Journal of Asthma

ISSN: 0277-0903 (Print) 1532-4303 (Online) Journal homepage: www.tandfonline.com/journals/ijas20

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To cite this article: Kurt Gehlsen, Angelica Carrasco, Jillian Hooghius & Stephen Pyles (31 Jul 2025): Neuromodulation for the treatment of moderate to severe asthma – a pilot first-in-human clinical study, Journal of Asthma, DOI: 10.1080/02770903.2025.2531501

To link to this article: https://doi.org/10.1080/02770903.2025.2531501

Published online: 31 Jul 2025.

JOURNAL OF ASTHMA
https://doi.org/10.1080/02770903.2025.2531501

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Neuromodulation for the treatment of moderate to severe asthma – a pilot first-in-human clinical study

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ABSTRACT

Objective: This was a small, uncontrolled, first-in-human clinical study that evaluated the safety and efficacy of neuromodulation in patients with moderate to severe asthma.

Methods: Patients diagnosed with chronic intractable pain and moderate or severe asthma on daily asthma medications were tested and subsequently implanted with a permanent spinal cord stimulator. Patients were followed for 12 months and monitored for changes in medication use, asthma control scores, quality of life, exacerbations, ER visits and hospitalizations.

Results: 11 patients were enrolled, 9 with asthma, and 2 with asthma plus COPD. 91% of patients achieved $a > 50\%$ reduction in all asthma medication usage. For all patients enrolled there was an 88% reduction in all asthma medication use and for patients with asthma alone, there was a 98% reduction in all medication use. 100% of enrolled patients reported an Asthma Control Test (ACT) >19 with improved breathing, no wheezing, no chest tightness, and no exacerbations (average increase of 13.3 points). 100% of the enrolled patients reported an improvement in quality of life with an average increase of 3.4 points using the Asthma Quality of Life Questionnaire (AQLQ). No ER visits or hospitalizations were reported due to asthma. There were no adverse events reported.

Conclusions: Neuromodulation provided clinically meaningful improvements in asthma symptoms without the need for asthma medications and without adverse events.

ARTICLE HISTORY
Received 26 April 2025
Revised 13 June 2025
Accepted 6 July 2025

KEYWORDS
Neuromodulation; asthma control; quality of life; medication use

1. Introduction

Asthma is a chronic disease affecting nearly 28 million people in the United States and more than 330 million people worldwide. Five to ten percent of patients have severe asthma. Societal costs in the United States due to asthma are estimated at $82 billion per year with severe asthma patients representing 50% of that cost burden (1). Asthma symptoms include trouble breathing, wheezing, coughing and tightness in the chest. Although there are numerous causes and triggers that induce an asthma attack, the underlying basis for symptoms is airway hyperresponsiveness, bronchoconstriction and mucus hypersecretion (2). There is no current cure for asthma and as such the current standard of care focuses on preventing asthma attacks.

Primary treatment for asthma includes a) anti-inflammatory drugs like inhaled or oral corticosteroids, b) bronchodilators like beta-2 receptor agonists which mimic sympathetic neuronal release of norepinephrine, and/or c) anti-cholinergic drugs which block parasympathetic release of acetylcholine, which is a bronchoconstrictor (2). In many cases, severe asthma patients are taking all three classes of drugs plus, in some cases, the approved monoclonal antibodies that target IgE, various inflammatory cytokines like IL-5, IL-4/IL13, and anti-TSLP. Additional cytokine and cytokine receptor targets are in development including anti-IL-9, anti-IL-25, anti-IL-33, and IL-4Ra, IL-5R and CRTH2 (3). Chronic use of asthma medication may cause adverse events and impair quality-of-life which have been reported exhaustively elsewhere (4–6). Solely targeting inflammation with drugs or biologics over that last 20 years has not altered asthma prevalence or mortality (2). Therefore, developing new treatment solutions that directly target lung neuronal dysfunction are warranted.

The first spinal cord stimulation (SCS) system was commercialized by Medtronic in 1968 for the treatment of chronic pain. The mechanism of action for SCS has also evolved and the current thinking is that SCS selectively activates or inhibits various pathways

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and nerve cells in the dorsal horn of the dorsal spinal column. SCS technology has made significant advances with several SCS products approved globally for numerous pain conditions (7).

