Interventional procedure overview of cryotherapy for chronic rhinitis

Contents

Table 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
AR	Allergic rhinitis
CGI-I	Clinical Global Impression of Improvement
FDA	Food and Drug Administration
IQR	Interquartile range
LOCF	Last observation carried forward
NAR	Non-allergic, non-infectious rhinitis
OR	Odds ratio
PNN	Posterior nasal nerve
RCT	Randomised controlled trial
RNS	Runny nose score
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
SNOT-22	22-item Sino-Nasal Outcomes Test
TNSS	Total Nasal Symptom Score
MAUDE	Manufacturer and User Device Facility Experience
MCID	Minimum clinically important difference
NOSE	Nasal obstruction symptom evaluation
rTNSS	Reflective Total Nasal Symptom Score
VAS	Visual Analog Scale

Indications and current treatment

Rhinitis is inflammation and swelling of the mucous membrane inside the nose. Chronic nasal inflammation lasts over a long period of time, usually longer than 12 weeks. Common symptoms include sneezing, itchiness, and a stuff or runny

nose. There are 3 main types of rhinitis: allergic rhinitis (AR), infectious rhinitis, and non-allergic, non-infectious rhinitis (NAR).

Treating rhinitis depends on the specific cause or diagnosis. Treatment options include:

- non-pharmacological treatments (such as avoidance of triggers and environmental controls)
- pharmacological treatments (such as steroid nasal sprays and oral antihistamines)
- surgery (such as posterior nasal neurectomy).

Unmet need

Rhinitis is a common condition. Although medication use improves symptoms in most people, some people continue to have rhinitis that is refractory to medical treatment and surgery may be considered. Surgery needs to be done in an operating room under general anaesthesia. In people whose symptoms do not respond to the pharmacological treatments, there is a need for alternative minimally invasive procedures that can be done in an outpatient setting under local anaesthesia.

What the procedure involves

This procedure is done under local anaesthesia. A probe is inserted into the nasal cavity, and the balloon tip is placed endoscopically in the posterior middle meatus. Once the tip is in contact with the targeted tissue over the branches of the posterior nasal nerve, nitrous oxide cryogen is released through the tip from the canister. This freezes the targeted mucosal tissue, with the aim of ablating the posterior nasal nerve. Cryogen is delivered for 30 to 60 seconds and the contralateral side is treated the same way if needed.

Outcome measures

The main outcomes include patient-reported outcomes (Total Nasal Symptom Score [TNSS], Nasal Obstruction Symptom Evaluation [NOSE], 22-item Sino-Nasal Outcomes Test [SNOT-22], Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] and Visual Analog Scale [VAS]) and clinician-completed assessment (clinical global impression of improvement [CGI-I]). The measures used are detailed in the following paragraphs.

The Reflective Total Nasal Symptom Score (rTNSS) rates 4 nasal symptoms (rhinorrhoea, nasal congestion, nasal itching, and sneezing) on a scale of 0 (no symptoms) to 3 (severe symptoms). The scores are summed to provide a total rTNSS with a range of 0 to 12. The minimum clinically important difference (MCID) for the rTNSS is -1.0 points and the threshold for response is at least 30% reduction relative to baseline. A variation of the TNSS questionnaire consists of 5 items (rhinorrhoea, nasal congestion, nasal itching, sneezing, difficulty sleeping because of nasal symptoms), with a total score of 0 to 15.

The NOSE evaluates 5 nasal symptoms: nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through nose, trouble sleeping, unable to get enough air through nose during exercise or exertion. Each symptom is rated on a scale of 0 (no problem) to 4 (severe problem). The sum of the symptom scores is multiplied by 5 to provide a total score that ranges from 0 to 100 (mild 5 to 25, moderate 30 to 50, severe 55 to 75, and extreme 80 to 100). A NOSE response is defined as a person having at least 1 NOSE class improvement or at least 20% NOSE score reduction from baseline.

The SNOT-22 assesses sinonasal symptoms in general, consisting of 22 items scored using a 5-point Likert scale, ranging from 0 (no problem) to 5 (problem as bad as it can be). A total SNOT-22 score ranges from 0 to 110, with higher

scores indicating worse symptoms. The MCID for the total SNOT-22 is -8.9 points.

The RQLQ contains 28 items, measuring impairments in 7 domains: activities, sleep, non-nose or eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions. Each item is rated on a 7-point scale, ranging from 0 (no impairment) to 6 (maximum impairment) and the overall RQLQ score is the mean of the 28 items, with higher scores reflecting lower quality of life. The MCID for the RQLQ is 0.5 points. The mini version contains 14 items, measuring impairments in 5 domains: activities, practical problems, nose symptoms, eye symptoms, and other symptoms. The MCID for the mini RQLQ is 0.4 points.

The 100-mm VAS is used to evaluate nasal symptoms of rhinorrhoea and congestion on a continuum over the previous week, with 0-mm representing no symptoms and 100-mm representing severe symptoms.

The CGI-I is a clinician-completed assessment, evaluating the clinician's impression of a patient's response to treatment based on their clinical observations. The CGI-I is a 7-point Likert scale that ranges from 1 (very much improved) to 7 (very much worse).

Evidence summary

Population and studies description

This interventional procedure overview is based on 1,620 people from 1 systematic review, 1 RCT, 3 single-arm trials, 1 case-control study, and 1 analysis of the MAUDE database. Of these 1,620 people, 1,554 had the procedure. The flow chart of the literature selection process for this rapid review of the literature is shown in figure 1. The key evidence is presented in table 2 and table 3, 2 relevant assessments are described in the 'existing assessments of this procedure' section, and another 12 relevant studies are listed in table 5.

Of the key evidence, 5 primary studies were published between 2020 and 2022. These studies were done in the US and follow-up durations ranged from 3 months to 2 years. People were recruited from multiple centres between 2017 to 2020. In these 5 studies, 277 people had cryotherapy (NAR, 64%; AR, 29%; mixed rhinitis, 7%). Four studies mainly focused on the safety and efficacy of cryotherapy for chronic rhinitis, while 1 study (Yoo 2020) determined what factors were associated with subjective improvement in rhinorrhoea after the procedure. For the systematic review, most studies were published between 1977 and 1997, with 1 study published in 2017. The follow-up periods ranged from 6 weeks to 6 years but countries for individual studies were not reported. Of the 15 studies included in the systematic review, 9 studies included people with NAR only, 1 study included people with AR only, 3 studies included AR and NAR, and 2 studies had information on people with mixed symptoms of AR and NAR. The analysis of the MAUDE database was included in the key evidence to provide a broader view of observed AEs with ClariFix therapy during the first 3 years of FDA approval (Singh 2021).

Table 2 presents study details.

