

Cryosurgical Ablation for Treatment of Rhinitis: Two-Year Results of a Prospective Multicenter Study

Randall A. Ow, MD; Ellen M. O'Malley, MS ; Joseph K. Han, MD; Kent K. Lam, MD; David M. Yen, MD

Objectives/Hypothesis: To assess the long-term (12–24 months) safety and effectiveness of cryoablation of the posterior nasal nerve as treatment for chronic rhinitis.

Study Design: A multicenter, prospective, single-arm clinical study.

Methods: The study was conducted from February 2017 to April 2020. Study endpoints included change from baseline in the reflective Total Nasal Symptom Score (rTNSS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), physician assessment of improvement using the Clinical Global Impression–Improvement (CGI–I), and the incidence of treatment-related adverse events.

Results: Ninety-one participants completed the study through the initial 12-month study period. Sixty-two participants consented to the long-term follow-up with 57 completing the 24-month follow-up. Significant improvements in the total rTNSS were reflected in a median change from baseline of -3.0 or -4.0 at all timepoints ($P < .001$). Greater than 80.0% of participants achieved the minimum clinically important difference (MCID) of improvement by ≥ 1 point on the rTNSS at all follow-ups. Total RQLQ scores indicated significant improvement ($P < .0001$) in quality of life. Over 77% of participants achieved the MCID (≥ 0.5 points) for the total RQLQ score. According to the CGI–I, $\geq 83.0\%$ experienced improvement at all but the 12-month visit (61.9%). One participant experienced two treatment-related serious adverse events (epistaxis and retained pledget). A total of 29 nonserious treatment-related AEs were reported in 23 participants; most events were transient and resolved with little to no intervention.

Conclusions: Cryotherapy significantly and clinically improves rhinitis symptoms and quality of life with outcomes that are durable through 24 months after treatment.

Key Words: Allergic rhinitis, chronic rhinitis, nonallergic rhinitis, cryotherapy, posterior nasal nerve cryoablation.

Level of Evidence: 4

Laryngoscope, 131:1952–1957, 2021

INTRODUCTION

Chronic rhinitis is a common disease with an estimated 2 billion people affected worldwide, including nearly 87 million in the United States.¹ The cardinal symptoms of rhinitis—rhinorrhea, congestion, itching, and sneezing—have a significant impact on the quality of life and productivity of people affected.²

Pharmacologic interventions are usually the first line of therapy; however, these first-line therapies frequently fail to control symptoms due to lack of efficacy or intolerance to treatment.³ For these patients, surgical interventions may

be indicated. Surgical options, such as vidian neurectomy and posterior nasal nerve (PNN) sectioning, have been shown to provide symptom relief but typically require general anesthesia in an operating room setting, and serious complications can occur.³ Cryoablation of the PNN has been known to be an effective treatment since the 1970s, but the devices were not fully optimized for endoscopic use and did not gain wide adoption.⁴

In June 2016, the United States Food and Drug Administration (FDA) cleared a novel cryotherapy device (Clarifix, Stryker Corporation, Plymouth, MN) designed specifically to facilitate an office-based, transnasal approach for cryoablation of the PNN. Hwang et al published a pilot study demonstrating the safety and feasibility of the device.⁵ Recently, the 9-month outcomes were reported for a larger cohort.⁶ Procedural success was high (100%) in this larger study performed under local anesthesia. Because peripheral neuroregeneration can occur at a rate of 1 to 6 inches per month,^{7,8} evaluating results beyond a year is important to determine durability of the treatment. We now report longer-term outcomes (12-month through 24-month) of this larger cohort of rhinitis patients to evaluate the safety and durability of the treatment modality.