A large body of evidence clearly establishes that the primary symptoms of asthma, namely, wheezing, dyspnea, chest tightness, cough, airway obstruction, mucus hypersecretion and airway hyperresponsiveness are linked to dysfunction of central and peripheral neuronal pathways (2). Chronic inflammation has been shown to lead to neuronal plasticity and dysfunction that is not reversed by currently used medications (2,8,9).

We hypothesized that neuromodulation in the upper thoracic region of the spinal cord could disrupt or reverse the neuronal dysfunction associated with asthma airway hyperresponsiveness. We report herein on the first clinical trial of spinal cord stimulation to treat patients with moderate or severe asthma. We reprogramed an approved SCS device used for pain management to investigate the ability of SCS to potentially provide a new, safe, and effective drug-free alternative for patients with asthma.

Following SCS implant, 100% of patients reported their asthma under control (ACT > 19, +13.3 pts), and 100% of patients reported an improvement in quality of life (AQLQ >5,+3.4 pts). Patients reported improved breathing, no wheezing or chest tightness and reported a mean reduction in all asthma medications by 88%. These results were agnostic to asthma phenotype and exacerbation triggers and came without any reported adverse events from the SCS implant. Patients additionally benefited by eliminating side effects associated with asthma medications.

2. Methods

2.1. Objectives and endpoints

Primary objectives included a) evaluate the clinical success of neuromodulation in reducing patient dependency on medications for asthma treatment, and b) assess any changes to the patient's asthma symptom scores when treated with neuromodulation. A secondary objective was to assess changes to the patient's perceived Quality of Life and the safety objective was to assess the safety of the implanted SCS device

Primary Endpoints were a) reduction in asthma medication use > 50% from baseline, and b) improved asthma symptom scores using the Asthma Control Test (ACT). The secondary Endpoint was improved Quality of Life score using the Asthma Quality of Life Questionnaire (AQLQ). The safety endpoint was the number of, and frequency of adverse events related to the implanted device characterized by type, severity, and duration.

As this was a small, hypothesis-generating study, all eligible asthma patients were enrolled, and various known asthma-related biomarkers were not evaluated. In addition, a control arm was not included as it was felt to be unethical to sham implant patients for 12 months in this initial first-in-human study.

2.2. Study population

Patients were enrolled for a permanent implant for asthma after meeting the following inclusion criteria: subject had a diagnosis of chronic pain and was a candidate for SCS; subject had moderate to severe asthma or asthma plus COPD, diagnosed by a physician, for a minimum of 1 year. Subject was actively being treated with one or all the following, inhalers – single drug or combination of drugs, oral medications, biologics, corticosteroids, and subject had no psychiatric contraindications that would prevent the subject from undergoing an implantation of a SCS.

Patients were excluded for the following criteria: subject had a BMI < 5 or > 35; subject required continuous anticoagulant medications; subject had a history of recurrent surgical, or current active infections (e.g. MRSA); subject had history of thoracic spine surgery; subject had history of coronary artery occlusive disease, angina, recent myocardial infarction, congestive heart disease, and/or coronary artery stent(s); subject had a recent cardiac stress test within the last 6 months with an ejection fraction of less than 50%.

2.3. Study design

This was a single-site, open-label, single-arm first-in-human study to evaluate spinal cord stimulation in the management of asthma symptoms, medication usage and quality-of-life for eleven subjects who met the inclusion and exclusion criteria.

Subjects had a diagnosis of chronic pain eligible for SCS and were also previously diagnosed with asthma or asthma plus COPD by their pulmonologist. Subjects enrolled in the study initially underwent a 3 to 5-day temporary trial implant period to assess patient responses to the SCS therapy andensure proper lead placement. Subjects that achieved greater than a 75% reduction in asthma symptoms as well as a 75% reduction in their pain symptoms throughout the trial period and did not experience any adverse events, received a permanently implanted stimulator for pain and asthma. Subjects were followed over pre-operative,

trial implantation, and permanent implantation periods, which lasted a combined total of 390 days. Throughout the duration of the study, subjects were instructed to continue their asthma medications and treatments on an as-needed basis. Subjects were asked to continue recording asthma attacks, medication usage, ER and hospital visits in their daily diaries.

