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Zalmanovici Trestioreanu A, Barua A, Pertzov B

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TABLE OF CONTENTS

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[Intervention Review]

Cyclamen europaeum extract for acute sinusitis

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ABSTRACT

Background

Acute sinusitis is a common reason for primary care encounters. It causes significant symptoms including facial pain, congested nose, headache, thick nasal mucus, fever, and cough and often results in time off work or school. Sinusitis treatment focuses on eliminating causative factors and controlling the inflammatory and infectious components. The frozen, dried, natural fluid extract of the *Cyclamen europaeum* plant delivered intranasally is thought to have beneficial effects in relieving congestion by facilitating nasal drainage, and has an anti-inflammatory effect.

Objectives

To assess the effectiveness of topical intranasal *Cyclamen europaeum* extract on clinical response in adults and children with acute sinusitis.

Search methods

We searched CENTRAL, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE, Embase, and trials registers (ClinicalTrials.gov; WHO ICTRP) in January 2018. We also searched the reference lists of included studies and review literature for further relevant studies and contacted trial authors for additional information.

Selection criteria

Randomised controlled trials comparing *Cyclamen europaeum* extract administered intranasally to placebo, antibiotics, intranasal corticosteroids, or no treatment in adults or children, or both, with acute sinusitis. Acute sinusitis was defined by clinical diagnosis and confirmed by nasal endoscopy or by radiological evidence.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. We used standard methodological procedures expected by Cochrane.

Main results

We included two randomised controlled trials that involved a total of 147 adult outpatients with acute sinusitis confirmed by radiology or nasal endoscopy who were assigned to *Cyclamen europaeum* nasal spray or placebo study arms for up to 15 days. The risk of selection and detection bias was unclear, as allocation concealment and blinding of outcome assessors were not reported in either study. Attrition was high (60%) in one study, although dropouts were balanced between study arms.

Neither study reported our two primary outcomes: proportion of participants whose symptoms resolved or improved at 14 days and 30 days. No serious adverse events or complications related to treatment were reported; however, more mild adverse events such as nasal

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and throat irritation, mild epistaxis, and sneezing occurred in *Cyclamen europaeum* group participants (50%) compared to placebo group participants (24%) (risk ratio 2.11, 95% confidence interval 1.35 to 3.29); moderate-quality evidence.

Authors' conclusions

The effectiveness of *Cyclamen europaeum* for people with acute sinusitis is unknown. Although no serious side effects were observed, 50% of participants who received *Cyclamen europaeum* reported adverse events compared with 24% of those who received placebo.

PLAIN LANGUAGE SUMMARY

Is *Cyclamen europaeum* extract effective for people with acute sinusitis?

Review question

We assessed the effectiveness of *Cyclamen europaeum* frozen, dried, natural fluid extract, an herbal medicine from the tuber of *Cyclamen europaeum*, given as a nasal spray compared with sham treatment (placebo) to resolve or improve acute sinusitis in adults and children.

Background

Acute sinusitis is a common condition that occurs when the bone cavities in the vicinity of the nose become inflamed from infection. Symptoms can include thick nasal mucus, congested nose, facial pain, headache, fever, and cough. Symptoms last up to eight weeks in adults and up to 12 weeks in children. Acute sinusitis is most often caused by viruses; complications can occur if the infection spreads. Acute sinusitis is a common condition that imposes significant costs.

A range of conservative treatments are available to treat acute sinusitis. Antibiotics are commonly prescribed, but clinical guidelines disagree about when antibiotics should be given to treat acute sinusitis. The few studies on *Cyclamen europaeum* extract given as nasal spray suggest that it may help by relieving nasal congestion.

Search date

The evidence is current to 18 January 2018.

Study characteristics

We included two studies involving 147 adults with acute sinusitis. Participants were randomly allocated to receive *Cyclamen europaeum* delivered as an intranasal spray or a non-active substance for up to 15 days.

Study funding sources

Pharmaceutical companies funded both studies.

Key results

We wanted to find out the proportion of participants whose symptoms resolved or improved up to 14 days and 30 days, but did not find any evidence. The included studies provided data for changes in symptom scores for acute sinusitis with treatment. One study reported improvement in facial pain up to seven days. Neither study reported complications or days off school or work.

