#)
9. Wang L, Wang Y, Wang Y, et al. Transcutaneous auricular vagus nerve stimulators: a review of past, present, and future devices. *Expert Rev Med Devices*. 2022;19(1):43-61. [PubMed](#)
10. Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. *J Inflamm Res*. 2018;11:203-213. [PubMed](#)
11. Mayo Clinic. Vagus nerve stimulation. 2020; <https://www.mayoclinic.org/tests-procedures/vagus-nerve-stimulation/about/pac-20384565>. Accessed 2022 Jul 28.
12. Mastitskaya S, Thompson N, Holder D. Selective vagus nerve stimulation as a therapeutic approach for the treatment of ARDS: a rationale for neuro-immunomodulation in COVID-19 disease. *Front Neurosci*. 2021;15:667036. [PubMed](#)
13. Badran BW, Huffman SM, Dancy M, et al. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms [non peer-reviewed preprint]. *Res Sq*. 2022;21.rs.3.rs-1716096.
14. Tornero C, Pastor E, Garzando MDM, et al. Non-invasive vagus nerve stimulation for COVID-19: results from a randomized controlled trial (SAVIOR I). *Front Neurol*. 2022;13:820864. [PubMed](#)
15. Canadian Epilepsy Alliance. Vagus nerve stimulation. 2022; <https://www.canadianepilepsyalliance.org/about-epilepsy/treatments/vagus-nerve-stimulation/>. Accessed 2022 Jul 28.
16. U.S. Food and Drug Administration. Emergency use of gammaCore Sapphire CV during the COVID-19 pandemic: fact sheet for healthcare providers: Coronavirus Disease 2019 (COVID-19). 2020 Jul 10; <https://www.fda.gov/media/139968/download>. Accessed 2022 Jul 28.
17. Kaniusas E, Szeles JC, Kampusch S, et al. Non-invasive auricular vagus nerve stimulation as a potential treatment for Covid19-originated acute respiratory distress syndrome. *Front Physiol*. 2020;11:890. [PubMed](#)
18. Baptista AF, Baltar A, Okano AH, et al. Applications of non-invasive neuromodulation for the management of disorders related to COVID-19. *Front Neurol*. 2020;11:573718. [PubMed](#)
19. Staats P, Giannakopoulos G, Blake J, Liebler E, Levy RM. The use of non-invasive vagus nerve stimulation to treat respiratory symptoms associated with COVID-19: a theoretical hypothesis and early clinical experience. *Neuromodulation*. 2020;23(6):784-788. [PubMed](#)
20. American Association for the Advancement of Science (AAAS). Pilot study suggests long COVID could be linked to the effects of SARS-CoV-2 on the vagus nerve: reports and proceedings: European Society of Clinical Microbiology and Infectious Diseases. *EurekaAlert!* 2022 Feb 11; <https://www.eurekaalert.org/news-releases/943102>. Accessed 2022 Jul 28.
21. Papadopoulou M, Bakola E, Papapostolou A, et al. Autonomic dysfunction in long-COVID syndrome: a neurophysiological and neurosonology study. *J Neurol*. 2022;269(9):4611-4612. [PubMed](#)
22. Rangon CM, Barruet R, Mazouni A, et al. Auricular neuromodulation for mass vagus nerve stimulation: insights from SOS COVID-19 a multicentric, randomized, controlled, double-blind French pilot study. *Front Physiol*. 2021;12:704599. [PubMed](#)
23. Assistance Publique, Hôpitaux de Paris. NCT05205577: Trial of auricular vagus nerve stimulation in painful Covid long (COLOSAT). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2022; <https://clinicaltrials.gov/ct2/show/NCT05205577>. Accessed 2022 Jul 28.
24. Casa Colina Hospital and Centers for Healthcare. NCT05225220: Multimodal investigation of post COVID-19 in females. *ClinicalTrials.gov*. Bethesda (MD): National Library of Medicine; 2022; <https://clinicaltrials.gov/ct2/show/NCT05225220>. Accessed 2022 Jul 28.
25. Czura CJ, Bikson M, Charvet L, et al. Neuromodulation strategies to reduce inflammation and improve lung complications in COVID-19 patients. *Front Neurol*. 2022;13:897124. [PubMed](#)



26. Burger AM, D'Agostini M. Response to "The use of non-invasive vagus nerve stimulation to treat respiratory symptoms associated with COVID-19: a theoretical hypothesis and early clinical experience". *Neuromodulation*. 2020;23(7):1042-1043. [PubMed](#)