Advancements in Neuromodulation:
A New Era for Respiratory Health

Neuromodulation is an approach that involves the use of devices to normalise or modulate nerve activity through the targeted delivery of electrical stimuli. Electrical stimuli can be delivered either invasively through surgical implantation of the device under the skin or non-invasively through the external application of a device to the skin. Applications for neuromodulation are increasing and include the use of deep brain stimulation (DBS) for Parkinson's disease and essential tremor, vagus nerve stimulation (VNS) for refractory epilepsy and depression, and transcutaneous electrical nerve stimulation (TENS) for menstrual cramps. These devices are already utilised widely, with an estimated 244,000 DBS devices implanted and 125,000 patients receiving VNS therapy worldwide alone.[1,2]

With a broad therapeutic scope and numerous ongoing active clinical trials involving neuromodulation devices, the neuromodulation market is poised for significant growth in the coming decade. According to a recent report by Markets and Markets, the global neuromodulation device industry was valued at $5.6 billion in 2022 and is expected to reach $11 billion by 2028.[3] Another emerging therapeutic application for neuromodulation, which will contribute to this growth, is the treatment of respiratory conditions. Neuromodulation techniques, which can target neural pathways involved in respiratory function, can be used as an adjunct to more conventional treatments and are already being used to improve respiratory symptoms.

Neuromodulation for Respiratory Health

Respiratory conditions are estimated to affect 16.8 million people and are responsible for 136,000 deaths each year in the UK alone.[4] Breathlessness, commonly referred to as dyspnoea, is a common feature of many respiratory conditions, including chronic obstructive pulmonary disorder (COPD) and pulmonary hypertension. Dyspnoea can be highly disabling and have a significant impact on a sufferer's ability to perform daily activities and their quality of life. Management of dyspnoea typically involves a combination of pharmacological drugs, pulmonary rehabilitation, and oxygen therapy. However, these treatments often lack efficacy, with one study finding that 53% of COPD patients still experience severe and persistent dyspnoea despite optimum inhaled medication and pulmonary rehabilitation.[5]

The mechanisms that give rise to dyspnoea are not well understood, but likely involve the integration of biochemical, mechanical and neural signals, which creates a mismatch between afferent inputs and efferent pulmonary responses.[6] Those neural pathways that have been implicated in dyspnoea include afferent neurons from the lungs and chest wall, the vagal nerve, and central areas of the brain, like the brainstem, cerebral cortex, and limbic system.[6] The involvement of neural signals in the pathophysiology of dyspnoea presents an avenue for the use of neuromodulation as a potential treatment.

Emerging Respiratory Neuromodulation Approaches

Several neuromodulation approaches are being investigated for their potential to reduce dyspnoea, including DBS, trigeminal nerve stimulation (TGNS), spinal cord stimulation (SCS) and VNS. There are currently no devices marketed specifically for the treatment of dyspnoea; however, this remains an area of active research with numerous ongoing clinical studies, examples of which are shown in Table 1.

DBS is an invasive approach that involves the surgical insertion of electrodes into the brain to stimulate specific areas, such as the motor thalamus, which is involved in the processing of sensory information, including that related to breathing. It is thought DBS may modulate signals relating to dyspnoea, such as the perception of "air hunger", described as the sensation of needing more air. One study involving 16 patients receiving DBS for the treatment of tremor reported relief of air hunger in 13 patients and a self-reported mean reduction in air hunger during stimulation of 14.4%.[7] Another study involving patients with bilateral electrodes for relief of essential tremor found that 10 out of 11 patients rated less air hunger with DBS on, with an overall mean ± standard deviation of 49±28 mm for the on state and 65±26 mm for the off state based on a visual analogue scale.[8] There is also some evidence that DBS can positively impact pulmonary function, with a recent study finding that DBS of subcortical brain areas improved peak expiratory flow rate by up to 14%.[9]

