

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of intranasal phototherapy for allergic rhinitis

Allergic rhinitis is inflammation of the inside of the nose caused by an allergen such as pollen or dust. This procedure involves putting a special light-emitting device into the nose for several minutes at a time. The aim is to reduce inflammation and so relieve the symptoms of allergic rhinitis, such as sneezing, itchiness and a blocked or runny nose.

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in November 2017.

Procedure name

- Intranasal phototherapy for allergic rhinitis.

Specialist societies

- British Society for Allergy and Clinical Immunology (BSACI)
- ENT UK
- Royal College of Physicians

Description of the procedure

Indications and current treatment

Allergic rhinitis is inflammation of the inside of the nose caused by an allergen such as pollen, house dust mites or mould. It causes symptoms such as sneezing, itchiness and a blocked or runny nose. Most people with allergic rhinitis have mild symptoms that can be easily and effectively treated. For some people, however, symptoms can be severe and persistent and have a significant impact on quality of life.

First-line treatments for allergic rhinitis include medication such as antihistamines and intranasal corticosteroids. For more severe or persistent symptoms that do not respond to medication, immunotherapy (sublingual or subcutaneous) is sometimes used.

What the procedure involves

Intranasal phototherapy involves using a device with light-emitting probes, which are inserted into the nasal cavity for several minutes at a time. Some devices are designed to be self-administered, whereas others are administered by a clinician. There are different devices available and the duration and dose of treatment varies. The devices use different frequencies of light, ranging from ultraviolet to infrared.

Intranasal phototherapy is claimed to increase local blood flow and suppress inflammation. The aim is to reduce the symptoms of allergic rhinitis.

Outcome measures

The Total Nasal Symptom Score (TNSS) is a patient-reported outcome measure that is commonly used to assess symptoms of rhinitis. The total score ranges from 0 to 12 and is the sum of 4 individual symptom scores for rhinorrhoea, nasal congestion, nasal itching and sneezing, each evaluated using a scale of 0=none, 1=mild, 2=moderate and 3=severe.

Efficacy summary

Total Nasal Symptom Score

In a systematic review of 13 studies (679 patients), there was a statistically significant decrease in the total nasal symptom score (TNSS) after intranasal phototherapy (n=113, standardised mean difference -1.77 , $p<0.0001$; $I^2>50\%$)¹. The scores for each individual symptom were also statistically significantly lower after intranasal phototherapy ($I^2>50\%$). In the 2 randomised controlled trials (RCTs) that compared phototherapy with antihistamine in the systematic review, the difference in TNSS was not statistically significant (effect size -0.28 , 95% confidence interval [CI] -0.67 to 0.11 ; $p=0.1661$). In the 4 RCTs in the systematic review that compared phototherapy with sham treatment, the TNSS was statistically significantly lower after phototherapy than after sham treatment (effect size -0.53 , 95% CI -0.80 to -0.26 ; $p=0.001$).

In an RCT of 62 patients with persistent allergic rhinitis comparing intranasal phototherapy with placebo, the TNSS was statistically significantly lower in patients who had phototherapy than in those who had placebo, at 12-week follow-up (3.87 versus 9.00, $p<0.001$)². In an RCT of 25 patients with persistent allergic rhinitis comparing intranasal phototherapy with placebo, there was a statistically significantly greater decrease in TNSS in patients who had phototherapy than in those who had placebo, at 10-week follow-up (-10.62

compared with -6.66 for morning symptoms and -10.47 compared with -7.19 for evening symptoms, $p < 0.01$)³.

Quality of life

In the systematic review, there was a statistically significant improvement in disease-specific quality-of-life scores after intranasal phototherapy for all domains (sleep, practical issues, non-hay-fever symptoms, nasal symptoms, limited activity, eye symptoms and emotional problems; $I^2 > 50\%$)¹. In the RCT of 62 patients, the total Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score was statistically significantly lower in patients who had phototherapy than in those who had placebo, at 12-week follow-up (9.74 versus 23.41 , $p < 0.001$)². All comparisons between baseline and 12-week scores were statistically significant in the phototherapy group ($p < 0.001$). There were no statistically significant differences between baseline 12-week scores in the placebo group. In an RCT of 65 patients, the mean scores for all RQLQ domains were statistically significantly better in patients who had intranasal phototherapy and medical treatment than in patients who had medical treatment alone, at 3-month follow-up⁴.

Medication use

In the RCT of 62 patients the mean dose of antihistamine used during the study was statistically significantly lower in the phototherapy group than in the placebo group (261.4 mg compared with 335.5 mg, $p < 0.001$)². In the RCT of 25 patients the mean dose of antihistamine used during the study was similar across the 2 groups (4.2 tablets/person/treatment cycle for phototherapy compared with 3.45 tablets/person/treatment cycle for placebo, $p = \text{not significant}$)³.

Endoscopic improvement

In an RCT of 79 patients, which was also included in the systematic review, 48% ($15/31$) of patients who had intranasal phototherapy had improvement in middle turbinate oedema compared with 12% ($2/17$) of patients who had sham treatment ($p = 0.0007$)⁹. Mild improvement of symptoms, assessed by endoscopy, was reported for 44% ($22/50$) of patients who had intranasal phototherapy and 21% ($6/29$) of patients who had sham treatment (p value not reported). Marked improvement of symptoms, assessed by endoscopy, was reported for 26% ($13/50$) of patients who had intranasal phototherapy and no patients who had sham treatment (p value not reported).

Safety summary

Nasal mucosal dryness

Severe nasal mucosal dryness, which was controlled with emollients, was reported in 2 patients who had intranasal phototherapy and no patients who had placebo in an RCT of 62 patients². Mild dryness, which resolved after treatment with nasal drops, was reported in 3 patients who had phototherapy in an RCT of 25 patients³. Nasal mucosal dryness, which was controlled with emollients, was reported in all patients who had intranasal phototherapy in an RCT of 77 patients. All patients except 1 considered the dryness to be mild⁶.

Nasal mucosal oedema

Severe nasal mucosal oedema, which was controlled with emollients, was reported in 1 patient who had intranasal phototherapy and no patients who had placebo in the RCT of 62 patients².

Nasal burning sensation or pain

Nasal burning sensation, which was controlled with emollients, was reported in 6% (2/31) patients who had intranasal phototherapy and no patients who had placebo in the RCT of 62 patients². Temporary and spontaneously resolving nasal pain was reported by 21% (3/14) of patients in the phototherapy group and 18% (2/11) of patients in the placebo group in the RCT of 25 patients³.

Headache

Headache was reported in 2 patients who had intranasal phototherapy and no patients who had placebo in the RCT of 62 patients². Headache was reported in 1 patient in each treatment group in the RCT of 25 patients³.

Epistaxis

Mild nosebleed when blowing the nose, which did not need treatment, was reported in 14% (2/14) of patients who had intranasal phototherapy and 18% (2/11) of patients who had placebo in the RCT of 25 patients. The authors noted that this was not directly related to the procedure³.

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not

list any anecdotal adverse events. They considered that the following was a theoretical adverse event: the possibility of malignant change in nasal epithelium (melanomas can occur inside the nose).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intranasal phototherapy for allergic rhinitis. The following databases were searched, covering the period from their start to 24 October 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the end of this overview for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	Patients with allergic rhinitis.
Intervention/test	Intranasal phototherapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on approximately 800 patients from 1 meta-analysis, 7 randomised controlled trials (4 of which were also included in the meta-analysis) and 1 case series (also included in the meta-analysis)¹⁻⁹.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed towards the end of this overview.