2.4. SCS device

Boston Scientific Spectra WaveWriter™ Alpha SCS System (WaveWriter) is a totally implanted system that delivers electrical stimulation to the dorsal column of the spinal cord and is FDA approved for the treatment of chronic pain and numerous related indications (10). All patients underwent a trial stimulation period with a temporary external trial stimulator, which is a component of the WaveWriter. The trial stimulation period of 3-5 days allows the clinician to determine if the patient will benefit from SCS. If the patient reports favorable results, the rechargeable, permanent implantable pulse generator is placed under the skin in either the upper buttock or lower flank, the leads are connected to the generator and implanted within the epidural space. Patients did not have the ability to interact with any of the device's control interfaces to adjust treatment parameters for asthma. One patient received the approved Nevro-HFX™ SCS system which was implanted and programmed in the same manner and with the same parameters as used with the WaveWriter (11).

2.5. Medication usage

The study required subjects to be treated daily with asthma medications prior to enrollment. The frequency and dosage of each medication used by the study subjects was recorded in a diary 30 days prior to implantation to establish their pre-implant baseline and then at 30-, 60-, 90-, 180-, and 360-days post implant. Throughout the study, subjects were encouraged to continue using their asthma medications as needed. When use of a medication was necessary, subjects recorded these incidences in the diary. The usage rates within each of the study evaluation timepoints were calculated and compared against the subject's baseline rates to determine treatment-related change in usage.

2.6. Analytical methods

Simple analytical methods to assess mean changes from baseline to 12-month endpoint for changes in ACT, AQLQ and medication use were considered best. This study was not designed or powered to support statistical analyses but rather to support our hypothesis and shape the design and power requirements for the planned randomized, controlled, multicenter study in severe asthma patients.

3. Results

3.1. Patient demographics

Patient ages ranged from 32 to 77 years and the sample population included both males ($n = 3$) and females ($n = 8$). The average age of the patients was 58 years. Multiple patients had histories of smoking ($n = 5$) and alcohol use ($n = 3$). All patients included within this investigation had a diagnosis of chronic pain, two patients had both COPD and asthma, and nine subjects had asthma only. All patients with asthma had either moderate (7 patients) or severe (4 patients) disease that required daily use of asthma medications. See Table 1 for a summary of the patient demographics.

3.2. Medication use

Patients used a variety of medications ranging from daily nebulized steroids, inhaled beta-2 agonists, anticholinergics, oral corticosteroids, combination inhalers and one on biologics. Some patients included anti-allergy drugs as well. The normalized dosage per month was calculated by multiplying the daily dosage by 30 days. Each use/puff was considered one dose for inhaled drugs. The baseline mean number of doses

Table 1. Patient demographics.

Characteristic	Baseline
Age, mean (range)	58 (32–77)
Gender (M/F)	3M/8F
BMI, mean (kg/m^2)	33.3
Smoker (yes)	5
Asthma duration in years, mean (range)	39 (8–70)
Asthma stage at diagnosis (moderate/severe)	5/4
Asthma plus COPD	2
Asthma classification[a] (# of patients)	Allergic (2) Environmental (6) Exercise (4)
Asthma triggers[a] (# of patients)	Allergies (2) Daily activities (1) Exercise (6) Medications (1) Smell (2) Weather (2) Cold air (1) Cold food (1)
ACT mean	8
AQLQ mean	1.9
Mean daily drug use by dose	165

[a]Several patients reported more than one cause for asthma and more than one trigger.

Table 2. Medication usage.

Patient Group (# of pts)	Baseline drug use (mean # of doses)	Post-implant drug use day 0-30 (mean # of doses)	Post-implant drug use day 31-60 (mean #of doses)	Post-implant drug use day 61-90 (mean # of doses)	Post-implant drug use day 91-180 (mean # of doses)	Post-implant drug use day 181-365 (mean # of doses)	% change in drug usage at 12 months
Asthma alone (9)	149	5	3	3	3	3	98%
Asthma + COPD (2)	240	184	184	184	184	184	23%
Severe Asthma (5)	203	5	3	3	3	3	99%
Moderate asthma (4)	66	0	0	0	0	0	100%

for all patients was 165 per month, ranging from 24 to 270 doses per month.