MATERIALS AND METHODS

Study Design and Population

This prospective, multicenter, interventional, single-arm study was conducted at six US investigational centers from

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

From the Sacramento Ear, Nose, and Throat (R.A.O.), Roseville, CA, U.S.A.; Clinical Affairs, Stryker ENT (E.M.O.), Plymouth, MN, U.S.A.; Otolaryngology (J.K.H., K.K.L.), Eastern Virginia Medical School, Norfolk, VA, U.S.A.; and the Specialty Physician Associates (D.M.Y.), Bethlehem, PA, U.S.A.

Editor's Note: This Manuscript was accepted for publication on January 29, 2021

The study was funded by Arrinex (now part of Stryker ENT). Dr Ow is a consultant for Stryker ENT, Aerin Medical, Optimose, and Smith Nephew. Ms O'Malley is an employee of Stryker ENT. Dr Yen is a consultant for Stryker ENT. Drs Han and Lam have no conflicts to disclose. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Randall A. Ow, MD, Sacramento Ear, Nose, and Throat Roseville, CA 95661.

E-mail: row@sacent.com

DOI: 10.1002/lary.29453

February 2017 to April 2020. The protocol was reviewed and approved for all centers by Advarra IRB, Columbus, MD (Pro00034526). All participants provided written informed consent before study participation. The study was registered at www.clinicaltrials.gov with the unique identifier NCT03181594.

Adult (≥ 18 years) patients with chronic rhinitis for 6 months or longer who were dissatisfied with medical management (minimum of 4 weeks on intranasal steroids) were considered for enrollment. Minimum enrollment requirements for the reflective Total Nasal Symptom Score (rTNSS)⁹ were two for rhinorrhea, one for congestion, and four overall. Participants were also required to have an allergy test on file or have one completed during the study period. Relevant exclusion criteria included clinically significant anatomic obstructions or previous sinonasal surgery that limited access to or modified the anatomy of the posterior nose, active infection or open wounds in the nasal or sinus cavities, nosebleeds in the past 3 months, coagulation disorders, or conditions with sensitivity to cold (eg, cryoglobulinemia, paroxysmal cold hemoglobinuria, cold urticaria, Raynaud's disease). Participants taking ipratropium bromide at enrollment were required to discontinue use a minimum of 3 days before the procedure and all participants were asked not to use ipratropium bromide for the duration of the study.

All participants were expected to undergo bilateral treatment with the commercially available ClariFix Cryotherapy device in accordance with the manufacturer's Instructions for Use (IFU). Treatment times varied from 30 to 60 seconds per location. All investigators were trained on the protocol and procedure before treating any study participants.

Participants underwent follow-up visits at 1, 3, 6, 9, and 12 months after treatment by office visit. An extended follow-up amendment was added to evaluate participants at 15, 18, 21, and 24 months after treatment by office visit or phone. Results of this study through the 9-month follow-up have been previously reported.⁶ Here, we focus on the 12-month through 24-month results.

The safety and efficacy analyses are based on all participants who received the ClariFix treatment.

Assessments

Efficacy endpoints of the study were the change from baseline in the reflective TNSS,⁹ change from baseline in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),¹⁰ and physician perception of improvement using the Clinical Global Impression–Improvement (CGI–I).¹¹ The changes from baseline in the individual symptoms of the rTNSS (rhinorrhea, congestion, sneezing, and itching) were also evaluated.

Safety endpoints were the incidence of treatment-related serious adverse events (SAEs) and nonserious treatment-related adverse events (AEs).

Statistical Analysis

The calculated sample size of 100 participants was based on a 90% power to detect a one-point change in the rTNSS (assuming a within participant 2.5-point SD) with an alpha level of 0.05 indicating statistical significance.

Continuous data are summarized using descriptive statistics: *n*, mean \pm SD for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data.

TABLE I.
Demographics and Baseline Characteristics.