Table 2 Summary of key efficacy and safety findings on intranasal phototherapy for allergic rhinitis**Study 1 Cho HK (2015)****Details**

Study type	Meta-analysis
Country	Not reported for individual studies included in review
Recruitment period	Search date: July 2014
Study population and number	n=679 (13 studies) ; 2 studies used antihistamine as a comparator and 4 studies used a sham treatment; the remaining 7 studies compared values before and after the procedure. Patients with allergic rhinitis.
Age and sex	Not reported
Patient selection criteria	Criteria for considering studies for review: randomised or case-controlled trials of the effect of any method of endonasal phototherapy, on allergic rhinitis symptoms or quality of life. Children or adults with a history of moderate to severe allergic rhinitis that was not controlled by conventional anti-allergy treatment were included. Studies with more than 8 people per treatment group were included, which compared the effect of phototherapy before and after treatment or with a control (sham or antihistamine). Studies were not eligible for inclusion if: patients had additional procedures, such as turbinoplasty; patients had significant nasal structural abnormalities, bronchial asthma, upper respiratory tract infection within the past 2 weeks, or a lower respiratory tract infection within 4 weeks before the start of the study; patients were treated with systemic corticosteroids within the previous 4 weeks, topical corticosteroids or cromolyn sodium within 2 weeks, antihistamines and decongestants within 1 week before the beginning of the study, or immunotherapy within the past 2 years; or multiple reports were based on the same trial data. Studies were excluded from the analysis if clinical outcomes of interest were not clearly reported with quantifiable data or if it was not possible to extract and calculate the appropriate data from the published reports. Only studies published in English were selected for inclusion.
Technique	Several different devices were used in the studies. Any method of endonasal phototherapy was included, such as UV and visible light, narrow-band red light, low-level energy laser, or far infrared ray.
Follow-up	1 to 12 months
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Two literature reviewers independently screened the abstracts and titles of all candidate studies. Data were extracted using standardised forms. The outcomes analysed were nasal symptom scores, disease-specific quality of life questionnaire assessments and endoscopy findings. The risk of bias for each study was evaluated using the Cochrane risk of bias tool.

Study population issues: Of the 13 studies, 9 included patients with seasonal allergic rhinitis and the other 4 included patients with perennial allergic rhinitis.

Key efficacy and safety findings

Efficacy				Safety		
Number of patients analysed: 679 (13 studies)				No safety outcomes were reported.		
Comparison of nasal symptoms scores before and after intranasal phototherapy (10 studies)						
	n	Standardised mean difference	p value			
Total symptom score	113	-1.77	<0.0001			
Nasal itching	227	-1.49	<0.0001			
Nasal obstruction	247	-1.69	<0.0001			
Rhinorrhoea	247	-1.93	<0.0001			
Sneezing	227	-2.23	<0.0001			
Significant interstudy heterogeneity was detected in all the scores ($I^2>50\%$)						
Improvement in disease-specific quality of life after intranasal phototherapy (4 studies)						
	n	Standardised mean difference	p value			
Sleep	181	-1.22	0.0354			
Practical issues	181	-1.60	0.0478			
Non-hay fever symptoms	191	-1.26	0.0050			
Nasal symptoms	181	-2.03	0.0303			
Limited activity	181	-2.18	0.0409			
Eye symptoms	181	-1.18	0.0121			
Emotional problems	181	-1.24	0.0081			
Significant interstudy heterogeneity was detected in all the scores ($I^2>50\%$)						
Change in endoscopic findings after intranasal phototherapy						
Nasal discharge and turbinate hypertrophy were significantly improved after phototherapy (log odds ratio -4.27 and -1.45, $p<0.0001$ and $p=0.0083$ respectively; 2 studies, $n=70$, $I^2<50\%$).						
Effect of phototherapy on allergic nasal symptoms in randomised controlled trials						
	Antihistamine (2 studies)			Sham (4 studies)		
	Effect size	I^2 (%)	p	Effect size	I^2 (%)	p
Nasal itching	-0.42 (-0.80 to -0.04)	0	0.0317	-0.53 (-0.86 to -0.21)	63.1	0.0014
Nasal obstruction	-0.51 (-0.90 to -0.13)	0	0.0093	-1.01 (-1.63 to -0.40)	78.9	0.0012
Rhinorrhoea	-0.39 (-0.78 to -0.01)	0	0.0434	-0.91 (-1.15 to -0.66)	0	<0.0001
Sneezing	0.09 (-0.69 to 0.88)	71.1	0.8191	-0.78 (-1.19 to -0.37)	45.9	0.0002
Total score	-0.28 (-0.67 to 0.11)	3.42	0.1661	-0.53 (-0.80 to -0.26)	0	0.001
Subgroup analysis according to type of allergic rhinitis – allergic nasal symptoms						
	Perennial allergic rhinitis			Seasonal allergic rhinitis		
	Effect size	I^2 (%)	p	Effect size	I^2 (%)	p
Nasal itching	-1.26 (-2.75 to 0.22)	93.6	0.0963	-1.58 (-2.32 to -0.83)	79.9	<0.0001
Nasal obstruction	-1.00 (-1.30 to -0.69)	0	<0.0001	-2.07 (-3.13 to -1.00)	87.8	0.0001
Rhinorrhoea	-1.26 (-2.17 to -0.36)	86.6	0.006	-2.28 (-3.13 to -1.44)	82.0	<0.0001
Sneezing	-1.71 (-3.63 to 0.21)	95.4	0.0809	-2.41 (-3.50 to -1.32)	90.2	<0.0001

Total score	-	-	-	-1.77 (-2.39 to -1.15)	64.1	<0.0001
Subgroup analysis according to type of allergic rhinitis – quality of life						
	Perennial allergic rhinitis			Seasonal allergic rhinitis		
	Effect size	I ² (%)	p	Effect size	I ² (%)	p
Sleep	-0.35 (-0.78 to 0.07)	0	0.1066	-1.64 (-2.95 to -0.34)	94.9	0.0131
Practical issues	-0.43 (-0.86 to 0.00)	0	0.05	-2.18 (-4.25 to -0.12)	97.6	0.0377
Non-hay fever symptoms	-0.68 (-1.12 to -0.24)	0	0.0024	-1.44 (-2.55 to -0.34)	92.3	0.0102
Nasal symptoms	-0.86 (-1.31 to -0.41)	0	0.001	-2.60 (-5.09 to -0.11)	98.1	0.04
Limited activity	-0.78 (-1.22 to -0.33)	0	0.0005	-2.87 (-5.60 to -0.14)	98.3	0.0391
Eye symptoms	-0.54 (-0.98 to -0.11)	0	0.0136	-1.48 (-2.65 to -0.31)	93.9	0.0131
Emotional problems	-0.43 (-0.87 to -0.01)	0	0.047	-1.64 (-2.45 to -0.83)	86.8	<0.0001

Study 2 Alyasin S (2016)

Details

Study type	Randomised controlled trial
Country	Iran
Recruitment period	April to July 2014
Study population and number	n=62 (31 intranasal phototherapy, 31 placebo) Patients with moderate to severe persistent allergic rhinitis.
Age and sex	Mean age 37 years (range 25 to 60); 63% (39/62) female
Patient selection criteria	<p>Inclusion criteria included: age 25 to 60 years; history or diagnosis of allergic rhinitis for at least 2 years before first clinic visit; allergy verified by a positive skin-prick test or specific IgE determination within 2 years before first visit, or at first visit; symptoms not responsive to previous local or systemic antihistamines or corticosteroids or patients did not want or could not have these treatments because of side effects or other reasons; moderate to severe disease, where the global severity score was more than 6 out of the 10-point scale in the last 3 days before enrolment.</p> <p>Exclusion criteria included: known light-induced skin disease (photodermatitis); ongoing fungal, viral or bacterial respiratory infection; abnormalities in the nose (such as severe septum deviation or polyps) that disturb phototherapeutical treatment, as judged by the investigator; drug contraindication (photosensitive drugs); patients younger than 25 years; pregnant women; patients unable to give informed consent; patients with nasopharyngeal tumours.</p> <p>The wash-out period was 4 weeks for systemic corticosteroids, 2 weeks for intranasal cromolyn sodium and intranasal corticosteroids, 3 days for intranasal decongestants, 1 week for intranasal or systemic antihistamines, and 5 years for immunotherapy.</p>
Technique	<p>Rhinolight (Rhinolight Ltd., Hungary) was used for intranasal phototherapy, which emits a combination of UVB (5%), UVA (25%) and visible light (70%). Treatments lasted 2 to 3 minutes. Each nasal cavity was irradiated 3 times a week for 2 weeks with increasing doses (from 1.6 J/cm² to 2.4 J/cm²).</p> <p>For the control group, a filter was used to cut out UV light, leaving only visible light.</p> <p>The only rescue medication allowed was cetirizine (10 mg/day).</p>
Follow-up	12 weeks
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: No losses to follow-up were reported. 69 patients were originally enrolled into the study: 34 in the treatment group and 35 in the placebo group. 4 patients in the placebo group withdrew from the study because of occupational or familial problems. In the treatment group, 3 patients were excluded from the study, 1 because of photosensitivity, and 2 because of severe nasal mucosal oedema and bleeding.

Study design issues: Prospective, randomised, single-blind, placebo-controlled trial. In the control group, patients were treated with visible light alone as a placebo. All patients were enrolled after the beginning of the pollen season. Each patient kept a diary of daily symptoms on a scale of 0 to 3 (0 indicating no symptoms and 1, 2 and 3 indicating mild, moderate and severe symptoms respectively). Scores were assessed by physicians other than the investigators. The efficacy of treatment was assessed by clinical findings, total nasal symptom scores (TNSS), global severity scores (GSS), and Rhinoconjunctivitis Quality of Life Questionnaires (RQLQ) scores.