Ten (10) of eleven (11) patients (91%) reported a greater than 50% reduction in medication use. Eight (8) of eleven (11) patients (73%) reported elimination of all asthma medication usage at day 360. These patients included three (3) patients with severe asthma and five (5) patients with moderate disease. One (1) patient with severe disease reduced medication use by 99%, used albuterol inhaler 3 times in a month. One patient with moderate asthma plus COPD reduced inhaled medication use by 14% and the other with moderate asthma plus COPD reduced medication use by 98.5%, used rescue inhaler 3 times in a month. All eight patients reported elimination of asthma symptoms not requiring medication within days of the SCS implant and had their full reductions within the first 30 days which carried to the end of the study. All patients continue to be seen by Investigator every 3 months since trial initiation. Most patients are two years' post-implant with several out three years and one 4 years post-implant and continue to report having no asthma symptoms and remain medication-free. See Table 2 for a summary of medication usage.

3.3. Asthma control Test

The Asthma Control Test (ACT) is a commonly used and validated questionnaire used to assess a patient's asthma control (12). ACT scores range from 5 (poor asthma control) to 25 (complete asthma control) with a score greater than 19 meaning a patient's asthma is controlled.

For all patients, the mean ACT score at pre-implant (baseline) was 8 (poorly controlled) even while all were taking multiple asthma medications. 12-months following SCS implant, 100% of the patients had an ACT greater than 19. The post-implant mean ACT score was 23 (range 22-24, average increase of 13.3 points) resulting in controlled asthma symptoms.

3.4. Quality of life

The Asthma Quality of Life Questionnaire (AQLQ) is a disease-specific health-related, validated quality of life instrument for patients with asthma (13). This assessment includes both the physical and emotional aspect of their disease. The AQLQ scores range from 1 (severely impaired) to 7 (not impaired at all).

Table 3. Summary of study endpoint results.

Endpoint – All asthma patients	Baseline	12-months post SCS implant
Number of patients having > 50% reduction in medication use	0/11	10/11 (91%)
Number of patients with ACT score >19	0/11	11/11 (100%)
Number of patients with AQLQ score > 5	0/11	11/11 (100%)

For all patients, the mean baseline score was 1.9 (highly impaired even on multiple asthma medications). 12-months following SCS implant, 100% of the patients had a AQLQ score greater than 5. The mean AQLQ score increased to 5.24 (range 5.1-6.1, average point increase of 3.33). See Table 3 for a summary of study endpoints.

3.5. Safety

No adverse events were reported that were not expected for both temporary and permanent SCS implant surgical procedures. One patient had a fall resulting in lead migration and opted to have the device removed months after completion of the 12-month trial period. One patient reported an ER visit for an RSV infection and considered unrelated to the SCS implant and asthma. One patient died of pancreatic cancer following completion of the trial period.

4. Discussion

Neuromodulation using spinal cord stimulation was first tried in patients in the 1960s and over the years SCS has been approved to treat a myriad of pain-related indications (7). We report herein on the first human clinical trial using spinal cord stimulation to treat patients with moderate to severe asthma. All patients enrolled realized a clinically meaningful improvement in their ACT scores (mean increase of 13.3 points) reflecting complete control of their asthma symptoms with 73% patients eliminating their need for asthma medications beginning within days after implantation.

Quality of Life measured by the AQLQ assessment was improved by a mean of 3.3 points, with all patients reporting a normal or near normal quality of life. There were no safety concerns for patients for both pain and asthma with each patient receiving a single implanted device with 2-3 leads to cover both pain and asthma.

We hypothesized based on pulmonary physiology and lung innervation pathways that stimulation of the upper thoracic spinal cord would lead to modulation of both the central and peripheral neurons (including visceral afferents and sympathetic efferents) leading to continuous bronchodilation, decreased mucous formation and inhibition of AHR – without the need for anti-inflammatory and other medications.