Figure 1 Flow chart of study selection

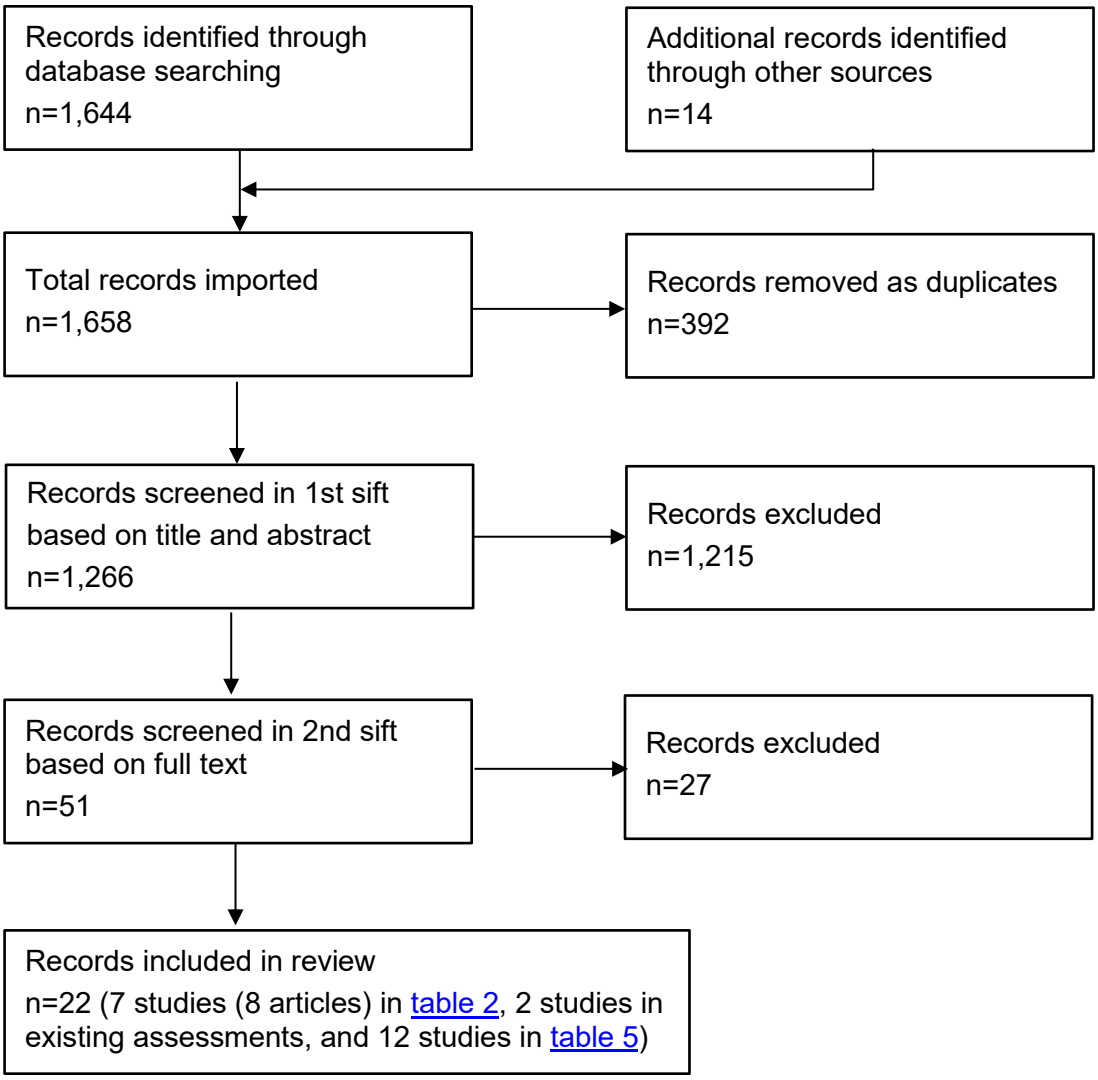

Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Del Signore (2022) US (12 centres)	133 (77: 56) • cryotherapy, n=68 (29 AR, 39 NAR) • sham, n=65 (28 AR, 37 NAR) 127 people included in the analysis	Mean 55.2 years	Single blinded RCT (NCT04154605)	Adults (≥21 years) with moderate to severe symptoms of chronic allergic or nonallergic rhinitis who were candidates for cryotherapy under local anaesthesia. A minimum baseline rTNSS of 4 was needed, with a minimum score of 2 for rhinorrhoea and 1 for nasal congestion.	Cryotherapy: bilateral procedure using the ClariFix device - the posterior middle meatus of each side was treated with a 30-second freeze/60-second thaw cycle. A second freeze/thaw cycle was allowed per side at the physician's discretion. Sham: same as cryotherapy except a cryogen canister was not loaded in the device.	90 days
2	Ow RA (2021) Chang (2020) US (6 centres)	100 (64:36) • AR: n=30 • NAR: n=70	Mean 58.8 years	Single-arm trial (NCT03181594)	Adults (≥18 years) with chronic rhinitis for 6 months or longer who were dissatisfied with medical management (minimum of 4 weeks on intranasal steroids); Minimum enrollment requirements for rTNSS: 2 for rhinorrhoea, 1 for congestion, and 4 overall.	Cryotherapy: bilateral treatment with the ClariFix device. Treatment times varied from 30 to 60 seconds per location.	24 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
3	Gerka Stuyt JA (2021) US (7 locations within a large health maintenance organisation system)	24 (12:12) • NAR: n=16 • AR: n=3 • Mixed rhinitis: n=5	Mean 60 years	Single-arm trial	Age over 18, diagnosis of chronic rhinitis, and failure of medical therapy for a duration of at least 3 months.	Cryoablation of the posterior nasal nerve using ClariFix.	1 year
4	Yen DM (2020) US (3 centres)	30 (132 treatments; 14: 16) • NAR: n=17 • AR: n=11 Rhinitis type not specified for 2 people.	Mean 60 years	Single-arm trial (NCT03791489)	Adults (≥18 years) with moderate to severe rhinorrhoea and mild to severe nasal congestion lasting at least 3 months.	Bilateral cryoablation of the posterior nasal nerve with the ClariFix device at both the middle meatus and inferior meatus.	3 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
5	Yoo F (2020) US (3 centres)	n=55 (25: 30) • AR: n=8 • NAR: n=34 • Mixed rhinitis: n=13	Mean 55.3 years	Case-control study (retrospective)	People for whom the ipratropium spray had not worked well enough (at least a 1-month trial of 0.06% ipratropium nasal spray, used as often as people felt necessary to control their rhinorrhoea).	Intranasal cryoablation using the ClariFix device.	Mean 170 days
6	Kompelli AR (2018) Country not reported	1,266 (15 studies; gender not reported) • NAR: 9 studies • AR: 1 study • AR and NAR: 3 studies • mixed symptoms of AR and NAR: 2 studies	Various	Systematic review	Studies with the primary objective of assessing the efficacy of cryotherapy on chronic rhinitis.	Cryotherapy using various devices (when reported, most of the studies used Frigitronics probes and only 1 study used the ClariFix device). Duration of therapy ranged from 5 to 8 seconds to 2 to 3 minutes.	6 weeks to 6 years
7	Singh AK (2021)	12 reported events	Not reported	Analysis of MAUDE database	Not reported.	Cryoablation of the posterior nasal nerve using ClariFix (Arrinex).	Not reported