Study population issues: There were no statistically significant differences in baseline demographic data between the 2 groups.

Key efficacy and safety findings

Efficacy						Safety		
Number of patients analysed: 62 (31 intranasal phototherapy versus 31 placebo)						Side-effects, number of patients		
Mean dose of cetirizine used during the study (3 months):							Intranasal photo-therapy	Placebo
<ul style="list-style-type: none"> Phototherapy group=261.4±98.9 mg Control group=335.5±60.8 mg, p<0.001 						Dryness	4	0
Symptom scores (mean±standard deviation)						Severe mucosal oedema	1	0
	Intranasal phototherapy		Placebo		p value*	Severe mucosal dryness	2	0
Parameter	Baseline	12 week follow-up	Baseline	12 week follow-up		Headache	2	0
Rhinorrhoea	2.74±0.682	1.32±1.013	2.58±0.672	2.65±0.661	<0.001	Nasal burning sensation	2	0
Sneezing	2.61±0.667	1.03±0.795	2.23±0.805	2.26±0.815	<0.001	The nasal mucosal dryness, oedema and burning sensation were controlled by emollients. The headache resolved within 2 weeks without any treatment.		
Nasal obstruction	2.10±0.831	0.97±1.048	2.19±0.703	2.23±0.762	<0.001			
Nasal itching	1.87±0.991	0.65±0.839	1.74±0.930	1.87±0.922	<0.001			
Total Nasal Symptom Score (TNSS)	9.29±1.901	3.87±2.680	8.74±1.770	9.00±2.000	<0.001			
Conjunctivitis	1.81±1.078	0.77±0.920	1.58±0.765	1.71±0.864	<0.001			
Palate itching	1.48±0.962	0.74±0.682	1.10±0.944	1.16±1.003	<0.001			
Global Severity Score (GSS)	12.65±3.14	5.39±3.730	11.10±2.37	11.55±2.87	<0.001			
* between group comparison								
All comparisons between baseline and 12-week scores were statistically significant in the phototherapy group (p<0.001).								
There were statistically significant improvements from baseline in TNSS and GSS after 2 weeks, 6 weeks and 12 weeks of treatment in the phototherapy group (p<0.001). There were no statistically significant differences in the placebo group.								
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores (mean±standard deviation)								
RQLQ domain	Intranasal phototherapy		Placebo		p value*			
	Baseline	12 week follow-up	Baseline	12 week follow-up				
Emotional function	3.84±1.393	1.69±1.194	3.55±1.410	3.55±1.179	<0.001			
Eye symptoms	2.81±1.078	1.74±0.965	2.58±0.765	2.71±0.864	<0.001			
Nasal symptoms	4.74±0.930	1.68±1.222	4.42±0.807	4.84±0.779	<0.001			
Non-eye and nose symptoms	3.0±0.775	1.39±0.715	2.97±0.893	3.45±1.150	<0.001			
Limited activity	2.84±0.680	1.10±0.790	3.06±1.181	3.06±1.389	<0.001			
Practical problems	2.68±0.871	1.16±0.860	2.58±1.119	2.71±1.039	<0.001			
Sleep quality	2.32±0.748	1.00±0.730	3.16±1.241	3.10±1.165	<0.001			
Total RQLQ score	22.22±2.96	9.74±3.99	22.32±2.86	23.41±3.12	<0.001			
* between group comparison of follow-up scores								
All comparisons between baseline and 12-week scores were statistically significant in the phototherapy group (p<0.001). There were no statistically significant differences in the placebo group.								
Abbreviations used: GSS, global severity score; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; TNSS, total nasal symptom score								

Study 3 Bella Z (2017)

Details

Study type	Randomised controlled trial
Country	Hungary
Recruitment period	November to March (year not reported)
Study population and number	n=25 (14 intranasal phototherapy, 11 placebo) Patients with moderate or severe persistent allergic rhinitis.
Age and sex	Mean 35 years; 28% (7/25) female
Patient selection criteria	Patients with moderate or severe persistent allergic rhinitis (symptom scores of 4 or more on a visual analogue scale of 0 to 10 for at least 2 symptoms, 1 of which was either nasal obstruction or rhinorrhoea, during 4 consecutive days). Allergy to house dust mite and mould was confirmed with a specific IgE or prick test. Patients who were taking drugs (such as photosensitisers, non-steroidal anti-inflammatory drugs, and antibiotics) were excluded. Washout periods were: 1 month for nasal or systemic corticosteroids, 2 weeks for antihistamine, 2 weeks for oral or intranasal decongestants, 1 month for leukotriene antagonists.
Technique	Rhinolight (Rhinolight Ltd., Hungary) was used for intranasal phototherapy, which emits a combination of UVB (5%), UVA (25%) and visible light (70%). Treatments lasted 2 to 3 minutes and there were 13 treatment sessions over a 6 week period. The dose ranged from 1.6 to 2.7 J/cm ² /nostril/treatment. For the placebo group, low-intensity visible light was given, using the same device with a special light filter.
Follow-up	1 month after the final treatment session
Conflict of interest/source of funding	None

Analysis

Follow-up issues: An additional 9 patients were enrolled into the study and randomised (7 in the phototherapy group and 2 in the placebo group), but they dropped out because of poor compliance or withdrawal. Data from these patients were not included in the analyses.

Study design issues: Prospective, randomised, double-blind, placebo-controlled trial. The primary endpoints were changes in clinical symptoms, nasal inspiratory peak flow parameters (PNIF), smelling ability, and the mucociliary function. Secondary endpoints were the quantity of oral antihistamine taken during the study and an assessment of the duration of effect. The follow-up was based in the nasal symptoms collected in the patient's diary and the PNIF changes. The standardised Smell Threshold test developed by the University of Pennsylvania was used to assess smelling ability. The mucociliary function was assessed by a saccharin test. Nasal mucosal sampling was also done in 18 patients (11 in the phototherapy group and 7 in the placebo group). The aim of this was to determine expression of the intracellular adhesion molecule 1 (ICAM-1), a marker of nasal mucosal inflammation in allergic rhinitis. Enrolment, randomisation and follow-up visits took place in a different department to the phototherapy. The method of randomisation is not described.

Study population issues: Baseline characteristics of the 2 groups are not described in detail.

Other issues: The treatment period of the study overlapped with a flu pandemic, and more than a quarter of randomised patients had to be excluded because of upper-airway infection.

Key efficacy and safety findings

Efficacy							Safety
Number of patients analysed: 25 (14 intranasal phototherapy, 11 placebo)							<p>There were no severe side effects.</p> <p>3 patients in the phototherapy group had mild dryness of the nasal mucosa, which resolved after treatment with nasal drops.</p> <p>2 patients in each group had mild nosebleed when blowing the nose; this was not directly treatment related and did not need any treatment.</p> <p>Temporary and spontaneously resolving nasal pain was reported by 3 patients in the phototherapy group and 2 in the placebo group.</p> <p>Headache and diarrhoea occurred in 1 patient in each group.</p>
Mean changes in nasal symptoms and nasal inspiratory peak flow parameters (PNIF) at the end of the treatment phase (week 6) and the follow-up (week 10) as compared with the scores before treatment							
	Week 6			Week 10			
	Intranasal phototherapy	Placebo	p	Intranasal phototherapy	Placebo	p	
<i>Morning symptoms</i>							
Sneezing	-2.16	-1.44	0.03	-1.97	-1.43	0.12	
Itching	-2.04	-1.95	0.78	-2.40	-1.47	0.00	
Rhinorrhoea	-2.46	-1.38	0.00	-3.16	-1.75	0.00	
Obstruction	-2.24	-1.52	0.02	-3.16	-1.99	0.00	
Total nasal score	-8.84	-6.30	0.02	-10.62	-6.66	0.00	
PNIF	19.31	6.79	0.00	27.28	11.82	0.00	
<i>Evening symptoms</i>							
Sneezing	-2.36	-1.57	0.02	-2.35	-1.72	0.06	
Itching	-2.28	-1.95	0.32	-2.73	-1.53	0.00	
Rhinorrhoea	-2.07	-1.54	0.10	-2.93	-1.99	0.00	
Obstruction	-1.69	-1.47	0.49	-2.47	-1.91	0.08	
Total nasal score	-8.38	-6.54	0.08	-10.47	-7.19	0.00	
PNIF	20.85	11.56	0.00	28.14	13.30	0.00	
Mucociliary function and smelling ability							
The measured mucociliary function and quantitative smell threshold data showed considerable variation and there were no statistically significant changes, either in time or in intergroup comparisons.							
Mean antihistamine (levocetirizine) consumption during the study							
<ul style="list-style-type: none"> • Phototherapy=4.21 tbl/person/treatment cycle • Placebo=3.45 tbl/person/treatment cycle (p=not significant) 							
Intracellular adhesion molecule I (ICAM-I) positive cells							
The number of ICAM-I positive cells was lower in the phototherapy group than in the placebo group, but the difference did not reach statistical significance.							
Abbreviations used: ICAM-I, intracellular adhesion molecule I; PNIF, nasal inspiratory peak flow parameters							