Characteristic	All participants <i>n</i> = 100	Long-term follow-up participants <i>n</i> = 62
Age (yr)	58.8 \pm 16.2	57.1 \pm 13.4
Sex		
Female	64 (64.0%)	40 (64.5%)
Male	36 (36.0%)	22 (35.5%)
Race		
White	90 (90.0%)	57 (91.9%)
Black/African American	3 (3.0%)	2 (3.2%)
Asian	2 (2.0%)	2 (3.2%)
Other or unreported	5 (5.0%)	1 (1.6%)
Ethnicity		
Not Hispanic or Latino	96 (96.0%)	62 (100.0%)
Hispanic or Latino	2 (2.0%)	0 (0.0%)
Unreported	2 (2.0%)	0 (0.0%)
Rhinitis type		
Allergic	30 (30.0%)	19 (30.6%)
Nonallergic	70 (70.0%)	43 (69.4%)
Duration of rhinitis (yr)		
<5	18 (18.0%)	9 (14.5%)
5–10	18 (18.0%)	11 (17.7%)
>10	64 (64.0%)	42 (67.7%)
Mean baseline rTNSS score	6.1 \pm 1.87	6.1 \pm 2.01
Mean baseline RQLQ score	3.1 \pm 1.01	3.0 \pm 1.04
Medical history		
None	24 (24.0%)	13 (21.0%)
Asthma	16 (16.0%)	11 (17.7%)
Migraine	20 (20.0%)	15 (24.2%)
Sinusitis	63 (63.0%)	40 (64.5%)
Facial pain	24 (24.0%)	17 (27.4%)
Ocular symptoms	22 (22.0%)	15 (24.2%)
Epistaxis	12 (12.0%)	8 (12.9%)

Results are presented as mean \pm SD or *n* (%).
rTNSS = reflective Total Nasal Symptom Score (rTNSS);
RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

Categorical variables are summarized using frequency counts and percentages. Ordinal-scaled variables are summarized using the frequency and percentage of observations within a category.

Significance of the change from baseline for participant-reported assessments is determined using a two-sided paired *t*-test. For data that are not normally distributed, Wilcoxon signed rank tests are used in place of the *t*-test. Normality is assessed by the Shapiro–Wilk test. Minimal clinically important differences (MCID) have been established as a reduction of 1 point in the rTNSS⁹ and 0.5 points for the RQLQ.¹²

All analyses are based on available data; no imputation for missing data was conducted and no adjustments for multiplicity were performed.

Subgroup analyses were conducted for TNSS outcomes by rhinitis type (allergic vs. nonallergic), baseline rTNSS (<7 vs. ≥ 7), and duration of rhinitis (<5, 5 to 10, and >10 years).

TABLE II.
Change from Baseline to Follow-up in the Total rTNSS.

Follow-up period (mo)	n	Baseline rTNSS score*	Follow-up rTNSS score	Change from baseline in rTNSS score	P value [†]	≥1 point improved
12	91	6.0 [5.0; 7.0]	3.0 [1.0; 4.0]	-3.0 [-4.0; -1.0]	<.001	73 (80.2%)
15	56	6.0 [5.0; 7.0]	2.0 [1.0; 4.0]	-4.0 [-5.0; -3.0]	<.001	50 (89.3%)
18	57	6.0 [5.0; 7.0]	2.0 [1.0; 4.0]	-3.0 [-5.0; -2.0]	<.001	50 (87.7%)
21	55	6.0 [5.0; 7.0]	2.0 [1.0; 4.0]	-4.0 [-5.0; -2.0]	<.001	48 (87.3%)
24	57	6.0 [5.0; 7.0]	2.0 [1.0; 4.0]	-4.0 [-5.0; -2.0]	<.001	46 (80.7%)

Results are presented as median [IQR] or n (%).

*The rTNSS has a range of 0 (no symptoms) to 12 (severe symptoms). A change from baseline of ≥1 point is considered the minimal clinically important difference (MCID).⁹

[†]P value is based on the Wilcoxon signed rank test.

IQR = interquartile range; rTNSS = reflective Total Nasal Symptom Score.