People who received *Cyclamen europaeum* rather than a non-active substance reported more side effects like nasal irritation, sneezing, and mild nasal bleeding. No major side effects occurred.

We found no evidence as to whether *Cyclamen europaeum* is effective or not.

Quality of the evidence

We assessed the quality of both studies and judged the evidence to be moderately reliable for the only outcome that could be assessed, that is side effects. One study had a high dropout rate (60%), but dropouts were described and balanced between study arms. We found consistent results between studies for adverse events. Neither study reported whether the outcomes assessors knew which treatments the participants received. Due to the small number of participants and weaknesses in study design, we cannot be sure of the result.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. *Cyclamen europaeum* compared to placebo for acute sinusitis

***Cyclamen europaeum* compared to placebo for acute sinusitis**

Patient or population: adults with acute sinusitis
Setting: outpatients in Germany and the USA
Intervention: *Cyclamen europaeum* topical intranasal spray (1.3 mg once daily in each nostril for up to 15 days)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with *Cyclamen europaeum*				
Proportion of participants with resolution or improvement of symptoms up to 30 days	-	-	-	-	-	No studies reported this outcome.
Proportion of participants with any adverse event	Study population		RR 2.11 (1.35 to 3.29)	147 (2 RCTs)	⊕⊕⊕⊖ Moderate	We downgraded the quality of the evidence as concealment of allocation to treatment and blinding of outcome assessors were not reported in the studies. Also, 1 study had a small sample size with a high attrition rate.
	240 per 1000	506 per 1000 (324 to 790)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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BACKGROUND

Description of the condition

Sinusitis is a common condition that carries a large healthcare economic burden (Feldt 2013). Acute sinusitis is inflammation of one or more of the paranasal sinuses, with symptoms lasting less than eight weeks in adults and less than 12 weeks in children (Georgy 2012; Kaliner 1997). Sinusitis is one of the 10 most common reasons for visits to primary care physicians, and it is the fifth most common diagnosis for which antibiotics are prescribed. Primary care physicians tend to consider acute sinusitis to be of bacterial origin and prescribe antibiotics in 85% to 98% of cases. However, most sinusitis cases are caused by viruses. According to epidemiological estimates, only 0.2% to 2% of viral upper respiratory tract infections in adults progress to bacterial rhinosinusitis (Snow 2001). A recent systematic review and meta-analysis reported that the prevalence of bacterial infection in acute sinusitis is likely to be greater than 2%, but this remains poorly defined (Shintani Smith 2015). Bacterial infections often resolve without antibiotic treatment. A multicentre prospective cohort study reported that antibiotics were prescribed in 71.2% of people with acute sinusitis (Dallas 2017).

Clinical signs and symptoms are not reliable indicators to effectively identify which cases of sinusitis should be treated with antibiotics. No accurate practice-based test exists to diagnose acute bacterial sinusitis; clinicians rely mostly on clinical findings for diagnosis. Signs and symptoms of acute bacterial sinusitis and prolonged viral upper respiratory tract infection are similar, resulting in frequent misclassification of viral infections. There is no evidence to effectively distinguish bacterial from viral acute rhinosinusitis using fever and facial, dental, or both facial and dental pain (Hauer 2014). Watchful waiting is supported by current guidelines within the first seven to 10 days after symptoms of upper respiratory tract infection symptoms appear (Aring 2016). Antibiotics and intranasal steroids have been recommended for acute bacterial rhinosinusitis, although most international guidelines do not recommend the use of antibiotics to treat mild, moderate, or uncomplicated acute rhinosinusitis (Dass 2016). There is no consensus as to when to use antibiotics; furthermore, overuse of antibiotics is an alarming problem among both patients and practitioners. Antibiotics should be prescribed for people with acute rhinosinusitis whose symptoms persist for more than 10 days, in the case of onset of severe signs or symptoms of high fever (> 39 °C) and purulent nasal discharge or facial pain lasting for at least three consecutive days, or worsening symptoms following a typical viral illness lasting for five days that was initially improving (Harris 2016; Kaplan 2014).

The common cold frequently involves the upper airways, including occlusion in the sinus cavities (Gwaltney 1994). In a retrospective analysis, rhinorrhoea, purulent secretions, sinus tenderness, and a history of sinusitis were significant predictors for diagnosing sinusitis (Little 2000; Zalmanovici Trestioreanu 2013).