Study 4 Tatar EC (2013)

Details

Study type	Randomised controlled trial
Country	Turkey
Recruitment period	December 2009 to March 2010
Study population and number	n=65 (32 intranasal phototherapy and medical treatment, 35 medical treatment alone) Patients with moderate to severe persistent allergic rhinitis.
Age and sex	Mean 31 years (phototherapy and medical treatment), 33 years (medical treatment alone) 63% (41/65) female
Patient selection criteria	Patients with a history of at least 2 years of moderate to severe persistent allergic rhinitis. The diagnosis was confirmed with positive skin tests, and all of the patients had house dust mite allergy. All of the patients had used antihistamines or intranasal steroids previously but not within 2 weeks of the start of the study. Exclusion criteria: patients with nasal polyps, nasal septal deviation, nasopharyngeal pathologies, asthma, acute respiratory infections.
Technique	Intranasal phototherapy was done with a combination of UV and visible light. It was applied twice a week for three weeks. Medical treatment consisted of topical mometasone fumate and oral levocetirizine for a month.
Follow-up	3 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective, randomised controlled trial. A randomisation list was created using simple randomisation. An investigator who was blinded to the study treatment allocated patients to each group using the randomisation list. The Rhinoconjunctivitis Quality of Life questionnaire (RQLQ) was used to assess symptom scores and visual analogues scores were obtained for the severity of allergic rhinitis.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups.

Key efficacy and safety findings

Efficacy								Safety
Number of patients analysed: n=65 (32 intranasal phototherapy and medical treatment, 33 medical treatment only)								<p>Dryness was reported in 34 patients during the study but it was not severe enough to stop treatment.</p> <p>Temporary anosmia was reported in 1 patient, which resolved within 1 week. The authors noted that this was probably because of oedema of the nasal mucosa. The article did not report which treatment group this patient was in.</p>
Symptom scores at baseline and at 3 month follow-up (mean)								
Parameter	Intranasal phototherapy and medical treatment			Medical treatment only			p value (between groups at follow-up)	
	Baseline	Follow-up	p value	Baseline	Follow-up	p value		
Nasal obstruction	2.58	1.21	<0.001	2.53	2.00	0.003	0.003	
Nasal itching	2.52	1.00	<0.001	2.47	1.84	0.001	0.006	
Rhinorrhoea	2.45	0.97	<0.001	2.50	1.84	<0.001	0.003	
Sneezing	2.70	1.13	<0.001	2.75	2.28	0.001	<0.001	
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores (mean)								
RQLQ domain	Intranasal phototherapy and medical treatment			Medical treatment only			p value (between groups)	
	Baseline	3 months	p value	Baseline	3 months	p value		
Emotional function	4.84	1.83	<0.001	4.96	2.57	<0.001	0.006	
Eye symptoms	4.80	1.63	<0.001	4.87	2.43	<0.001	0.015	
Nasal symptoms	5.36	2.35	<0.001	5.04	3.41	0.001	<0.001	
Non eye non nasal symptoms	4.92	2.07	<0.001	5.27	2.96	0.001	0.002	
Limited activity	4.92	2.31	<0.001	5.00	3.27	<0.001	0.001	
Practical problems	5.15	2.31	0.001	5.04	1.93	0.002	0.003	
Sleep quality	4.88	1.97	<0.001	4.95	2.71	<0.001	0.008	
Mean visual analogue scores								
Follow-up	Intranasal phototherapy and medical treatment		Medical treatment only		p value between groups			
	Mean	p value	Mean	p value				
Baseline	8.88		8.41		0.051			
1 month	2.15	<0.001	4.63	<0.001	0.001			
3 months	5.42	<0.001	6.31	0.001	0.016			
Abbreviations used: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire								

Study 5 Cingi C (2010) – also included in the meta-analysis by Cho HK et al. (study 1)**Details**

Study type	Randomised controlled trial
Country	Turkey
Recruitment period	Year not reported; study was done out of the pollen season
Study population and number	n=79 (41 intranasal phototherapy, 38 placebo) Patients with moderate to severe persistent allergic rhinitis.
Age and sex	Mean age not reported but paper states that there was no difference between the 2 groups ($p=0.392$). 63% (50/79) female
Patient selection criteria	Patients with a history of at least 2 years of moderate to severe persistent allergic rhinitis that was not controlled by anti-allergy drugs. Positive skin test results and an elevated level of specific IgE antibody confirmed the diagnosis. Exclusion criteria: significant nasal structural abnormalities, asthma, upper or lower respiratory tract infection within 4 weeks or nasopharyngeal pathology diagnosed by endoscopy. Patients who had used any of the following drugs were excluded: systemic corticosteroids within 4 weeks, topical corticosteroids within 2 weeks, membrane stabilisers within 2 weeks, antihistamines within 1 week, nasal decongestants within 3 days, or immunotherapy within 5 years of the start of the study.
Technique	Rhinolight (Rhinolight Ltd., Hungary) was used for intranasal phototherapy, which emits a combination of UVB (5%), UVA (25%) and visible light (70%). Treatment times increased from 2 to 3 minutes (dose increased from 1.6 J/cm ² to 2.4 J/cm ²) and there were 3 sessions a week for 2 weeks. In the placebo group, a special filter was used so that only visible light was emitted. No rescue medication was allowed.
Follow-up	1 month after the end of treatment
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective, randomised, single-blind, placebo-controlled trial. Computer-generated randomisation was used to assign patients to each group. The main outcome was the total nasal symptom score (TNSS), assessed by the patient. Nasal symptoms included in the study were nasal obstruction, nasal itching, nasal discharge and sneezing. All symptoms were graded on a 4-point scale using the following system: 0, none; 1, mild (symptoms are present but not particularly bothersome); 2, moderate (symptoms that are bothersome but do not interfere with daily activities); and 3, severe (symptoms that are bothersome and interfere with daily activities or disturb sleep).

Study population issues: Baseline characteristics of the 2 groups are not described in detail.

Other issues: The most common allergens that the patients were sensitive to were mites and pollens.

Key efficacy and safety findings

Efficacy							Safety
Number of patients analysed: 79 (41 intranasal phototherapy, 38 placebo)							<p>Dryness was the only side effect reported in the phototherapy group.</p> <p>The authors noted that they now routinely advise patients to use a seawater gel during the treatment period, to prevent dryness.</p>
Total nasal symptom scores (mean±standard deviation)							
Symptom	Intranasal phototherapy			Placebo			
	Baseline	After treatment	p	Baseline	After treatment	p	
Nasal obstruction	2.64±0.12	0.85±0.16	<0.001	2.35±0.12	1.13±0.18	<0.01	
Nasal itching	2.68±0.14	0.75±0.14	<0.001	2.55±0.12	1.01±0.16	<0.01	
Nasal discharge	2.48±0.10	0.45±0.11	<0.001	2.65±0.13	1.06±0.12	<0.01	
Sneezing	2.56±0.16	0.5±0.11	<0.001	2.38±0.12	1.02±0.14	<0.01	
Total nasal symptom scores decreased in both groups but the decrease in the phototherapy group was statistically significant when compared with placebo (p<0.001).							