An ad hoc analysis using the last observation carried forward (LOCF) was used to assess the effect of discontinued participants on the rTNSS outcome. In this analysis, the last rTNSS available from each discontinued participant is carried forward through the remaining follow-up periods. The median change from baseline and the percent achieving MCID were calculated using this imputation method.

All statistical analyses were performed by an independent statistician using SAS (version 9.4), unless otherwise noted.

RESULTS

A total of 100 participants were enrolled at six US investigational sites between February 2017 and April 2018. Ninety-one participants (91.0%) completed the study through the initial 12-month study follow-up period (four withdrew, four lost to follow-up, and one died). Sixty-two participants consented to the long-term follow-up extension with 57 (91.9%) completing the 24-month follow-up (three died, one withdrew, and one lost to follow-up).

Demographic and baseline characteristics of the enrolled participants and the long-term extension cohort are presented in Table I. The baseline rTNSS of 6.1 indicates a moderate level of disease. The demographics and medical history of the participants in the long-term follow-up are consistent with the initial population.

The median changes from baseline in the rTNSS are shown in Table II and Figure 1. There are statistically significant improvements in the total rTNSS at all timepoints between 12- and 24-month follow-ups. Greater than 80.0% of participants achieved the MCID at all follow-ups. All rTNSS subscores were significantly improved ($P < .01$) at all timepoints except nasal itching at the 18-month ($P = .054$) and 24-month periods ($P = .133$). The LOCF analysis demonstrated only a slight reduction in the median change from baseline (-3.0 vs. -4.0) at 24 months and percent of participants who met the MCID for the change from baseline in rTNSS (77.0% vs. 80.7%) at 24 months.

Subgroup analyses found that there were no statistically significant differences ($P > .05$) in the rTNSS median change from baseline between the allergic and nonallergic participants or by duration of rhinitis (<5 years, 5–10 years, >10 years) at follow-ups through 24 months. There were statistically significant differences ($P < .05$) in the rTNSS median change from baseline between participants with baseline TNSS values <7 and those with baseline values ≥7, with higher baseline scores resulting in more improvement at all follow-ups except 12 and 24 months (both $P = .059$).

Participants completed the RQLQ at baseline and at the 18- and 24-month follow-up visits. RQLQ results are

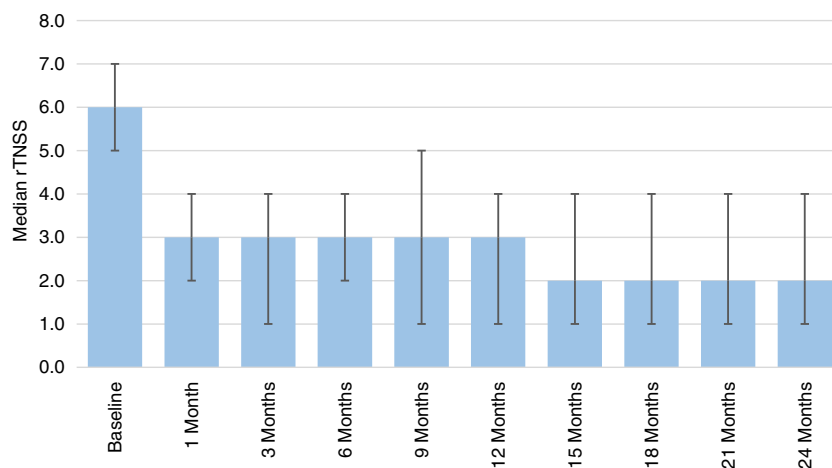


Fig. 1. Change in median total reflective Total Nasal Symptom Score (rTNSS) over time. Error bars indicate the interquartile range at each time point. Follow-up periods through 9 months were reported previously by Chang et al.⁶

TABLE III.
Change from Baseline to Follow-up in Total RQLQ Scores.