Diagnosis is often confirmed by sinus imaging, and computed tomography of the sinuses is helpful for people whose symptoms do not improve with treatment. Radiography is not recommended for evaluating acute uncomplicated sinusitis (Aring 2016).

Sinusitis is accompanied by inflammation of the contiguous nasal mucosa; hence, rhinosinusitis has become the preferred term (Snow 2001). Inflammation of nasal mucosa and blockage of the sinus ostium play an essential role in the development of sinusitis (Tutkun 1996). The characteristic signs and symptoms of rhinosinusitis are sinus obstruction, mucus retention, and infection. Complications can occur through intracranial extension of the infection.

Description of the intervention

The term *Cyclamen europaeum* has been applied to several related species of *Cyclamen*, but strictly applies to *Cyclamen purpurascens*. The tuber of *Cyclamen europaeum* (*Cyclamen purpurascens*), a member of the Primulaceae family, has been used in herbal medicine for a range of indications; it is reported to be a drastic purgative. An extract of the tuber has been used for sinusitis in the form of nasal spray known as Nasodren and Sinuforte (Micromedex 2.0).

How the intervention might work

Sinusitis treatment focuses on eliminating causative factors and controlling the inflammatory and infectious components (Becker 2003; Passali 2016). The frozen, dried, natural fluid extract of the *Cyclamen europaeum* plant delivered intranasally is thought to have beneficial effects in relieving congestion by facilitating nasal drainage, and has an anti-inflammatory effect (Mashkova 2010). Beneficial effects were observed when used either as a monotherapy for mild or moderately severe disease or in combination with other agents for the treatment of acute or exacerbated chronic rhinosinusitis (Savvateeva 2010). Including *Cyclamen europaeum* in combined therapy for mild and moderately severe acute rhinosinusitis and exudative otitis media may make it possible to avoid drainage procedures and shorten the duration of antibacterial treatment. Simultaneous acceleration of the recovery of functional activity of the endonasal mucosa suggests a pronounced antirecurrence action of this therapy (Bogomil'skii 2010). When *Cyclamen europaeum* extract was used in comparison to saline for patients with chronic sinusitis and nasal polyps undergoing endoscopic sinus surgery, a significant improvement in patients' symptoms, nasal endoscopic signs, and patient satisfaction was reported. These results are thought to be connected to activities of the extract in facilitating nasal drainage and clearing the paranasal sinuses (Mullol 2009).

Why it is important to do this review

Key points of agreement in clinical guidelines regarding therapy for acute rhinosinusitis include efficacy of symptomatic treatment and the importance of reducing unnecessary antibiotic use. However, there is no consensus in guidelines regarding when antibiotics should be considered as a reasonable treatment strategy (Meltzer 2011). The management of rhinosinusitis depends on the duration and severity of symptoms. A variety of conservative and pharmacological interventions are available, although physicians can find it difficult to develop a cohesive and logical approach to sinusitis treatment (Benninger 1997; Libman 2017; Rosenfeld 2015; Sharp 2015). Antibiotics are not needed for mild to moderate sinusitis within the first week of illness. A greater likelihood of bacterial rhinosinusitis after 10 days makes antibiotic therapy a reasonable option (Van den Broek 2014). Around 80% of participants with acute sinusitis treated without antibiotics improved within two weeks (Ahovuo-Saloranta 2014). In a Cochrane Review, a small clinical benefit

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was observed in participants treated with antibiotics (Ahovuo-Saloranta 2014). A recent systematic review found that antibiotic treatment provided more symptomatic relief within the first days of treatment compared to placebo, but after 10 days both groups had similar improvement rates (Burgstaller 2016). Avoiding antibiotics for acute sinusitis could reduce antibiotic adverse effects, antibiotic resistance, and healthcare costs (Smith 2012). Another Cochrane Review did not find clear evidence for efficacy of nasal irrigations, decongestants, and antihistamines for acute sinusitis in children (Shaikh 2014). The use of adjunctive medications for acute sinusitis, such as antihistamines, decongestants, and systemic and nasal corticosteroids, also remains controversial (Shrum 2001; Venekamp 2014; Zalmanovici Trestioreanu 2013). Recent studies have tested *Cyclamen europaeum* extract, a novel phytotherapeutic product marketed in Europe and delivered intranasally, for its effectiveness in relieving symptoms in acute sinusitis, and found the treatment to be effective (Mullol 2009; Pfaar 2012). A recent prospective observational study reported that *Cyclamen europaeum* given as a monotherapy appears to be more effective than other monotherapies and combination therapies and at a lower cost per cured patient (Mullol 2013). However, a systematic review addressing the effectiveness of this therapy has not been conducted.