Study 6 Albu S (2013) – also included in the meta-analysis by Cho HK et al. (study 1)**Details**

Study type	Randomised controlled trial
Country	Romania
Recruitment period	March to August 2009
Study population and number	n=77 (39 intranasal phototherapy, 38 antihistamine [azelastine hydrochloride nasal spray]) Patients with moderate to severe grass-pollen induced seasonal allergic rhinitis.
Age and sex	Mean 31 years (phototherapy), 34 years (antihistamine), p=0.15 62% (48/77) female
Patient selection criteria	Patients with a history of at least 2 years of moderate to severe grass pollen-induced seasonal allergic rhinitis poorly controlled by anti-allergy drugs. The diagnosis was confirmed by positive skin prick tests and an elevated level of specific IgE antibody. Exclusion criteria: patients who smoked; patients with severe autoimmune disease or neoplastic disease; pregnancy; patients who had used any of the following drugs: leukotrienes or beta-mimetic drugs, systemic corticosteroids within 4 weeks, topical corticosteroids within 2 weeks, membrane stabilisers within 2 weeks, antihistamines within 1 week, nasal decongestants within 3 days, or immunotherapy within 5 years before the beginning of the study. Patients with significant nasal structural deformities or perennial rhinitis, acute or chronic rhinosinusitis or nasal polyps were also excluded.
Technique	Rhinolight (Rhinolight Ltd., Hungary) was used for intranasal phototherapy, which emits a combination of UVB (5%), UVA (25%) and visible light (70%). There were 3 sessions a week for 2 weeks and the dose was increased from 1.6 J/cm ² to 2.4 J/cm ² . The control treatment was azelastine hydrochloride nasal spray, 2 sprays per nostril, once daily with a total dose of 1.1 mg, and continued consistently until the last visit. No rescue medication was allowed during the study period.
Follow-up	End of treatment period (2 weeks)
Conflict of interest/source of funding	None

Analysis

Follow-up issues: 80 patients were originally randomised: 1 patient in the phototherapy group stopped treatment because of a modified holiday schedule and 2 patients in the control group dropped out because of upper respiratory tract infections.

Study design issues: Prospective, randomised, open controlled study. Patients were assigned to the treatment groups according to the date of application. Each patient kept a diary of symptoms on a scale of 0 to 3 (0 indicating no symptoms and 1, 2, 3 indicating mild, moderate and severe symptoms respectively) for nasal obstruction, nasal itching, rhinorrhoea, and sneezing during the treatment. The total nasal symptom score (TNSS) was also calculated. Quality of life was assessed using the Romanian validated form of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), which has 28 questions in 7 domains (activity limitation, sleep problems, nose symptoms, eye symptoms, non-nose or eye symptoms, practical problems and emotional function). Nasal airflow was measured objectively using active anterior rhinomanometry. Sample size was estimated considering the power of the study to be 80% with 5% level of significance. A mean of 3.55 and a standard deviation of 1.05 for RQLQ were used for the calculations and a change in score of at least 0.5 was considered to be of clinical significance. A sample size of 36 in each group was calculated, which was raised to 40 to allow for drop-outs.

Study population issues: There were no statistically significant differences in the 2 groups with regard to age, disease duration or clinical scores at baseline.

Key efficacy and safety findings

Efficacy								Safety
Number of patients analysed: n=77 (39 intranasal phototherapy, 38 antihistamine [azelastine hydrochloride nasal spray])								<p>The only side effect in the intranasal phototherapy group was dryness of the nasal mucosa, which occurred in all patients. This was controlled by emollients. All patients except 1 considered the dryness to be mild.</p> <p>The only adverse event in the antihistamine group was a bitter taste, reported by 5 patients.</p>
Symptom scores at baseline and after 14 days of treatment (mean±standard deviation)								
Parameter	Intranasal phototherapy			Antihistamine therapy			p value (between groups)	
	Baseline	Day 14	p value	Baseline	Day 14	p value		
Nasal obstruction	2.75±0.70	0.91±0.54	<0.00001	2.51±0.83	1.35±0.91	<0.00001	0.038	
Nasal itching	2.77±0.75	0.67±0.82	<0.00001	2.56±0.87	0.95±0.98	<0.00001	0.23	
Nasal discharge	2.62±0.81	0.85±0.47	<0.00001	2.43±0.91	1.05±0.72	<0.00001	0.25	
Sneezing	2.85±0.72	0.95±0.52	<0.00001	2.42±0.65	0.71±0.55	<0.00001	0.09	
Total nasal symptom score	8.87±2.43	3.75±2.35	<0.00001	8.42±1.92	4.15±2.86	<0.00001	0.6	
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores (mean±standard deviation)								
RQLQ domain	Intranasal phototherapy			Antihistamine therapy			p value (between groups)	
	Baseline	Day 14	p value	Baseline	Day 14	p value		
Limited activity	3.81±1.78	1.70±0.90	<0.0001	3.47±1.55	1.91±0.95	<0.0001	0.4	
Sleep	3.12±1.44	1.85±1.12	<0.0001	3.58±1.63	2.45±1.20	0.0009	0.05	
Non-hay fever symptoms	2.05±1.15	1.10±0.75	<0.0001	2.45±1.42	1.35±0.65	<0.0001	0.2	
Practical problems	2.95±1.65	1.45±0.85	<0.0001	3.15±1.40	1.35±0.75	<0.0001	0.7	
Nasal symptoms	4.10±2.20	1.75±1.10	<0.0001	3.85±2.10	2.30±1.95	<0.0001	0.047	
Eye symptoms	1.31±0.77	0.70±0.60	0.0002	1.45±0.63	0.55±0.40	<0.0001	0.6	
Emotional function	1.88±1.12	0.80±0.55	<0.0001	1.90±1.42	0.60±0.45	<0.0001	0.7	
Overall score	3.65±1.39	1.37±0.74	<0.0001	3.80±1.75	1.58±0.85	<0.0001	0.2	
Mean total nasal resistance (Pa/cm³/s)								
	Intranasal phototherapy			Antihistamine therapy				
Baseline	0.42±0.18			0.45±0.15				
Day 14	0.36±0.16			0.37±0.12				
p value	0.12			0.11				

Abbreviations used: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire

Study 7 Cingi C (2009) – also included in the meta-analysis by Cho HK et al. (study 1)

Details

Study type	Case series
Country	Turkey
Recruitment period	Year not reported; study was done out of the pollen season
Study population and number	n=100 Patients with moderate to severe allergic rhinitis.
Age and sex	Mean 35 years (range 18 to 52); 69% (69/100) female
Patient selection criteria	Patients with a history of at least 2 years of moderate to severe allergic rhinitis that was not controlled by anti-allergy drugs. Positive skin tests confirmed the diagnosis. Exclusion criteria: patients with significant nasal structural abnormalities, asthma, an upper or lower respiratory tract infection within 4 weeks or nasopharyngeal pathology diagnosed by endoscopy. Patients who had used any of the following drugs were also excluded: systemic corticosteroids within 4 weeks, topical corticosteroids within 2 weeks, membrane stabilisers within 2 weeks, antihistamines within 1 week, nasal decongestants within 3 days or immunotherapy within 5 years before the beginning of the study.
Technique	Rhinolight (Rhinolight Ltd., Hungary) was used for intranasal phototherapy, which emits a combination of UVB (5%), UVA (25%) and visible light (70%). There were 3 sessions a week for 2 weeks, increasing from 2 minutes for the first treatment to 3 minutes for the final treatment, and the dose was increased from 1.6 J/cm ² to 2.4 J/cm ² . No rescue medication was allowed during the study period.
Follow-up	3 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: No losses to follow-up were described.

Study design issues: Prospective case series with consecutive patients. The signs and symptoms of allergic rhinitis were scored jointly by the investigator and patient. The efficacy was assessed with clinical findings, total nasal symptom score (TNSS), and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). The same physicians recorded the clinical findings of lower turbinate colour and turbinate congestion before and after the treatment. Rating scales from 0 to 3 were used (0=none, 1=mild, 2=moderate and 3=severe).