Follow-up period (mo)	n	Baseline RQLQ score*	Follow-up RQLQ score	Change from baseline in RQLQ score	P value [†]	≥0.5 point improved
18	54	3.2 [2.4; 3.8]	0.8 [0.3; 1.7]	-2.1 [-3.1; -1.1]	<.0001	45 (83.3%)
24	57	3.0 [2.4; 3.7]	0.5 [0.3; 1.4]	-2.1 [-3.0; -0.8]	<.0001	44 (77.2%)

Results are presented as median [IQR] or n (%).

*The 28 items on the RQLQ are rated on a seven-point scale from 0 (no impairment) to 6 (maximum impairment). The total RQLQ score is the mean of all 28 responses and the seven individual domain scores are the means of the items within those domains. A reduction from baseline of ≥0.5 point is considered the minimal clinically important difference (MCID).

[†]P values are based on the Wilcoxon signed rank test.

IQR = interquartile range; RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

presented in Table III. The total RQLQ scores indicate significant improvement ($P < .0001$) in quality of life at 18 and 24 months post procedure. Over 75% of participants achieved the MCID (≥0.5 points) from baseline in the total RQLQ score at both time periods post procedure. All RQLQ domains demonstrated statistically significant improvements ($P < .01$) at both time periods; eye symptoms were the least impacted scores.

Clinician perception of the participants' improvement (as measured by the CGI-I, Fig. 2) indicate that, with the exception of the 12-month visit, over 80% of participants were judged by the physician to have improved over baseline at each long-term visit. At the 12-month visit, more participants were assessed as showing no change (26.1%).

During the study duration, a total of five participants started using ipratropium bromide due to persistent rhinitis symptoms. Three of the five were included in the 9-month results paper by Chang et al.⁶ Two additional participants started ipratropium bromide during the longer-term follow-up.

A total of 29 treatment-related AEs (including two serious events) were previously reported by Chang et al.⁶ Two additional related nonserious AEs were identified since

their report: dizziness during the procedure and sinusitis at 28 days post procedure. Including these two events, all the related AEs occurred within the initial 90-day follow-up window after treatment. The four unrelated deaths were all due to various cancers in participants older than 65.

DISCUSSION

This is the first report of long-term safety and efficacy outcomes beyond the 1-year follow-up for participants treated with the ClariFix Cryotherapy device. A previous pilot study reported 1-year outcomes on a small group of participants ($n = 15$).⁵ Chang et al reported outcomes through 9 months on the current population.⁶ Here we report the longer-term outcomes from 12 months through 24 months for the population Chang et al reported on.

In the pilot study, Hwang et al reported statistically significant ($P < .001$) rTNSS mean changes from baseline of -3.6, -3.5, -3.9, and -4.3 at 30, 90, 180, and 365 days after treatment, respectively.⁵ However, since only 15 of the 30 participants were available at the last follow-up, the 365-day outcome was deemed suggestive, not definitive. Yen et al reported rTNSS median change from