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes

Del Signore (2022)	Response (≥30% reduction in rTNSS relative to baseline) at 90 days: cryotherapy, 73.4% (47/64); sham, 36.5% (23/63); p<0.001
	rTNSSs:
	• cryotherapy: baseline, 8.0±1.6; 90 days, 4.3±2.4; mean change, -3.7 (95% CI -4.3 to -3.1), p<0.001
	• sham: baseline, 8.1±1.9; 90 days, 6.3±2.5: mean change, -1.8 (95% CI -2.5 to -1.1), p<0.001
	• between-group p value: <0.001
	rTNSSs – individual items:
	• mean change in rhinorrhoea: cryotherapy, -1.2 (95% CI -1.4 to -1.0); sham, -0.4 (95% CI -0.6 to -0.2); p<0.001
	• mean change in nasal congestion: cryotherapy, -1.2 (95% CI -1.4 to -1.0): sham, -0.8 (95% CI -1.0 to -0.6); p<0.001
	• between-group changes in nasal itching and sneezing: p>0.05
	The multivariate model showed that only the cryotherapy arm (odds ratio [OR] for treatment compared with sham: 3.430 [95% CI, 1.827 to 6.43; p=0.0001]) and the rTNSS value at baseline (OR: 1.321 [95% CI 1.095 to 1.593; p=0.0036]) were associated with the outcome.
	Total standardised RQLO(S) scores:
	• mean change at 90 days from baseline: cryotherapy, -1.5 (95% CI -1.8 to -1.2); sham, -0.8 (95% CI -1.1 to -0.5); between groups, p<0.001
	• MCID of ≥0.5-point improvement at 90 days: cryotherapy, 82.8% (53/64); sham, 52.4% (33/63)
		Procedure-related serious adverse event (AE):
		• Anxiety/panic attack after cryotherapy: n=1. Vital signs were normal.
		Procedure-related nonserious AEs: 43 AEs in 35 people
		• Cryotherapy group: AEs in 32 patients
		  ○ Pain/discomfort: n=25
		  ○ Headache: n=4
		  ○ Nasal congestion: n=2
		  ○ Transient roof of mouth numbness: n=2
		  ○ Vasovagal reaction: n=1
		  ○ Watery eyes: n=2
		  ○ Anxiety/panic attack: n=1
		  ○ Dizziness/light headedness: n=1
		  ○ Drug reaction (decongestant): n=1
		  ○ Sinusitis, n=1
		• Sham group: AEs in 3 patients
		  ○ Pain/discomfort: n=1

First author, date	Efficacy outcomes	Safety outcomes
	RQLQ(S) domain scores were more improved in the cryotherapy arm compared with the sham arm for 5 of the 7 domains (non–hay fever symptoms: p=0.007; practical problems: p=0.002; nasal symptoms: p<0.001; eye symptoms: p=0.020; emotions: p<0.001) and approached statistical significance for sleep (p=0.050). NOSE scores: • mean changes at 90 days from baseline: cryotherapy, -29.9 (95% CI -35.8 to -24.0); sham, -14.8 (95% CI -21.2 to -8.4); between groups, p<0.001 • response rate: cryotherapy, 81.3% (52/64); sham, 54.0% (34/63)	○ Vasovagal reaction: n=1 ○ Vomiting: n=1 These events were typically resolved within 1 to 2 hours of the procedure and common interventions included over-the-counter pain medications and warm beverages.
Ow RA (2021) Chang MT (2020)	Mean rTNSS score: baseline, 6.1±1.9; 30 days, 2.9±1.9; 90 days, 3.0±2.3; 180 days, 3.0±2.1; 270 days, 3.0±2.4; all p values <0.001. rTNSS reaching MCID (30% reduction in baseline score): 76 of 97 (78.4%) patients had clinically meaningful improvement at 30 days, 71 of 96 (74.0%) at 90 days, 75 of 95 (78.9%) at 180 days, and 65 of 92 (70.7%) at 270 days. Median change from baseline to follow ups in rTNSS score: • 12 months (n=91): -3.0 (Interquartile Range [IQR] -4.0 to -1.0); p<0.001; ≥1 point improved (MCID), 80.2% (n=73) • 15 months (n=56): -4.0 (IQR -5.0 to -3.0); p<0.001; ≥1 point improved, 89.3% (n=50) • 18 months (n=57): -3.0 (IQR -5.0 to -2.0); p<0.001; ≥1 point improved, 87.7% (n=50) • 21 months (n=55): -4.0 (IQR -5.0 to -2.0); p<0.001; ≥1 point improved, 87.3% (n=48) • 24 months (n=57): -4.0 (IQR -5.0 to -2.0); p<0.001; ≥1 point improved, 80.7% (n=46)	Treatment-related AEs: n=31 • Nasal: n=12 ○ Bloody discharge: n=1 ○ Burning sensation: n=1 ○ Epistaxis: n=2 (1 was severe and required hospitalisation) ○ Hyperaemia: n=1 ○ Middle turbinate haematoma: n=1 ○ Mucous: n=1 ○ Ostia newly noted: n=2 ○ Pain: n=1 ○ Retained pledget: n=1 ○ Synechiae: n=1 • Head/face: n=6

First author, date	Efficacy outcomes	Safety outcomes
	All rTNSS subscores were significantly improved (p<0.01) at all timepoints except nasal itching at the 18-month (p=0.054) and 24-month periods (p=0.133). The last observation carried forward (LOCF) analysis showed only a slight reduction in the median change from baseline (−3.0 versus −4.0) at 24 months and percent of people who met the MCID for the change from baseline in rTNSS (77.0% compared with 80.7%) at 24 months. There were statistically significant differences (p<0.05) in the rTNSS median change from baseline between people 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=0.059), but not between AR and NAR or by duration of rhinitis at follow-ups through 24 months. Mean RQLQ scores: baseline, 3.0±1.0; 90 days, 1.5±1.2; p<0.001 Analysis of RQLQ subdomains showed statistically significant improvement in each (all p<0.001). Median change from baseline to follow up in total RQLQ scores: • 18 months (n=54): -2.1 (IQR -3.1 to -1.1); p<0.0001; ≥0.5 point improved (MCID), 83.3% (n=45) • 24 months (n=57): -2.1 (IQR -3.0 to -0.8); p<0.0001; ≥0.5 point improved, 77.2% (n=44) All RQLQ domains showed statistically significant improvements (p<0.01) at both time periods; eye symptoms were the least impacted scores. Five people started using ipratropium bromide because of persistent rhinitis symptoms. CGI-I: Clinician perception of peoples' improvement indicated that, except for the 12-month visit, over 80% of people were judged by the physician to have	○ Facial pain: n=2 ○ Headache: n=3 ○ Migraine: n=1 ○ Dizziness: n=1 • Ocular: n=3 ○ Dry eyes: n=2 ○ Watery eyes: n=1 • Oral: n=5 ○ Bad taste: n=1 ○ Numbness: n=1 ○ Swollen sensation: n=1 ○ Teeth sensitivity: n=1 ○ Dry mouth: n=1 • Sinus: n=4 ○ Sinusitis: n=4 All the related AEs occurred within 90 days after treatment. Unrelated deaths: n=4 due to various cancers Device malfunctions: n=5, all involving the lack of cryogen flow from the device cannister. However, each device malfunction was immediately resolved by the

First author, date	Efficacy outcomes	Safety outcomes
	improved over baseline at each long-term visit. At the 12-month visit, more people were assessed as showing no change (26.1%).	replacement of a new cryogen canister.
Gerka Stuyt JA (2021)	All procedures were well tolerated and able to be completed without major technical difficulties or device malfunction. Mean 12-hour TNSS score: baseline, 6.92±2.8; 30 days, 3.17±2.4; 90 days, 2.92±1.4; 1 year, 3.08±2.6; when comparing with baseline, all p values <0.001 • NAR: baseline, 7.1±3.1; 30 days, 3.0±2.0; 90 days, 3.5±1.0; 1 year, 3.13±3.0; all p values <0.001 • Mixed rhinitis: baseline, 6.4±2.1; 30 days, 4.0±3.6; 90 days, 2.0±1.2; 1 year, 3.2±2.2; all p<0.05 • AR: baseline, 6.67±3.2; 30 days, 2.67±2.5; 90 days, 1.33±1.5; 1 year, 2.6±0.6; all p>0.05 Mean 2-week TNSS score: baseline, 7.75±3.1; 30 days, 3.79±2.1; 90 days, 3.88±1.8; 1 year, 3.76±2.1; when comparing with baseline, all p values <0.001 • NAR: baseline, 7.75±3.6; 30 days, 4.21±1.7; 90 days, 4.56±1.7; 1 year, 3.94±2.4; all p<0.001 • Mixed rhinitis: baseline, 7.2±1.6; 30 days, 3.4±3.0; 90 days, 3.3±0.8; 1 year, 4.0±1.4; all p<0.05 • AR: baseline, 8.67±2.5; 30 days, 2.33±2.5; 90 days, 1.67±2.0; 1 year, 3.3±1.1; all p>0.05 Statistically significant decrease in TNSS was observed in all subdomain symptoms (nasal congestion, rhinorrhoea, nasal itching, sneezing, and difficulty sleeping) evaluated at all time points, except for nasal itching at 30 days compared with baseline (0.28±0.6 versus 0.5±0.7; p=0.15).	Not reported