Key efficacy and safety findings

Efficacy						Safety
Number of patients analysed: 100						No safety outcomes were reported.
Symptom scores						
There was a statistically significant difference between the scores for nasal discharge, nasal obstruction, sneezing, nasal itching and turbinate oedema before and after intranasal phototherapy ($p < 0.001$). There were no statistically significant differences between the results at 1 and 3 month follow-up.						
Mean results of all variables in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).						
Domain of RQLQ	Before treatment	1 month follow-up	3 month follow-up	p value (before treatment compared to after treatment)	p value (difference between 1 and 3 month follow-up)	
Limited activities	4.18	1.33	2.55	<0.05	<0.05	
Sleep	3.15	1.75	2.34	<0.05	<0.05	
Non-hay fever symptoms	2.40	1.04	1.25	<0.05	<0.05	
Practical problems	3.02	1.27	1.97	<0.05	<0.05	
Nasal symptoms	4.20	1.60	2.56	<0.05	<0.05	
Eye symptoms	1.17	0.64	0.75	<0.05	Not significant	
Emotional function	2.13	0.96	1.44	<0.05	<0.05	
There was no association with age or gender and RQLQ variable results.						
Abbreviations used: RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire						

Study 8 Emberlin JC (2009) – also included in the meta-analysis by Cho HK et al. (study 1)**Details**

Study type	Randomised controlled trial
Country	UK
Recruitment period	October 2008 to January 2009
Study population and number	n=101 (50 intranasal phototherapy, 51 placebo) Patients with hay fever.
Age and sex	Mean 27 years (range 18 to 65); 42% (42/101) female
Patient selection criteria	<p>Patients with a history of hay fever in the grass pollen season during both of the last 2 years with symptoms that have needed treatment or remedies from pharmacies or on prescription; positive skin prick test result for grass done within the last 2 years; age 18 years or over.</p> <p>Exclusion criteria included: history of asthma; people with nasal deformities leading to obstruction; people with perennial rhinitis or nasal polyposis; pregnant or lactating women; and other adverse medical conditions such as sinusitis, cardiac, renal or hepatic disease. In addition, the following exclusions were applied just before the pollen challenge: patients with upper respiratory viral infections; patients who had used oral antihistamines in the previous week or corticosteroids in the last 30 days; patients who appeared to have or reported any symptoms of illness; patients who had not used the device for the correct time; patients who had symptoms of cold or rhinitis lasting more than 2 days or flu during the therapy time or on the day of the trial. Patients with occasional extra-seasonal rhinitis were not excluded from joining the trial but they were excluded if they were having such symptoms during the use of the device or at the time of the pollen challenge.</p>
Technique	<p>The allergy reliever SN-206 (Lloyds Pharmacy) device was used for intranasal phototherapy, which emits infrared light (652 nm and 940 nm), delivering 0.54 joules/cm² per 3-minute cycle.</p> <p>The placebo devices looked like the active devices but emitted low intensity visible light that had a red tinge because of coloured plastic covers. Instead of delivering the light high into the nostrils, the light was emitted at the base of the probe beneath the nostrils. The placebo and active devices were in identical boxes, labelled A and B, and were given to the patients unopened.</p> <p>Patients were told to use the device for 3 minutes 3 times a day, 5 to 6 hours apart for 14 days before the pollen challenge. An allergen challenge of grass pollen was then delivered to the nostrils.</p>
Follow-up	150 minutes after pollen challenge
Conflict of interest/source of funding	The trial and publication of the article were sponsored by Lloyds Pharmacy. The company had no role in designing or conducting the trial, or drafting, writing or reviewing the manuscript.

Analysis

Follow-up issues: An additional 11 patients were randomised but did not complete the trial: 8 patients did not keep the appointment for the challenge test or could not attend on a suitable date, 1 stopped using the device, 1 had symptoms of a severe viral infection and 1 had a previously undisclosed history of sinusitis.

Study design issues: Randomised, double-blind, placebo-controlled trial. Patients were assigned to a treatment group by stratified random sample based on age range, gender and severity of reported symptoms. The allocations were made based on throw of a dice. The identities of the 2 groups were blinded until after the trial. The primary outcome measures were observed severity scores for symptoms (sneezing, running nose and running eyes) and the amount of eosinophil cationic proteins (ECPs) present in nasal secretions. The secondary outcome measures were symptom scores reported by the patient (itching of nose, itching of throat, itching of mouth or palate, itching of eyes), nasal peak inspiratory flow and nasal peak expiratory flow. Compliance in the use of the device was monitored by diary cards and by interview with the patients before the pollen challenge.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups.

Key efficacy and safety findings

Efficacy										Safety
Number of patients analysed: 101 (50 intranasal phototherapy, 51 placebo)										No safety outcomes were reported.
Symptom scores										
	Intranasal phototherapy				Placebo					
	Total score	Mean (SD)	Range	CI	Total score	Mean (SD)	Range	CI	p value	
Sneezing	182	3.6 (3.6)	0 to 15	0.9	280	5.5 (4.4)	0 to 18	1.2	≤0.05	
Itching eyes	117	2.3 (4.2)	0 to 20	1.2	152	3.0 (3.5)	0 to 13	1.0	Not significant	
Running eyes	88	1.8 (3.4)	0 to 17	0.9	163	3.2 (3.2)	0 to 11	0.9	≤0.05	
Itching nose	407	8.1 (7.4)	0 to 38	2.1	527	10.3 (2.6)	0 to 22	0.7	Not significant	
Running nose	494	9.9 (7.1)	0 to 35	1.9	697	13.7 (2.3)	0 to 29	0.6	≤0.05	
Itching throat	323	6.5 (7.4)	0 to 30	2.1	396	7.8 (8.7)	0 to 28	2.4	Not significant	
Itching mouth	164	3.3 (6.0)	0 to 30	1.7	297	5.8 (8.0)	0 to 25	2.2	≤0.05	
Overall total	1,775	35.5 (24.8)	3 to 142	6.9	2,512	49.3 (26.2)	13 to 127	7.2	≤0.01	
Percentage difference in scores between intranasal phototherapy and placebo										
	Total scores active/placebo				Total mean active/placebo					
Sneezing					35					
Itching eyes					23					
Running eyes					46					
Itching nose					23					
Running nose					29					
Itching throat					18					
Itching mouth					45					
Eosinophil cationic proteins (ECPs)										
There was a wide variance in both groups. No statistically significant differences were found either when comparing the pattern of results for the various times after challenge or when comparing the individual results between the 2 groups at specific sample times.										
Nasal flow readings										
There were no statistically significant differences in the nasal flow readings between the groups.										
Abbreviations used: CI, confidence interval; SD, standard deviation										

Study 9 Neuman I (1997) – also included in the meta-analysis by Cho HK et al. (study 1)**Details**

Study type	Randomised controlled trial
Country	Israel
Recruitment period	Early summer months (year not reported)
Study population and number	n=79 (50 intranasal phototherapy, 29 sham illumination) Patients with perennial allergic rhinitis (results for an additional 11 patients with nasal polyposis were also reported separately)
Age and sex	<ul style="list-style-type: none"> Intranasal phototherapy: mean 26.5 years (range 12 to 68); 60% (30/50) female Sham: mean 24 years (range 12 to 52); 38% (11/29) female
Patient selection criteria	<p>All patients had daily symptoms despite antihistamines and local corticosteroid spray treatments. The diagnosis of allergic rhinitis was based on definite symptoms of nasal itching, rhinorrhoea, sneezing, nasal obstruction or mouth breathing, as well as positive reactions to epicutaneous tests to perennial inhalant antigens. Skin prick testing was done for house dust mite, cockroach, moulds, feathers, grass pollen, weed pollens, sage pollen, and local tree pollens.</p> <p>Exclusion criteria included: severe deviation of the nasal septum causing bilateral nasal obstruction; purulent postnasal drip flowing from an oedematous and hyperaemic infundibulum or with streaks of purulent discharge flowing across the Eustachian tube orifice, identified by endoscopy; patients who were recovering from an upper respiratory tract infection or had used nasal or oral corticosteroids less than 30 days before the start of the study. Patients in whom the endoscopic examination was equivocal and CT revealed sinus disease were also excluded from the study.</p>
Technique	<p>The device used for intranasal phototherapy was a Bionase unit (Amcor Ltd., Israel), which emits red light at 660±5 nm. A push button switch on the control box activates the 2 light emitting diode probes for 4.4 minutes, during which time 1 Joule of light energy is delivered. Patients were told to place the probes into their nostrils as deeply as possible and then press the button. The device was used 3 times a day for 14 consecutive days.</p> <p>Bionase devices with internally disconnected light emitting probes were used for sham illumination in the placebo group.</p> <p>No medications were allowed during the 2 weeks of phototherapy.</p>
Follow-up	Patients were followed up for approximately 1 year but detailed results are only given for the 2-week follow-up, at the end of the treatment period.
Conflict of interest/source of funding	The research was supported in part by Amcor Ltd., Israel.

Analysis

Follow-up issues: The paper states that patients were followed up for approximately 1 year but no details are given with regard to completeness of follow-up.

Study design issues: Randomised double-blind, placebo-controlled clinical trial. The method of randomisation is not described. Patients recorded their symptoms daily in the evening throughout the study period. At the end of the 2-week treatment, an objective assessment of rhinitis symptoms was done by videotaped endoscopy. The specialist who did the endoscopy was not informed of which treatment group the patient was in. The videotapes of each patient before and after treatment were compared and evaluated by the authors at the end of treatment.