TGNS is a non-invasive approach involving stimulation of the trigeminal nerve, commonly used to treat refractory chronic facial pain syndromes. The trigeminal nerve plays a role in sensing airflow, protecting the airway, and the perception of breathlessness. Evidence for the use of TGNS comes from experiments involving the use of inhaled L-menthol or blowing cool air onto the face/nose, both of which can selectively stimulate the trigeminal nerve and have been shown to help relieve breathlessness.[10] Evidence using devices in this area is sparse; however, several feasibility trials are underway exploring the use of TENS for COPD-related dyspnoea (Table 1). TGNS stimulation may alleviate dyspnoea by modulating neural signals involved in the inspiratory neural drive and the perception of breathlessness.[10]

SCS is an approach that usually involves the surgical implantation of electrodes and the delivery of small electrical currents to the spinal cord and is commonly used for the treatment of chronic neuropathic pain syndromes. The spinal cord carries motor commands between the brain and respiratory muscles, including the diaphragm and intercostal muscles and transmits sensory information back to the brain. SCS has been primarily applied to the treatment of dyspnoea resulting from spinal cord injuries. One study involving 11 subjects with cervical spinal cord injury found that five days of transcutaneous SCS in combination with inspiratory muscle training led to a significant improvement in dyspnoea, thoracic muscle strength and forced vital capacity.[11] A similar study involving 10 tetraplegics receiving daily SCS found that it improved muscle strength to restore cough and inspiratory function.[12] It has been suggested that SCS acts to relieve dyspnoea by modulating neural pathways involved in respiratory control and by reducing the sensation of breathlessness.

Trial sponsor	Target indication	Estimated enrolment	Device name	Device type	Trial phase	Registration
Clinica Gema Leon	COVID-19	104	N/A	Non-invasive stimulation	N/A	NCT06544395
Universidad Rey Juan Carlos	Long COVID	44	N/A	Non-invasive stimulation	N/A	NCT06456502
Hospital San Carlos, Madrid	Post COVID-19 syndrome	40	N/A	Transcranial direct current stimulation	N/A	NCT05753202
University of New Mexico	Long COVID	60	N/A	Intermittent theta burst stimulation	II	NCT06940609
Université de Sherbrooke	COPD with severe dyspnoea	8	GammaCore	Transcutaneous VNS and trigeminal TENS	N/A	NCT06985628
University of Oklahoma	Pulmonary Hypertension	50	Parasymtm	Tragus stimulation	I/II	NCT06802380

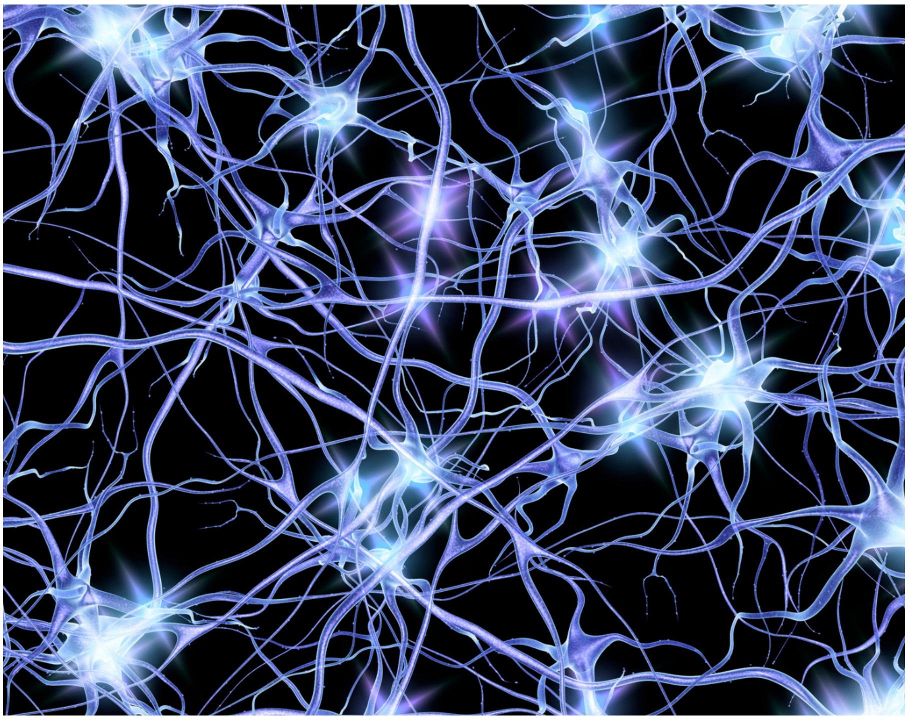
Table 1. Ongoing clinical studies involving the use of various neuromodulation strategies for respiratory conditions. (COPD, chronic obstructive pulmonary disorder; TENS, transcutaneous electrical nerve stimulation; VNS, vagus nerve stimulation)