First author, date	Efficacy outcomes	Safety outcomes
	A proportion of people had eliminated or reduced medication use to manage their rhinitis compared with baseline: 66.7% (12/18). • NAR: 66.6% (8/12) • Mixed rhinitis: 100% (3/3) • AR: 33.3% (1/3) 77.8% of people (14/18) responded that they felt the procedure was effective and would do it again if needed. At 1 year, of 24 people, 6 were lost to follow up.	
Yen DM (2020)	Mean pain score in 40% of people who experienced pain during the procedure: 1.0±2.0 (on a scale of 0 to 10). No treatments stopped because of pain. rTNSS: median (IQR) • Baseline, 7.0 (IQR 5.0 to 9.0) • 1 month: 3.5 (IQR 2.0 to 6.0); change from baseline, -3.5 (IQR -5.0 to -2.0); p<0.001; ≥1-point improvement (MCID), 80.0% (24/30) • 3 months: 2.5 (IQR 2.0 to 5.0); change from baseline, -4.0 (IQR -6.0 to -1.0); p<0.001; ≥1-point improvement, 86.7% (26/30) NOSE (n=29): baseline, 56.9±28.1; 3 months, 25.5±24.5; mean change, -31.4±34.4; p<0.001 89.7% (26/29) of people were considered to have NOSE response (1 assessment was not done). SNOT-22 (n=29): baseline, 45.6±19.9; 3 months, 21.4±16.4; mean change, -24.2±21.1; p<0.001; 75.9% (22/29) of people achieved the MCID of -8.9 points for the overall SNOT-22 score at 3 months. Nasal symptom VAS (n=30): baseline, 75.9±21.4; 3 months, 36.0±29.2; mean changes, -39.9±34.7; p<0.001	No serious adverse events reported. Non-serious adverse events: n=40 (in 24 patients) • Sinusitis (unrelated to the device or procedure): n=1 • Headache: 40% (12/30) • Post-procedure pain or discomfort (facial, jaw, tooth, occipital, treatment site, unspecified): 33.3% (10/30) • Palate numbness: 26.7% (8/30) The events needed no to minimal intervention and typically resolved the same day as the procedure. All related events were transient and resolved before the 3-month visit.

First author, date	Efficacy outcomes	Safety outcomes
	Mini RQLQ (n=30): baseline, 2.7 (IQR 2.2 to 3.6); 3 months, 1.1 (IQR 0.4 to 1.9); median change, -1.8 (IQR -2.3 to -0.7); p<0.0001; 86.7% (26/29) of patients achieved the MCID of -0.4 points for the total mini RQLQ score at 3 months. The median change in total score and each of the 5 subscale scores of the mini RQLQ showed statistically significant improvement over baseline at the 3-month follow-up (p<0.0001 for total, activities, practical problems, nasal symptoms, and other symptoms; p=023 for eye symptoms). CGI-I at 3 months: • Improvement: 89.7% (26/29) • No change: n=2 • Worse: n=1 • No assessment: n=1	
Yoo F (2020)	Primary compared with revision procedure: 92.7% (n=51) compared with 7.3% (n=4) Concurrent septoplasty: 14.6% (n=8) SNOT-22 RNS: baseline, 4.2±1.0 (n=55); first visit, 2.30±1.84 (n=50); second visit, 1.95±1.79 (n=38); third visit, 2.60±1.68; comparing with baseline, all p values <0.05 • ≥1-point improvement in RNS: n=39 • ≥2-point improvement in RNS: n=33 Number of people who trialled ipratropium spray: n=48 • Response with ipratropium (n=33): baseline, 4.30±0.92; first follow up, 2±1.50 (n=30); second follow up: 2±1.53 (n=25); third follow up: 3±1.56 (n=12); fourth follow up, 3±0.89 (n=5); fifth follow up: 4±2.12 (n=2)	Complications: 20.7% (n=13) • Headache: 7.5% (n=4) • Facial pain: 11.3% (n=6) • Palate numbness: 5.7% (n=3)

First author, date	Efficacy outcomes	Safety outcomes

	• No response with ipratropium (n=15): baseline, 4.40±112; first follow up, 3.57±2.06 (n=14), second follow up: 3±1.95 (n=10); third follow up, 5 (n=1); fourth and fifth follow ups: not applicable
	• Ipratropium response compared with no response: p<0.05 at the first and second follow ups
	Ipratropium spray response was the only factor predicted cryoablation success.
	• ≥1-point improvement in RNS
	  ○ Ipratropium response: 84.9% (28/33)
	  ○ Ipratropium non-response: 33.3% (5/15)
	  ○ p=0.001
	• ≥2-point improvement in RNS:
	  ○ Ipratropium response: 75.8% (25/33)
	  ○ Ipratropium non-response: 20% (3/15)
	  ○ p=0.001
	None of the other factors, including gender, age, diagnosis, smoking status, primary vs revision procedure, presence of rhinorrhoea triggers, office vs operating room setting, or concurrent septoplasty, affected cryoablation response.	

Kompelli AR (2018)	Obstructive symptoms and rhinorrhoea: • Reduction in obstructive symptoms (5 studies): 63.4% to 100% • Reduction in rhinorrhoea symptoms (5 studies): 77% to 100% • Patient-reported improvements without stratifying results based on symptom type (7 studies): general improvements, 67% to 100%	Complications associated with cryotherapy: 6 studies (n=641) • Hwang (2017): ○ Day 1: n=12 (44%) noted severe ear blockage, n=1 (4%) noted severe nasal dryness

First author, date	Efficacy outcomes	Safety outcomes
	• TNSS (1 study – Hwang 2017): reduction from baseline (6.2±0.5) to 30 days (2.6±0.3), 90 days (2.7±0.4), 180 days (2.3±0.5), and 365 days (1.9±0.3) (p<0.001). Patient-reported obstruction reduced from 1.9±0.2 to 0.5±0.2, and rhinorrhoea reduced from 2.4±0.8 to 1.2±0.2. Effectiveness of cryotherapy for NAR, AR and mixed chronic rhinitis: • NAR (9 studies): improvement of overall symptoms, 67% to 95.7% • AR (4 studies): overall symptoms improvement, 63.4% to 80% • Mixed chronic rhinitis (2 studies): decrease in overall symptom burden, 92.5% to 100%	○ Day 7: n=2 (7%) noted severe nasal dryness, n=1 (4%) noted severe ear blockage ○ Day 27: n=1 (4%) epistaxis • Varshney (1997): infection (n=1), slight/moderate slough formation (n=16), adhesion (n=1), and excessive scarring (n=2) • Bumsted (1990): epistaxis (n=3), prolonged nasal crusting (n=3), and rhinosinusitis (n=2) • Scoppa (1985): nasal adhesions (n=2), nasal infection (n=2), and secondary haemorrhage (n=1) • Principate (1997): postoperative bleeding (n=37) • Puhakka (1997): repeat procedures (exact number not reported)
Singh AK (2021)	Not reported.	Adverse events: n=12 (3 occurred during the procedure and 9 occurred after the procedure) Epistaxis: n=9 (including 2 had a history of nosebleeds, 4 had a history of hypertension, and 3 had taken anticoagulant medications.)