Study population issues: The duration of nasal symptoms ranged from 1 to 16 years (mean 5 years). 20 (40%) patients in the intranasal phototherapy group and 12 (41%) patients in the control group had concomitant asthma. The authors state that there were no significant differences in sex or age between the 2 groups.

Key efficacy and safety findings

Efficacy				Safety		
Number of patients analysed: 79 (50 intranasal phototherapy versus 29 sham)				The authors stated that there were no adverse side effects of phototherapy after 1 year follow-up.		
Estimated severity of symptoms before treatment, n (%)						
Symptom	Severity	Intranasal phototherapy	Sham			
Nasal obstruction	Normal	1 (2%)	0 (0%)			
	Mild	2 (4%)	3 (10%)			
	Moderate	20 (40%)	12 (41%)			
	Severe	27 (54%)	14 (48%)			
Rhinorrhoea	Normal	2 (4%)	1 (3%)			
	Mild	6 (12%)	5 (17%)			
	Moderate	16 (32%)	10 (35%)			
	Severe	26 (52%)	13 (45%)			
Oedema of middle turbinate	Normal	19 (38%)	12 (41%)			
	Mild	25 (50%)	14 (48%)			
	Moderate	3 (6%)	2 (7%)			
	Severe	3 (6%)	1 (3%)			
Nasal itching	Normal	13 (26%)	4 (14%)			
	Mild	32 (64%)	18 (62%)			
	Moderate	5 (10%)	7 (24%)			
	Severe	0 (0%)	0 (0%)			
Headache	Normal	26 (52%)	18 (62%)			
	Mild	24 (48%)	10 (35%)			
	Moderate	0 (0%)	0 (0%)			
	Severe	0 (0%)	0 (0%)			
Cough (postnasal drip)	Normal	21 (42%)	16 (55%)			
	Mild	20 (40%)	8 (28%)			
	Moderate	8 (16%)	5 (17%)			
	Severe	1 (2%)	0 (0%)			
Number (%) of patients with improvement or deterioration after intranasal phototherapy or sham illumination						
	Intranasal phototherapy		Sham			
	Subjective	Objective	Subjective	Objective		
No improvement	13 (26%)	15 (30%)	21 (72.5%)	23 (79%)		
Mild improvement	25 (50%)	22 (44%)	5 (17%)	6 (21%)		
Marked improvement	11 (22%)	13 (26%)	2 (7%)	0 (0%)		
Deterioration	1 (2%)	0 (0%)	1 (3.5%)	0 (0%)		
Patients with accompanying septal deviation reported a lower rate of improvement.						
Improvement in individual symptoms after intranasal phototherapy or sham illumination						
	Intranasal phototherapy		Sham		p value	
	Subjective	Objective	Subjective	Objective	Subjective	Objective
Nasal obstruction	80% (39/49)	61% (30/49)	31% (9/29)	21% (6/29)	0.016	-
Rhinorrhoea	81% (39/48)	65% (31/48)	14% (4/28)	7% (2/28)	0.0004	-
Oedema of middle turbinate	-	48% (15/31)	-	12% (2/17)	-	0.0007
Nasal itching	76% (28/37)	-	32% (8/25)	-	0.019	-
Headache	70% (17/24)	-	20% (2/10)	-	0.023	-
Cough (postnasal drip)	69% (20/29)	-	21% (3/13)	-	0.004	-
Overall					0.021	0.0006

The authors reported that phototherapy had no effect on patients with nasal polyposis.	
The authors noted that the benefit of treatment continued throughout the 1 year follow-up, but no results were presented.	

Validity and generalisability of the studies

- There is 1 RCT from the UK⁸.
- Most of the studies used subjective outcome measures.
- The timing of a study may have an impact on the efficacy outcomes, for example if it is done during the pollen season.
- Some studies only included patients with persistent allergic rhinitis and others only included patients with seasonal allergic rhinitis.
- Most of the studies excluded patients with septum deviation, nasal polyps and rhinosinusitis.
- In 1 study, intranasal phototherapy was used with medical therapy and compared with medical therapy alone to determine if there was an additive effect⁴.
- There is more than 1 device available and different devices emitting different wavelengths of light for differing lengths of exposure were used in the included studies.
- None of the studies reported long-term outcomes.

Existing assessments of this procedure

The 2017 British Society of Allergy and Clinical Immunology guideline for the diagnosis and management of allergic and non-allergic rhinitis¹⁰ states:

‘The levels of evidence for all complementary therapies, including acupuncture, herbal medicine, phototherapy and homoeopathy are not considered sufficient for recommendation for clinical use at present.’

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for intranasal phototherapy for allergic rhinitis were submitted and can be found on the [NICE website](#).

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. 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.

Issues for consideration by IPAC

None other than those described above.

References

1. Cho HK, Jeong YM, Lee HS et al. (2015) Efficacy of endonasal phototherapy for relieving the symptoms of allergic rhinitis: Meta-analysis. *American Journal of Rhinology & Allergy* 29: 283–91
2. Alyasin S, Nabavizadeh SH, Houshmand H et al. (2016) Short time efficiency of rhinophototherapy in management of patients with allergic rhinitis resistant to medical therapy. *Iranian Journal of Allergy, Asthma, and Immunology* 15: 317–27
3. Bella Z, Kiricsi A, Viharosne EDR et al. (2017) Rhinophototherapy in persistent allergic rhinitis. *European Archives of Otorhinolaryngology* 274: 1543–50
4. Tatar EC, Korkmaz H, Surenolu U et al. (2013) The effects of rhinophototherapy on quality of life in persistent allergic rhinitis. *Clinical and Experimental Otorhinolaryngology* 6: 73–7
5. Cingi C, Cakli H, Yaz A et al. (2010) Phototherapy for allergic rhinitis: a prospective, randomized, single-blind, placebo-controlled study. *Therapeutic advances in respiratory disease* 4: 209–13
6. Albu S, Baschir S (2013) Intranasal phototherapy versus azelastine in the treatment of seasonal allergic rhinitis. *Auris, nasus, larynx* 40: 447–51
7. Cingi C, Yaz A, Cakli H et al. (2009) The effects of phototherapy on quality of life in allergic rhinitis cases. *European Archives of Otorhinolaryngology* 266: 1903–8
8. Emberlin JC, Lewis RA (2009) Pollen challenge study of a phototherapy device for reducing the symptoms of hay fever. *Current medical research and opinion* 25: 1635–44
9. Neuman I, Finkelstein Y (1997) Narrow-band red light phototherapy in perennial allergic rhinitis and nasal polyposis. *Annals of Allergy, Asthma & Immunology* 78: 399–406
10. Scadding GK, Kariyawasam HH, Scadding G, et al. (2017) BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007). *Clin Exp Allergy* 47: 856–89.