VNS involves the delivery of electrical stimulation to the vagal nerve and can be achieved using both invasive and non-invasive methods. The vagal nerve forms a vital component of the parasympathetic nervous system and plays an essential role in regulating numerous processes, including respiration. The feasibility of using VNS to treat dyspnoea was evaluated in 25 subjects who presented in the emergency department for the treatment of moderate to severe acute asthma.[13] VNS treatment did not result in any serious adverse events and was associated with improvements in forced expiratory volume in one second (FEV1) and perceived dyspnoea.[13] Another clinical trial is currently underway evaluating the potential of VNS in patients with severe COPD and significant exertional dyspnoea (Table 1).[14] It is understood that VNS affects respiratory function by modulating sensory afferents related to dyspnoea and parasympathetic signals.

Challenges and Future Directions

The use of neuromodulation for the treatment of dyspnoea faces numerous barriers, which may limit its utility. The neural pathways underlying dyspnoea are not completely understood currently, and by extension, understanding of the mechanisms by which neuromodulation exerts its effects in dyspnoea is also limited. The pathways involved may also differ between patients, and the responses to stimulation may vary depending on the underlying disease pathology. Further, clinical evidence to support the use of neuromodulation in the relief of dyspnoea is quite limited, with many studies being early-stage or involving a small number of participants, making it difficult to reach definitive conclusions about its efficacy. Other barriers include the need for invasive implantation procedures for some devices, such as those used for DBS, which are associated with risks such as bleeding, infection and the formation of blood clots. This procedure may pose even greater risks in patients with comorbidities or severely compromised respiratory function. Moreover, many available neuromodulation devices were not developed specifically to be used for respiratory conditions, and consequently, stimulation parameter duration may not be optimal for relieving dyspnoea.

Future work in this area will undoubtedly involve the use of advanced neuroimaging techniques to better unravel the mechanisms underlying dyspnoea and the mechanism of action of neuromodulation in different disease states. Research will also focus on refining existing neuromodulation approaches through the more precise targeting of associated neural pathways and the optimisation of stimulation parameters. Other developments will include the use of novel stimulation approaches such as the closed-loop systems, combining physiological monitoring and stimulation devices to deliver personalised and adaptive neuromodulation based on real-time feedback on the patient's respiratory status. Additionally, there is a need for larger-scale studies using a wider range of patient populations to better



evaluate their efficacy, as well as long-term studies, to determine if these benefits are sustained over time.

Combine Neuromodulation Strategies and Conquer

Undoubtedly, neuromodulation represents a promising approach for the management of dyspnoea associated with respiratory conditions. Early clinical studies suggest that a range of neuromodulation strategies, including DBS, TGNS, SCS and VNS, can help to alleviate dyspnoea and improve respiratory function in selected patient populations. However, current evidence of the efficacy of these approaches remains limited, with most trials involving small patient populations and short-term observations. Further research is needed to better understand the mechanisms underlying neuromodulation in respiratory pathways, optimise stimulation parameters, and establish efficacy through additional clinical studies. Future developments may also include the integration of stimulation and cardiopulmonary monitoring devices which may further enhance the benefits of these approaches in improving respiratory health.

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Dr. Bipin Patel

Bipin Patel Ph.D. is the CEO and Founder of electronRx, a deep-tech startup developing novel chronic disease and hospital patient management solutions. He is a key digital health thought-leader with over 20 years' experience in medical engineering, drug development and commercialisation and holds a PhD in Medical Engineering from UCL, UK.

Email: enquiries@electronRx.com