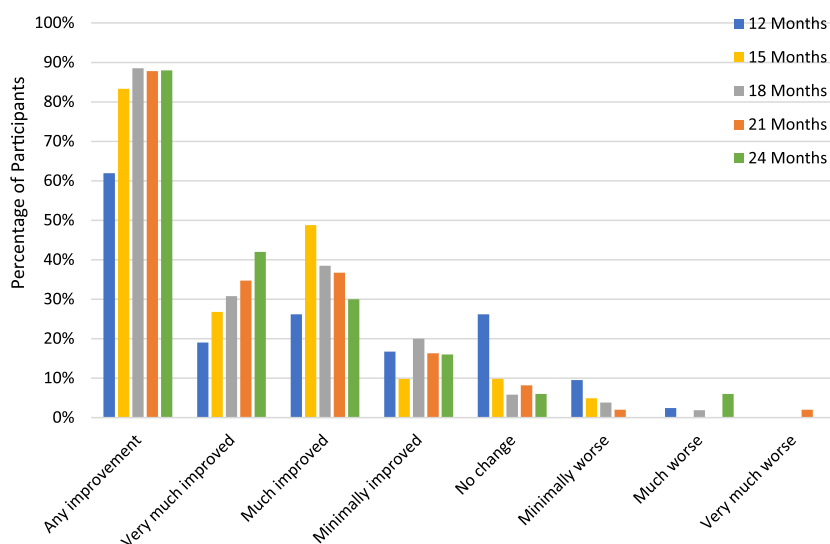


Fig. 2. Clinical global impression of improvement (CGI-I). The CGI-I is a physician-completed survey indicating the perception of patient improvement compared with baseline. The any improvement category is the sum of the very much improved, much improved, and minimally improved categories.

baseline of -4.0 at 3 months in a cohort of 30 chronic rhinitis patients treated with cryotherapy at both the inferior and middle meatus.¹³ In the earlier outcomes of this study, Chang et al reported rTNSS mean changes from baseline of -3.2 at 30 days, and -3.1 at 90, 180, and 270 days after treatment.⁶ Our continued follow-up of these participants demonstrates that the improvement in this population is durable with the median changes from baseline of -3.0 in 91 participants at 12 months. Follow-up in 62 participants who continued in the extension study demonstrates continued durability and suggests the possibility of more improvement (median change from baseline -4.0) at follow-ups after 12 months.

We did not detect any significant difference in rTNSS outcomes between allergic and nonallergic rhinitis participants. However, we did find significantly greater symptom improvement in participants with baseline rTNSS ≥ 7 compared with baseline rTNSS < 7 . This may help physicians set realist expectations for rhinitis patients with baseline rTNSS score that are < 7 . This phenomenon is similar to that observed in chronic rhinosinusitis patients, in that those with higher SNOT-22 scores demonstrate significantly greater improvement after endoscopic sinus surgery.¹⁴

Yen et al reported significant quality of life improvements after cryotherapy using the mini RQLQ. They noted a median change from baseline of -1.8 (IQR: -2.3 , -0.7 , $P < .0001$) at 3 months.¹³ Chang et al previously reported a significant improvement over baseline in the mean total RQLQ of -1.5 at 90 days ($P < .001$).⁶ Our results indicate further quality of life improvements with median total RQLQ changes from baseline of -2.1 at both 18 and 24 months after treatment ($P < .0001$).

All related AEs were reported within the initial 90-day post procedure period, supporting the long-term safety of the cryotherapy treatment.

The transnasal application of cryotherapy to the PNN serves as an effective and minimally invasive alternative to conventional surgical methods, such as vidian neurectomy and posterior nasal neurectomy, to manage chronic rhinitis. Both vidian neurectomy and posterior nasal neurectomy are meant to reduce the autonomic innervation of the nasal cavity through the transection of their targeted nerves under general anesthesia in the operative setting. Vidian neurectomy, however, can be associated with the potential development of dry eyes or facial numbness as a surgical complication, while posterior nasal neurectomy may result in incomplete clinical responses if reinnervation of the PNN occurs. The advantage of the current cryotherapy technology is its intended in-office use with local anesthesia, reducing the time and costs of surgical options for chronic rhinitis. The duration of therapeutic effect of cryotherapy, in comparison to that of vidian neurectomy and posterior nasal neurectomy, nonetheless, has not been clearly established.

Strengths of this study include the relatively large population of participants, many who were followed through 24 months after treatment, and the use of multiple validated assessments to evaluate various participant outcomes. Limitations include the single-

arm design without a concurrent control arm and the loss nearly 30% of the participants after the 12-month follow-up because of the requirement for additional consent for the study extension protocol. However, using the LOCF analysis, there did not appear to be a substantial impact on the rTNSS outcomes from participants who did not continue into the long-term follow-up. At 24 months, between the observed and imputed rTNSS outcomes, there was a -1 difference (-4.0 vs. -3.0) in the change from baseline and 3% difference (80% vs. 77%) in the percent of participants who achieved the MCID. Despite these limitations, we believe the longer-term outcomes of this study provide valuable information to clinicians interested in pursuing this therapy for their rhinitis patients.