First author, date	Efficacy outcomes	Safety outcomes
		8 of the 9 people had severe symptoms and were hospitalised, and 5 of the 8 hospitalised patients were treated with sphenopalatine artery ligation or embolisation. In 1 case, the epistaxis was thought to be secondary to a retained nasal pledget, instead of a consequence of device usage. Nasal swelling or infection: n=2 (managed medically without hospitalisation) Device malfunction: n=1 (at time of procedure) No mortalities were reported.

Procedure technique

All 5 primary studies used the ClariFix device (FDA approved). The cryotherapy treatment was done according to the manufacturer's instructions. For each treatment, cryogen was delivered for 30 to 60 seconds in duration. Cryotherapy could be done in the outpatient clinic setting (in most cases) or the operating room, and was used as a primary or revision procedure.

For the 15 studies included in the systematic review, there was little consistency in the duration of therapy or devices used. Duration of therapy ranged from 5 to 8 seconds to 2 to 3 minutes. When reported, various devices were used, with Frigitronics probes used in most studies and the Clarifix device used in only 1 study.

Efficacy

Rhinitis symptom relief

TNSS

The outcomes of TNSS were reported in 5 studies, with rTNSS used in 4 studies and its variation in 1 study. There was statically significant improvement in rTNSS across these studies, with 73% of people whose symptoms responded to the treatment and at least 80% of people who had clinically meaningful improvements.

In the RCT of 133 people who had cryotherapy or sham procedure, Del Signore (2022) found that there were statistically significantly improvements in the mean total rTNSS at 90 days after treatment in both groups (cryotherapy, from 8.0 [SD 1.6] at baseline to 4.3 [SD 2.4] at 90 days; sham group, from 8.1 [SD 1.9] to 6.3 [SD 2.5]). Between-group comparison showed that there was a statistically significantly greater improvement in the cryotherapy group (mean change: -3.7, 95% CI -4.3 to -3.1) than the sham group (mean change: -1.8, 95% CI -2.5 to -

1.1). The proportion of people whose symptoms responded to the treatment (with at least 30% reduction in rTNSS relative to baseline) was statistically significantly higher in the cryotherapy group (73%, 47/64) than the sham group (37%, 23/63) at 90 days. Regarding the individual rTNSS domains, there were statistically significantly greater improvements for rhinorrhoea and nasal congestion in the cryotherapy group than the sham group, but not for nasal itching and sneezing. The multivariate model showed that only the cryotherapy arm and the rTNSS value at baseline were associated with the outcome of at least 30% improvement in the rTNSS (Del Signore 2022).

In the single-arm trial of 100 people, Ow (2021) reported that there were statistically significant improvements in the total rTNSS at 12-month (n=91; median change, -3.0, IQR -4.0 to -1.0) and 24-month follow-ups (n=57; median change, -4.0, IQR -5.0 to -2.0). More than 80% of people achieved the MCID of ≥1 point improvement at these follow-up durations. All rTNSS domains also statistically significantly improved at these timepoints, except for nasal itching at 24 months.

In the single-arm trial of 30 people, Yen (2020) reported that there were statistically significant improvements in the total rTNSS at 1 month (median change, -3.5, IQR -5.0 to -2.0) and 3 months (-4.0, IQR -6.0 to -1.0). Of the 30 people, 80% and 87% of people achieved the MCID at 1- and 3-month follow ups, respectively.

In the systematic review of 15 studies (n=1,266), Kompelli (2018) reported that rTNSS was used in 1 study only, showing statistically significantly improvement up to 1 year after cryotherapy (baseline, 6.2±0.5; 30 days, 2.6±0.3; 90 days, 2.7±0.4; 180 days, 2.3±0.5; and 365 days, 1.9±0.3).

In the single-arm trial of 24 people, Gerka Stuyt (2021) used the variation of the TNSS and found that there was statistically significant improvement in the mean

12-hour TNSS up to 1 year after procedure (baseline, 6.92 [SD 2.8]; 30 days, 3.17 [SD 2.4]; 90 days, 2.92 [SD 1.4]; 1 year, 3.08 [SD 2.6]). Statistically significant improvements were also seen with the 2-week TNSS from 7.75 [SD 3.1] at baseline to 3.79 [SD 2.1], 3.88 [SD 1.8] and 3.76 [SD 2.1] at 30 days, 90 days and 1 year, respectively. Statistically significant improvement in TNSS was seen in all domains (nasal congestion, rhinorrhoea, nasal itching, sneezing, and difficulty sleeping) at all timepoints, except for nasal itching at 30 days compared with baseline (0.28 [SD 0.6] compared with 0.5 [SD 0.7]). When considering different types of rhinitis, authors also reported statistically significantly improvements in 12-hour and 2-week TNSS at 1 year for NAR and mixed rhinitis but not for AR:

- Mean 12-hour TNSS score:
    - NAR: baseline, 7.1±3.1; 1 year, 3.13±3.0; $p<0.001$
    - Mixed rhinitis: baseline, 6.4±2.1; 1 year, 3.2±2.2; $p<0.05$
    - AR: baseline, 6.67±3.2; 1 year, 2.6±0.6; $p>0.05$
- Mean 2-week TNSS score:
    - NAR: baseline, 7.75±3.6; 1 year, 3.94±2.4; $p<0.001$
    - Mixed rhinitis: baseline, 7.2±1.6; 1 year, 4.0±1.4; $p<0.05$
    - AR: baseline, 8.67±2.5; 1 year, 3.3±1.1; $p>0.05$

NOSE

NOSE was assessed and reported in 2 studies, with 80% to 90% of people considered to have response in their symptoms. Del Signore (2022) reported that there was a statistically significantly greater improvement in NOSE scores in the cryotherapy group (mean change: −29.9, 95% CI −35.8 to −24.0) than the sham group (mean change, −14.8, 95% CI −21.2 to −8.4) at the 90-day visit. The NOSE response rate was 81% (52/64) in the cryotherapy group and 54% (34/63) in the sham group. Yen (2020) reported that the mean NOSE score statistically significantly improved from baseline to 3 months (mean change, -31.4 [SD 34.4]),

with 90% (26/29) of people considered to have NOSE response in their symptoms.

SNOT-22

SNOT-22 (RNS) was used in 2 studies. Yen (2020) reported that the mean SNOT-22 score statistically significantly decreased from baseline to 3 months (-24.2 [SD 21.1]; p<0.001), with 76% (22/29) of people achieving the MCID of -8.9 points for the total score. In terms of runny nose determined using the RNS from SNOT-22, Yoo (2020) reported that the mean scores statistically significantly decreased from 4.2 (SD 1.0) at baseline to 2.30 (SD 1.84) at the first visit, 1.95 (SD 1.79) at the second visit and 2.60 (SD 1.68) at the third visit (mean 170 days). After the procedure, 71% (39/55) of people had clinically meaningful improvements in running nose (≥1-point improvements in RNS). Authors also reported that ipratropium spray response was the only factor associated with improvement in RNS.

Nasal symptoms relief

Yen (2020) reported that nasal symptoms of rhinorrhoea and congestion, measured using a 100-mm VAS, statistically significantly improved from baseline (75.9±21.4) to 3 months (36.0±29.2), with a mean change of -39.9 (SD 34.7).