Additional relevant papers

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bella Z, Kadocsa E, Kemeny L et al. (2010) Narrow-band UVB phototherapy of nasal polyps: results of a pilot study. <i>Journal of Photochemistry and Photobiology</i> . 100: 123–7	Case series n=13 FU=12 weeks	Nasal obstruction symptom scores and quality of life (NOSE) improved at end of treatment compared to baseline. Treatments were well tolerated and no device related adverse events were reported.	Small case series.
Brehmer D, Schon MP (2011) Endonasal phototherapy significantly alleviates symptoms of allergic rhinitis, but has a limited impact on the nasal mucosal immune cells. <i>European Archives of Otorhinolaryngology</i> 268: 393–9	Case series n=10	All patients showed a significant clinical benefit post-treatment as assessed by standardised instruments, including total nasal symptom score, nasal congestion score, nasal itching score, sneezing score, nasal secretion score and impairment-to-health score. However, we found no significant morphological changes, to, or quantitative differences in, the CD1a+, CD4, CD8 or CD31 cells before and 14 days after treatment.	Small case series.
Brehmer D (2010) Endonasal phototherapy with Rhinolight for the treatment of allergic rhinitis. <i>Expert review of medical devices</i> 7: 21–6	Review	Endonasal phototherapy with the Rhinolight device (Rhinolight Ltd, Szeged, Hungary) for the treatment of immunoglobulin E-mediated allergic rhinitis is a new option that utilizes the immunosuppressive effects of UV radiation. The method directs a combination of UV-B (5%), UV-A (25%) and visible light (70%) into the nasal cavity, and its effectiveness has been demonstrated in one double-blind, placebo-controlled study.	A more recent review with a meta-analysis is included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Csoma Z, Ignacz F, Bor Z et al. (2004) Intranasal irradiation with the xenon chloride ultraviolet B laser improves allergic rhinitis. <i>Journal of Photochemistry and Photobiology</i> 75: 137–44	Case series n=18	In the low-dose group, 7 patients completed the study, and there was no improvement in the nasal symptoms. In the medium-dose group, the XeCl UVB irradiation significantly inhibited the rhinorrhoea, the sneezing, the nasal obstruction and the total nasal score ($p<0.05$). The XeCl UVB excimer laser also inhibited the allergen-induced skin prick test in a dose-dependent manner. These results suggest that the XeCl UVB excimer laser might serve as a new therapeutic tool in the treatment of allergic rhinitis.	Small case series. Study is included in meta-analysis by Cho HK et al., 2015.
Csoma Z, Koreck A, Ignacz F et al. (2006) PUVA treatment of the nasal cavity improves the clinical symptoms of allergic rhinitis and inhibits the immediate-type hypersensitivity reaction in the skin. <i>Journal of Photochemistry and Photobiology</i> 83: 21–6	Case series n=17	PUVA treatment of the nasal cavity significantly decreased the nasal symptoms of the patients with allergic rhinitis. Treatment of the skin with PUVA also significantly suppressed the allergen-induced wheal formation in the SPT reaction. These data suggest that intranasal PUVA phototherapy is also an effective modality in the treatment of allergic rhinitis.	Small case series. Study is included in meta-analysis by Cho HK et al., 2015.
Garaczi E, Boros-Gyevi M, Bella Z et al. (2011) Intranasal phototherapy is more effective than fexofenadine hydrochloride in the treatment of seasonal allergic rhinitis: results of a pilot study. <i>Photochemistry and Photobiology</i> 87: 474–7	RCT n=31 FU=2 weeks	Total nasal symptom score was significantly decreased in the rhinophototherapy group, but no significant change was observed in the fexofenadine HCl group after 2 weeks of treatment.	Small RCT which is included in meta-analysis by Cho HK et al., 2015.
Kemeny L, Koreck A (2007) Ultraviolet light phototherapy for allergic rhinitis. <i>Journal of Photochemistry and Photobiology</i> 87: 58–65	Review	Mechanism of action of phototherapy is complex, it reduces the antigen presenting capacity of dendritic cells, induces apoptosis of immune cells and inhibits synthesis and release of pro-inflammatory mediator from several cell types. Therefore, intranasal phototherapy may represent an alternative treatment of allergic rhinitis and other inflammatory and immune mediated mucosal diseases.	A more recent review with a meta-analysis is included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Koreck AI, Csoma Z, Bodai L et al. (2005) Rhinophototherapy: a new therapeutic tool for the management of allergic rhinitis. <i>The Journal of Allergy and Clinical Immunology</i> 115: 541–7	RCT n=49	Rhinophototherapy was tolerated well and resulted in a significant improvement of clinical symptoms for sneezing ($p<0.016$), rhinorrhoea ($p<0.007$), nasal itching ($p<0.014$), and total nasal score ($p<0.004$). None of the scores improved significantly in the control group. Scores for nasal obstruction slightly improved after mUV/VIS treatment and significantly increased in the control group ($p<0.017$). In the nasal lavage, phototherapy significantly reduced the number of eosinophils and the level of eosinophil cationic protein and IL-5. In vitro irradiation of T cells and eosinophils with mUV/VIS light dose-dependently induced apoptosis. Furthermore, mUV/VIS irradiation inhibited the mediator release from RBL-2H3 basophils.	Small RCT, which is included in meta-analysis by Cho HK et al., 2015.
Koreck A, Szechenyi A, Morocz M et al. (2007) Effects of intranasal phototherapy on nasal mucosa in patients with allergic rhinitis. <i>Journal of Photochemistry and Photobiology</i> 89: 163–9	Case series n=8	Immediately after last treatment Comet assay of nasal cytology samples showed a significant increase in DNA damage compared to baseline. Ten days after the last irradiation a significant decrease in DNA damage was observed compared to data obtained immediately after finishing the treatment protocol. Difference between baseline and 10 days after last treatment was not statistically significant. Two months after ending therapy, DNA damage detected by Comet assay in patients treated with intranasal phototherapy was similar with that of healthy individuals.	Small case series.
Lee HM, Park MS, Park IH et al. (2013) A comparative pilot study of symptom improvement before and after phototherapy in Korean patients with perennial allergic rhinitis. <i>Photochemistry and Photobiology</i> 89: 751–7	Case series n=42	Following treatment, significant improvement in the clinical symptoms of nasal obstruction ($p<0.001$), rhinorrhoea ($p=0.005$), sneezing ($p=0.001$) and itching ($p=0.003$) was reported by 68% of perennial allergic rhinitis patients. The overall RQLQ	Small case series, which is included in meta-analysis by Cho HK et al., 2015.

		scores significantly improved by 45% from the baseline with the treatment after 4 weeks.	
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Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Leong SC (2011) Rhinophototherapy: gimmick or an emerging treatment option for allergic rhinitis? <i>Rhinology</i> 49: 499–506	Review	Clinical use of intranasal phototherapy appears to be safe and well tolerated. Most studies demonstrated symptomatic improvement and quality of life scores. No improvement in objective measures of nasal airflow was demonstrated. Beneficial effects of phototherapy on inflammatory markers remain equivocal. Phototherapy treatment results in DNA damage but does not appear to predispose to carcinogenesis. However, long-term prospective studies are required to verify this. The quality of published studies was variable and thus the current strength of recommending intranasal phototherapy is currently weak.	A more recent review with a meta-analysis is included.
Mitchell D, Paniker L, Sanchez G et al. (2010) Molecular response of nasal mucosa to therapeutic exposure to broad-band ultraviolet radiation. <i>Journal of Cellular and Molecular Medicine</i> 14: 313–22	Case series n=30	The data suggest that the UV-induced DNA damage response of respiratory epithelia is very similar to that of the human epidermis and that nasal mucosa is able to efficiently repair UVB induced DNA damage.	Small case series that focuses on histological changes.
Moustafa Y, Kassab AN, El Sharnoubi J et al. (2013) Comparative study in the management of allergic rhinitis in children using LED phototherapy and laser acupuncture. <i>International Journal of Pediatric Otorhinolaryngology</i> 77: 658–65	RCT n=40	There was a significant improvement in the severity score symptoms in both groups through and by the end of the follow up period.	Small RCT, which is included in meta-analysis by Cho HK et al., 2015.
Wong B, Fu B, Oyarzabal M (2012) The use of intranasal phototherapy in allergic rhinitis/hayfever. <i>Clinical Otolaryngology</i> 37: 192	Review	Intranasal phototherapy appears to be a useful addition to the armament of treatment we use in the management of allergic rhinitis. Its use should be considered in cases which commonly used drugs are either contraindicated or have insufficient efficacy.	A more recent review with a meta-analysis is included.
Yildirim YS, Apuhan Tayfun, Kocoglu E (2013) Effects of intranasal phototherapy on nasal microbial flora in patients with allergic rhinitis. <i>Iranian Journal of</i>	Case series n=31	The study found that after intranasal phototherapy, the scores for total nasal symptoms decreased significantly but bacterial proliferation was not significantly different before and	Small case series, which is included in meta-analysis by Cho HK et al., 2015.

Allergy, Asthma, and Immunology 12: 281–6		after phototherapy. We have shown that intranasal phototherapy does not change the aerobic nasal microbial flora in patients with perennial allergic rhinitis.	
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Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	24/10/2017	Issue 10 of 12, October 2017
HTA database (Cochrane)	24/10/2017	Issue 4 of 4, October 2016
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	24/10/2017	Issue 9 of 12, September 2017
MEDLINE (Ovid)	24/10/2017	1946 to October Week 2 2017
MEDLINE In-Process (Ovid)	24/10/2017	October 23, 2017
EMBASE (Ovid)	24/10/2017	1996 to 2017 Week 43
PubMed	24/10/2017	n/a
BLIC (British Library)	25/10/201	n/a

Trial sources searched 25/09/2017

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

Websites searched 25/09/2017

- 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)
- EuroScan
- 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.

1	exp rhinitis/
2	Conjunctivitis, Allergic/
3	Sinusitis/

4	((allerg* or season* or perennial*) adj4 (rhinitis* or rhino*)).ti,ab.
5	(hayfever* or hay fever*).ti,ab.
6	Nasal Obstruction/ or Nasal Mucosa/
7	((nostril* or nose* or nasal* or palate or eye or eyes or eyelids or auditory canal) 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*)).ti,ab.
8	(Sneez* or Rhinosinusi* or Rhinoconjunctivitis* or Pollenosi*).ti,ab.