Most asthma symptoms are the result of changes in both peripheral and central neuronal pathways. Chronic inflammation can activate neurons and drive neuronal plasticity resulting in nerve cell growth and altered nerve function (8,9). Afferent neurogenesis leads to increased output from the lungs to the central nervous system, results in increased excitability, increased activation threshold and increased activation of the efferent neurons (2,8,9).

Parasympathetic efferent changes lead to increased output to the parasympathetic ganglia which causes acetylcholine release and increased cholinergic tone, hence, bronchoconstriction and increased mucous formation. Taken together, these peripheral and central neuronal changes contribute to the symptoms and pathogenic features of asthma, including, cough, wheezing, mucous secretion, dyspnea, airway hyperresponsiveness (AHR), and airway remodeling (2,8,9).

To put our results in perspective, recent publications recommend a new primary endpoint, namely "clinical remission", to allow comparison across various treatments, including biologics (14,15). Clinical remission is defined as a composite endpoint that includes an ACT score >20, positive changes in lung function (changes in FEV1), no exacerbations and no oral steroid use. Using this endpoint to analyze numerous phase 3 clinical trials in severe asthma patients administered various biologics (Dupilumab, Benralizumab, Tezepelumab, Mepolizumab, or combinations of these antibodies) in combination with other asthma medications; the average clinical remission rate was 30% (range 14-43%) (15). The reimbursed cost of the approved biologics averages $38,000.00 per year (1). In comparison, the full reimbursed cost of the neuromodulation system which includes the temporary and permanent leads, both surgical procedures and the implanted device is approximately $35,000.00 as a one-time cost (16).

Using this same definition of clinical remission for the severe asthma patients enrolled in our clinical study and substituting elimination of all asthma medications as opposed to only oral steroid elimination, we obtained an 73% clinical remission rate. The limitations of our study include not randomized, small size, no control arm, performed at a single center, no statistical analyses, did not measure inflammatory biomarkers, and did not prospectively use the above definition of clinical remission (ACT > 20/improved FEV1/no steroids), but rather looked at each component separately. We are currently planning a pivotal, prospective, randomized, controlled, multi-center clinical study to determine the safety and efficacy of neuromodulation to treat patients with severe asthma. The study is designed to randomize patients to either SCS or Physician's choice including biologics. The primary endpoint will be clinical remission as defined above along with exploratory subgroup analyses and endpoints to include critical biomarkers along with additional secondary endpoints, QoL and safety.

5. Conclusions

Current asthma treatments have not changed the prevalence, mortality or burden of this disease for patients and the healthcare system. Patients require numerous medications which, in many cases, come with side effects, cost, do not control the patient's asthma symptoms and adversely affect the patient's quality of life. All patients enrolled in this study reported a clinically meaningful control of their asthma, elimination of asthma symptoms, reduction or elimination of all asthma medications and their associated side effects, and SCS treatment came with an improvement in quality of life. These preliminary findings suggest that neuromodulation may offer a promising alternative for patients with moderate to severe asthma.

Authors' contributions

Stephen Pyles, Angelica Carrasco and Jillian Hooghius contributed to the study design, trial management, data collection, data management, reviewing and editing the manuscript. Kurt Gehlsen contributed to data audits, data analysis and manuscript preparation. All authors read and approved the final manuscript.

Disclosure statement

Stephen Pyles has several patents covering the use of neuromodulation to treat respiratory diseases and is a founder and shareholder of Spiro Medical, Inc. Dr. Pyles is an advisor to Boston Scientific, Inc. Jillian Hooghius is a clinical

representative for Boston Scientific, Inc. Kurt Gehlsen is a founder, shareholder and CEO of Spiro Medical, Inc.

Ethical approval and consent to participate

All patients signed informed consent, and no ethics approval was required as this was a single site pilot study using an approved medical device for a new indication.

Funding

There was no grant or industry funding for this study.

Data availability statement

All data generated or analyzed during this study are included in this published article other than patient videotaped assessments. This study enrolled two patients with COPD alone and their data has been excluded from the manuscript.

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