In the systematic review, Kompelli (2018) reported reduction in obstructive symptoms in 63% to 100% of people (5 studies), and reduction in rhinorrhoea in 77% to 100% of people (5 studies). Authors also described patient-reported improvements without stratifying results based on symptom type, with general improvements ranging from 67% to 100% (7 studies). When considering different types of rhinitis, Kompelli (2018) found improvement of overall symptoms in 67% to 96% of people with NAR (9 studies), in 63% to 80% of people with AR (4 studies), and in 93% to 100% of people with mixed chronic rhinitis (2 studies).

Improvement in quality of life

Quality of life measured using RQLQ was reported in 3 studies, with 2 studies using the standardised version and 1 using the mini version. All 3 studies showed statistically significantly improvement after cryotherapy and 77% to 87% of people had clinically meaningful improvements.

Del Signore (2022) reported that both cryotherapy and sham groups showed statistically significant improvements in RQLQ after treatment. However, the cryotherapy group presented statistically significantly greater improvement (−1.5, 95% CI −1.8 to −1.2) over the sham group (−0.8, 95% CI −1.1 to −0.5) at the 90-day visit. At the same follow-up point, 83% (53/64) of people in the cryotherapy group achieved the MCID of ≥0.5-point improvement in the RQLQ compared with 52% (33/63) of people in the sham group. For the individual RQLQ domains, the cryotherapy group had statistically significantly greater improvements in 5 of the 7 domains compared with the sham group (non-hayfever symptoms, practical problems, nasal symptoms, eye symptoms and emotions).

Ow (2021) reported that there were statistically significant improvements in the total RQLQ at 18 months (median change: -2.1, IQR -3.1 to -1.1) and 24 months (median change, -2.1, IQR -3.0 to -0.8). Over 77% of people achieved the MCID from baseline in the total RQLQ at both follow-up periods. All RQLQ domains showed statistically significant improvements at both time periods, with eye symptoms being the least impacted domain.

Yen (2020) found that statistically significant improvement in the mini RQLO at 3-month follow up over baseline (median change: -1.8, IQR -2.3 to -0.7), with 87% (26/29) of people achieving the MCID (≥0.4 points). There were statistically significant improvements in all 5 domains at 3 months, with eye symptoms being the least impacted domain.

CGI-I

CGI-I was used in 2 studies to evaluate clinician's perception of people's improvement. Ow (2021) found that except for the 12-month visit, over 80% of people had improvement over baseline at each long-term visit through 24 months. Yen (2020) reported that 90% (26/29) of people experienced improvement at 3-month posttreatment.

Reduction in medications

Gerka Stuyt (2021) found that, when compared with baseline, 67% (12/18) of patients eliminated or reduced the use of medication to manage their rhinitis at 24 months after cryotherapy.

Safety

Nasal adverse events

Epistaxis

Epistaxis was reported in 3 studies. Singh (2021) analysed the MAUDE database and found 12 reported events. Of these events, 9 people experienced epistaxis (including 2 had a history of nosebleeds, 4 had a history of hypertension, and 3 had taken anticoagulant medications). Of the 9 people, 8 people's symptoms were severe, and they were hospitalised. In 1 person, epistaxis was thought to be secondary to a retained nasal pledget, instead of a consequence of device use. Authors stated that there was a possibility that the reported episodes of epistaxis were unrelated to the ClariFix intervention because history of epistaxis, oral anticoagulants and hypertension were associated with increased risk of epistaxis.

Chang (2020) reported that epistaxis happened in 2 people (2%) within 90 days after cryotherapy, with 1 being severe and needing hospitalisation. In the systematic review by Kompelli (2018), epistaxis was reported in 4 people (2 studies).

Other nasal adverse events

Singh (2021) described that nasal swelling or infection was experienced in 2 people and these were managed medically without hospitalisation.

Del Signore (2022) reported pain or discomfort at the treatment site in 25 people (39%) and nasal congestion in 2 people (3%) who had cryotherapy, and pain or discomfort in 1 person (2%) who had a sham procedure.

Chang (2020) reported nasal adverse events, including bloody discharge (n=1), burning sensation (n=1), hyperaemia (n=1), middle turbinate haematoma (n=1), mucous (n=1), ostia newly noted (n=2), pain (n=1), retained pledget (n=1) and synechiae (n=1) within 90 after cryotherapy.

Yen (2020) found that post-procedure pain or discomfort (facial, jaw, tooth, occipital, treatment site, unspecified) was experienced in 10 (33%) people (the exact data for nasal pain or discomfort was not reported).

In the systematic review by Kompelli (2018), severe nasal dryness was reported in 1 person (4%) at day 1 after cryotherapy and in 2 people (7%) at day 7 (1 study). Authors also reported that nasal infection (n=3; 2 studies), slight or moderate slough formation (n=16; 1 study), nasal adhesion (n=3; 2 studies), excessive scarring (n=2; 1 study), prolonged nasal crusting (n=3; 1 study), and postoperative bleeding (n=38; 2 studies).

Sinusitis or rhinosinusitis

Sinusitis or rhinosinusitis was reported in 5 studies. Del Signore (2022) found that sinusitis happened in 1 person who had cryotherapy but not in people who had a sham procedure. Ow (2021) and Chang (2020) reported that sinusitis was experienced in 4 people within 90 days after cryotherapy. Yen (2020) described that sinusitis was developed in 1 person, but this was unrelated to the device or

procedure. Kompelli (2018) stated that rhinosinusitis was reported in 2 people after cryotherapy in 1 of the 15 studies included in the systematic review.

Head or face adverse events

Del Signore (2022) found that headache was experienced in 4 people and dizziness or light headedness in 1 person in the cryotherapy group but not in people in the sham group. Ow (2021) and Chang (2020) reported 6 head or face adverse events, including facial pain in 2 patients, headache in 3 people, migraine in 1 person and dizziness in 1 person within 90 days after cryotherapy. Yen (2020) described that headache happened in 12 people (40%) who had cryotherapy. Yoo (2020) reported that headache was experienced in 4 people (7.5%) and facial pain in 6 people (11.3%) after cryotherapy.

Oral adverse events

Del Signore (2022) found that transient roof of mouth numbness was experienced in 2 people and vasovagal reaction in 1 person in the cryotherapy group and vasovagal reaction in 1 person in the sham group. Yen (2020) described that palate numbness happened in 8 people (27%) after cryotherapy. Yoo (2020) reported that palate numbness was developed in 3 people (6%) after treatment.

Chang (2020) reported 5 oral adverse events, including bad taste in 1 person, numbness in 1 person, swollen sensation in 1 person, teeth sensitivity in 1 person and dry mouth in 1 person within 90 days after cryotherapy.

Ocular adverse events

Del Signore (2022) reported that watery eyes was experienced in 2 of the 64 people who had cryotherapy but not in people who had a sham procedure. Ow (2021) reported 3 ocular adverse events, including 2 people with dry eyes and 1 person with watery eyes within 90 days after cryotherapy.

Ear blockage

In the systematic review by Kompelli (2018), severe ear blockage was reported in 12 people at day 1 and 1 person at day 7 after the procedure (1 study).

Anxiety or panic attack

Del Signore (2022) found that 1 person had an anxiety or panic attack (procedure-related serious AE) while the person was still in the clinic after successful cryotherapy. Vital signs were normal.

Others

Del Signore (2022) reported that drug reaction (decongestant) was experienced in 1 of the 64 people who had cryotherapy but not in people who had a sham procedure.

In the systematic review by Kompelli (2018), there were repeat procedures reported in 1 study, but the exact number was not described.

Device malfunction was described in 2 studies. Singh (2021) found 1 device malfunction at time of procedure. Chang (2020) reported 5 device malfunctions, all involving the lack of cryogen flow from the device cannister. However, each device malfunction was immediately resolved by the replacement of a new cryogen canister.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

There were no anecdotal and theoretical adverse events identified in addition to those that were reported in the literature.