CONCLUSION

Cryotherapy with the ClariFix device significantly and clinically improves rhinitis symptoms and quality of life that are durable through 24 months after treatment. Symptom improvement is comparable in patients with allergic and nonallergic rhinitis. Higher baseline rTNSS is associated with greater improvement at follow-up. Adverse events are typically transient, nonserious, and resolve with little to no intervention. Compared to alternate surgical therapies, cryoablation is a safe, effective, office-based therapy providing sustained clinical improvement for chronic rhinitis patients.

ACKNOWLEDGMENTS

The authors thank April Slee, MSc of New Arch Consulting for the statistical analysis. The authors also thank the other investigators and study coordinators: Timothy Fife, MD, Vardenik (Rose) Khalatyan, and Marcy Adame, Sacramento Ear, Nose, and Throat, Roseville, CA; Laura Stone, EVMS Otolaryngology, Norfolk, VA; Jeff Bedrosian, MD and David Campbell, Specialty Physician Associates, Bethlehem, PA; Jerome Hester, MD and Jokasta Cordon, California Sleep Institute, Palo Alto, CA; Jacob Johnson, MD and Wendy Zhu, San Francisco Otolaryngology Medical Group, San Francisco, CA; Nathan Nachlas, MD, Vanessa McDowell, PA-C, and Patricia Fonseca, Ear Nose and Throat Associates of South Florida, Boca Raton, FL.

REFERENCES

1. Settipane RA. Epidemiology of vasomotor rhinitis. *World Allergy Organ J* 2009;2:115–118. [Values updated for 2020 world population estimate of 7.8 billion].
2. Vandenplas I, Vinnikov D, Blanc PD, et al. Impact of rhinitis on work productivity: a systematic review. *J Allergy Clin Immunol Pract* 2018;6:1274–1286.
3. Yan CH, Hwang PH. Surgical management of nonallergic rhinitis. *Otolaryngol Clin North Am* 2018;51:945–955.
4. Kompelli AR, Janz TA, Rowan NR, Nguyen SA, Soler ZM. Cryotherapy for the treatment of chronic rhinitis: a qualitative systematic review. *Am J Rhinol Allergy* 2018;32:491–501.
5. Hwang PH, Lin B, Weiss R, Atkins J, Johnson J. Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. *Int Forum Allergy Rhinol* 2017;7:952–956.
6. Chang MT, Song S, Hwang PH. Cryosurgical ablation for treatment of rhinitis: a prospective multicenter study. *Laryngoscope* 2020;130:1877–1884.

7. Hsu M. Significance of clinical treatments on peripheral nerve and its effect on nerve regeneration. *J Neurol Disord* 2014;2:100168.
8. Fawcett JW, Keynes RJ. Peripheral nerve regeneration. *Annu Rev Neurosci* 1990;13:43–60.
9. Downie SR, Andersson M, Rimmer J, et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. *Allergy* 2004;59:406–414.
10. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;21:77–83.
11. Guy W, ed. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare; Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration; 1976.
12. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol* 1996;98:843–845.
13. Yen DM, Conley DB, O'Malley EM, Byerly TA, Johnson J. Multiple site cryoablation treatment of the posterior nasal nerve for treatment of chronic rhinitis: an observational feasibility study. *Allergy Rhinol* 2020; 11:1–7. <https://doi.org/10.1177/2152656720946996>.
14. Rudmik L, Soler ZM, Mace JC, DeConde AS, Schlosser RJ, Smith TL. Using preoperative SNOT-22 score to inform patient decision for endoscopic sinus surgery. *Laryngoscope* 2015;125:1517–1522.