Five professional expert questionnaires for this procedure were received. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

No professional expert questionnaires were submitted.

Validity and generalisability

In the main evidence, there was a lack of ethnic diversity in the study populations, with most people reported as being white. Most studies only reported follow-up data within 1 year. Ow (2021) stated that because peripheral neuroregeneration can occur at a rate of 1 to 6 inches per month, evaluating results beyond a year is important to determine durability of the treatment.

There was variation in patient inclusion criteria and device used. Except for the systematic review that included studies (all but one published between 1977 and 1997) using different devices, all other recent studies (published between 2020 and 2022) used the FDA-approved device (ClariFix). Four studies were industry-sponsored (Del Signore 2022; Ow 2021; Yen 2020) and declarations of interest by 1 or more authors were reported in 4 studies (Del Signore 2022; Ow 2021; Yen 2020; Yoo 2020).

There was an adequately powered RCT, but perprotocal analysis instead of intention-to-treat analysis was done (Del Signore 2022). This RCT showed that cryotherapy was superior to sham for improving chronic rhinitis symptoms and quality of life. This study reported a relatively short-term follow up (90 days), but extended follow up is currently being done.

Of the 3 single-arm trials, 1 trial (Ow 2021) reported 24-month outcomes, but nearly 30% of people were lost after the 12-month follow up because of the

requirement for additional consent for the study extension protocol. The LOCF analysis did not appear to be a substantial impact on the rTNSS outcomes from people 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 in the change from baseline and 4% difference in the percentage of people who achieved the MCID. Authors concluded that future studies would be needed to show longer-term improvement and sustained results without using additional medications. The other 2 trials (Gerka Stuyt 2021; Yen 2020) were limited by small sample size and short follow up.

In the systematic review by Kompelli (2018), most articles were deemed Oxford Centre for Evidence-Based Medicine level 4 with 1 article being level 2c. Authors stated that although cryotherapy appeared safe and efficacious, heterogeneous past investigations with low-quality evidence made strong, evidence-based recommendations difficult to make. Authors also recommended that further study with validated metrics and controlled populations is certainly warranted and should be encouraged.

The FDA's MAUDE database was reviewed and analysed by Singh (2021) to identify adverse events relating to the use of ClariFix. However, there were several limitations, including the small number of reports included and reporting bias inherent to the MAUDE database, unknown complication rates, and lack of longitudinal outcome data and patient information. Authors concluded that the results accentuate the need for careful patient selection when offering ClariFix and the need for further observational studies.

Overall, evidence showed statistically significantly and clinically improvements in rhinitis symptoms (TNSS, NOSE, SNOT-22) and quality of life (RQLQ). Evidence also indicated that baseline TNSS value was associated with its outcome (TNSS response; Del Signore 2022) and that ipratropium spray response was associated with improvement in RNS (Yoo 2020). Most adverse events were

non-serious, and there were a few serious adverse events including epistasis, severe ear blockage, severe nasal dryness, and anxiety/panic attack.

There are 2 ongoing trials, detailed below:

- ClariFix Rhinitis Randomised Controlled Trial (NCT04154605); US; RCT (crossover assignment); actual enrollment, n=133; estimated study completion date, July 2022.

- Study of the ClariFix Cryoablation Device in Patients with Chronic Rhinitis - New Zealand (ACTRN12614000468628); New Zealand; non-randomised clinical trial; target sample size, n=30; status, recruiting.

Existing assessments of this procedure

The Triological Society reviewed the evidence to seek answering whether in-office PNN ablation is an effective treatment for the symptoms of AR (Davies 2022). Based on 4 single-arm prospective cohort studies (level 3) and 1 RCT (level 2), it was recommended that “although the number of randomised controlled trials (RCTs) is lacking, given the consistency of earlier prospective single-arm cohort studies, combined with the support of newer well-designed RCTs, there is enough evidence to support PNN as an effective treatment for allergic rhinitis symptoms, particularly nasal congestion, and rhinorrhoea. Given the favourable side effect profile of in-office PNN, there appears to be a role for cryoablation or radiofrequency neurolysis in treating symptoms of AR. Future studies should confirm these findings with additional RCTs using sham control procedures, longer follow-up, and larger and more diverse patient populations.”

The Japanese guidelines for allergic rhinitis 2020 (Okubo 2020) described an evidence-based step-by-step strategy for treatment. Operative treatment for AR was recommended as appropriate, such as cryosurgery and laser surgery.

Related NICE guidance

Interventional procedure

- NICE's interventional procedures guidance on Intranasal phototherapy for allergic rhinitis (published: 13 June 2018) (Recommendation: research).

Professional societies

- ENT UK (the British Association of Otorhinolaryngology).

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

References

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3. Chang MT; Song S; Hwang PH (2020) Cryosurgical ablation for treatment of rhinitis: A prospective multicenter study. The Laryngoscope 130(8): 1877-84
4. Gerka Stuyt JA, Luk L, Keschner D et al. (2021) Evaluation of in-office cryoablation of posterior nasal nerves for the treatment of rhinitis. Allergy and Rhinology 12
5. Yen DM, Conley DB, O'Malley EM et al. (2020) Multiple site cryoablation treatment of the posterior nasal nerve for treatment of chronic rhinitis: an observational feasibility study. Allergy and Rhinology 11

6. Yoo F, Kuan EC, Batra PS et al. (2020) Predictors of rhinorrhea response after posterior nasal nerve cryoablation for chronic rhinitis. International forum of allergy & rhinology 10(7): 913-9
7. Kompelli AR, Janz TA, Rowan NR et al. (2018) Cryotherapy for the Treatment of Chronic Rhinitis: A Qualitative Systematic Review. American journal of rhinology & allergy 32(6): 491-501
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9. Davies C, Gorelik D, Lane AP et al. (2022) Is posterior nasal nerve ablation effective in treating symptoms of allergic rhinitis? Laryngoscope
10. Okubo K, Kurono Y, Ichimura K et al. (2020) Japanese guideline for allergic rhinitis. Allergology International 69: 311-345

Methods

NICE identified studies and reviews relevant to cryotherapy for chronic rhinitis from the medical literature. The following databases were searched between the date they started to 2 November 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- People with chronic rhinitis.

- Intervention or test: cryotherapy.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	02/11/2022	1946 to November 01, 2022
MEDLINE In-Process (Ovid)	02/11/2022	1946 to November 01, 2022
MEDLINE Epubs ahead of print (Ovid)	02/11/2022	November 01, 2022
EMBASE (Ovid)	02/11/2022	1974 to 2022 November 01
EMBASE Conference (Ovid)	02/11/2022	1974 to 2022 November 01
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	02/11/2022	Issue 11 of 12, November 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	02/11/2022	Issue 10 of 12, October 2022
International HTA database (INAHTA)	02/11/2022	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 exp rhinitis/
2 Rhinorrhea/
3 (rhiniti* or rhinorr* or Rhinosinusiti* or Rhinoconjunctiviti*).tw.
4 Nasal Obstruction/ or Nasal Mucosa/
5 ((nostril* or nose* or nasal* or palate) adj4 (run* or inflammat* or itch* or block* or irritat* or mucus* or mucosa* or discharg* or drain* or obstruct* or oedema* or congest* or drip* or runny* or symptom* or catarrh* or epitheli*)).tw.
6 "schneiderian membrane*".tw.
7 (Sneez* or Pollenosi*).tw.
8 or/1-7
9 Cryosurgery/ or cryotherapy/
10 Freezing/
11 ((freez* or cold) adj4 (therap* or surg* or ablat* or method* or technique* or procedure* or treatment*)).tw.
12 cryo*.tw.
13 (("Posterior nasal nerve*" or PNN) adj4 (cryo* or ablat* or modulat* or neuromodulat* or neurectom*)).tw.
14 or/9-13
15 8 and 14
16 clarifix.tw.
17 15 or 16
18 animals/ not humans/
19 17 not 18
20 limit 19 to english language

Other relevant studies

Other potentially relevant studies (conducted 1985 or after) to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Balai E, Gupta KK, Jolly K et al. (2022) Posterior nasal nerve neurectomy for the treatment of rhinitis: a Systematic Review and Meta-Analysis. European annals of allergy and clinical immunology	Systematic review and meta-analysis (descriptive analysis) n=463 (8 studies)	This systematic review identified there is some limited evidence to suggest cryotherapy or radiofrequency ablation of the posterior nasal nerve can improve TNSS in adults. However, this is from a limited number of trials with short follow up. Future research should focus on prospective RCTs with more people and medium to long term follow up to help draw more valid conclusions regarding the true effectiveness of PNNN in this patient cohort.	This systematic review combined the results of 6 studies using cryotherapy, 1 study using radiofrequency, and 1 study using laser. All the 6 studies relevant to cryotherapy are included in the main evidence of this overview. The systematic review undertook a meta-analysis of the 2 RCTs available, 1 RCT (Del Signore 2021) is included in the main evidence of this overview and the other RCT (Stolovlzky 2021) assessed the effect of radiofrequency neurolysis.
Fan T, Chandna M, Gorelik D et al. (2022) Correlation between middle turbinate insertion in relation to	Case-control (retrospective) n=31	The OR of patients failing in-office procedures for chronic rhinitis due to unfavourable MT attachment was 8.2	This study evaluated the relationship of the middle turbinate attachment to the sphenopalatine

sphenopalatine foramen and failure rates of cryotherapy and radiofrequency treatment for chronic rhinitis. International Forum of Allergy and Rhinology		(95% CI 0.9 to 76.6; p=0.07). This study reinforces the existence of great disparities for natural middle turbinate anatomy.	foramen (SPF) to treatment failure rates for chronic rhinitis.
Gorelik D, Choi A, Desisto N et al. (2022) Indirect comparison of the efficacy of radiofrequency neurolysis and cryotherapy in the treatment of chronic rhinitis. International Forum of Allergy and Rhinology	Indirect comparison of radiofrequency neurolysis and cryotherapy n=141 (2 studies)	The findings suggest that radiofrequency and cryotherapy are equally efficacious in treating chronic rhinitis. Direct comparison of the 2 devices in a long-term RCT is necessary to confirm the results.	Of the 2 included studies, only 1 study (Del Signore 2022) is for cryotherapy and included in the main evidence.
Haight JS and Gardiner GW (1989) Nasal cryosurgery and cautery: should the septum be treated and is a diagnosis relevant? The Journal of otolaryngology 18(4): 144-50	Non-randomised comparative study n=48 (cryosurgery, n=12; cautery, n=12) follow up: 10 to 16 weeks	The results showed that there is no benefit to treating the septum, and that cryosurgery is more effective in those whose symptoms respond to topical steroids, while cautery works better in those who do not. Histology showed no change in the capacitance vessels (sinusoids) after either modality, and xylometazoline caused a marked decrease in nasal resistance, suggesting that vascular smooth muscle function was intact. Irrespective of the change in airway resistance, most patients felt that there had been an improvement.	Studies with larger samples or better designs using a modern device are included in the main evidence.

Hwang PH, Lin B, Weiss R et al. (2017) Cryosurgical posterior nasal tissue ablation for the treatment of rhinitis. International forum of allergy & rhinology 7(10): 952-6	Pilot study n=27 Follow up: 1 year	Office-based cryotherapy of the PNN region is safe and well tolerated. Symptom scores were significantly decreased by 7 days postprocedure and remained lower at 30, 90, 180, and 365 days.	This study was included in Kompelli (2018) in the main evidence.
Senanayake P, Wong E, McBride K et al. (2022) Efficacy of vidian neurectomy and posterior nasal neurectomy in the management of nonallergic rhinitis: a systematic review. American journal of rhinology & allergy 36(6): 849-871	Systematic review n=229 (9 studies) Cryotherapy: 3 studies	Endoscopic vidian neurectomy (EVN), surgical posterior nasal neurectomy (SPNN), and cryoablative posterior nasal neurectomy (CPNN) are similarly efficacious for patients with NAR refractory to medical management. SPNN and CPNN are associated with lower rates of complications (dry eye and palatal/cheek numbness) compared with EVN.	Of the 3 relevant studies, 2 studies (Yoo 2020; Chang 2020) are included in the main evidence and 1 study (n=14; Virani 2021) in the appendix.
Steele TO, Hoshal SG, Kim M et al. (2020) A preliminary report on the effect of gabapentin pretreatment on periprocedural pain during in-office posterior nasal nerve cryoablation. International forum of allergy & rhinology 10(2): 159-64	Non-randomised comparative study n=26	Pre-procedure gabapentin significantly reduces immediate and delayed post procedural patient discomfort following PNN cryoablation.	This study focused on the effect of gabapentin on patient-reported pain following PNN cryoablation.
Varshney S and Chandra K (1997) Cryosurgery in allergic rhinitis. Indian Journal of	Case series n=104	The results drawn the inference that cryosurgery provides an excellent relief with regards to symptoms of	This study was included in Kompelli (2018) in the main evidence.

Otolaryngology and Head and Neck Surgery 49(1): 66-9		nasal obstruction while a satisfactory one in rhinorrhoea. Overall it provides great benefit to the patient's symptoms which can further be improved upon with more experience in this regard.	
Virani FR, Wilson MD, Beliveau AM et al. (2021) The impact of surgical posterior nasal nerve cryoablation on symptoms and disease-specific quality of life in patients with chronic rhinitis. Ear, Nose and Throat Journal	Case series n=14 Follow up: mean 16.5 weeks	This study shows that PNN cryoablation significantly improves symptoms and disease specific quality of life in patients with allergic and non-allergic rhinitis as measured by TNSS and mini-RQLQ.	Studies with larger samples or better designs are included in the key evidence.
Wengraf CL, Gleeson MJ, Siodlak MZ (1986) The stuffy nose: a comparative study of two common methods of treatment. Clinical otolaryngology and allied sciences 11(2): 61-8	Case series n=13 Follow up: 6 weeks	Rhinomanometry suggests that cryotherapy causes more destruction of the submucosal vascular plexus than submucosal diathermy. Scanning electron microscopy 6 weeks postoperatively shows that both treatment modalities cause widespread damage to the mucociliary epithelium.	This study was included in Kompelli (2018) in the main evidence.
Wojdas A, Zielnik-Jurkiewicz B, Rapiejko P et al. (2004) Surgical treatment of nasal obstruction in allergic and non-allergic rhinitis. International Review of Allergology and Clinical Immunology 10(2): 55-8	Non-randomised comparative studies n=102	Based on obtained material and results, authors proved conchoplasty to be more effective, and outcomes of nasal obstruction therapy in allergic rhinitis are better. Authors obtained nasal airflow resistance referential values using	Limited outcomes reported.

		active anterior rhinometry method.	
Yan CH and Hwang PH (2018) Surgical management of nonallergic rhinitis. Otolaryngologic clinics of North America 51(5): 945-955	Review	A study of office-based cryotherapy in people with vasomotor rhinitis and allergic rhinitis showed that TNSS decreased significantly up to 365 days after treatment, particularly in the symptoms of rhinorrhoea and congestion. There were no postoperative instances of dry eyes or palate numbness.	Review article