OBJECTIVES

To assess the effectiveness of topical intranasal *Cyclamen europaeum* extract on clinical response in adults and children with acute sinusitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Children and adults with acute sinusitis. Acute sinusitis was defined by a clinical diagnosis (including purulent nasal discharge and congestion, cough beyond seven days, facial pain, and fever) and radiological evidence or nasal endoscopy. We included trials in mixed populations with acute and non-acute sinusitis if outcomes were reported separately for these subgroups.

Types of interventions

Intranasal *Cyclamen europaeum* extract (any preparation, dose, or duration of treatment) compared to placebo, antibiotics, intranasal corticosteroids, or no treatment. We included studies reporting combined interventions only if both treatment arms received the same co-interventions, except for *Cyclamen europaeum* extract.

Types of outcome measures

Primary outcomes

1. Proportion of participants with resolution or improvement of symptoms up to 14 days.
2. Proportion of participants with resolution or improvement of symptoms up to 30 days.

Secondary outcomes

1. Proportion of participants with any adverse event.
2. Proportion of participants who developed complications.
3. Days off school or work.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 1), part of the Cochrane Library (www.cochranelibrary.com) (accessed 18 January 2018), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE Ovid (1946 to 18 January 2018), and Embase.com (1974 to 18 January 2018). We searched CENTRAL and MEDLINE with the search strategy detailed in Appendix 1. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE; sensitivity-maximising version (2008 revision): Ovid format (Lefebvre 2011). We adapted the search strategy for Embase (see Appendix 2). There were no language or publication restrictions.

Searching other resources

We searched the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en; search strategy in Appendix 3), and ClinicalTrials.gov (www.clinicaltrials.gov; search strategy in Appendix 4) on 1 February 2018. We inspected the reference lists of all identified studies and review literature for further relevant studies. We contacted trial authors for additional information (see Characteristics of excluded studies).

Data collection and analysis

Selection of studies

Two review authors (AZT, AB) independently screened titles and abstracts of all studies identified as a result of the search for potential inclusion in the review. We retrieved the full-text study reports or publications of studies deemed potentially relevant, and two review authors (AZT, AB) independently screened the full-text studies for inclusion, and identified and recorded reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (BP) when necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009). We did not impose any language restrictions.

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. Two review authors (AZT, AB) extracted study characteristics from the included studies. We planned to extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.

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2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (AZT, AB) independently extracted outcome data from the included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. Any disagreements were resolved by consensus or by involving a third review author (BP). One review author (AZT) transferred data into the Review Manager 5 file (Review Manager 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AB) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (AZT, AB) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by involving a third review author (BP). We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where necessary, we considered blinding separately for different key outcomes. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

We included trials if they met the following criteria:

1. a randomisation method is described that would not allow the investigator or participant to know or influence the intervention group before the eligible participant entered into the study (low risk of bias); and
2. randomisation is stated but no information on the method used is available (unclear risk of bias).

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and planned to report any deviations in the Differences between protocol and review section.

Measures of treatment effect

We analysed dichotomous data by calculating the risk ratio (RR) and risk difference (RD) for each trial with the uncertainty in each result expressed as a 95% confidence interval (CI). We analysed continuous outcomes when normally distributed by using the mean and standard deviation from each study and calculating the mean difference (MD) and the 95% CI. We expressed the results according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We performed all analyses on the basis of intention-to-treat.

Unit of analysis issues

We included randomised controlled trials with standard designs and parallel groups in the review. Participants were included only once in the analyses.

Dealing with missing data

We tried to contact study authors to obtain missing data.

Assessment of heterogeneity

We assessed heterogeneity by inspection of the graphical presentations and I^2 statistic for heterogeneity. Values of 25%, 50%, and 75% corresponded to low, medium, and high levels of heterogeneity.

Assessment of reporting biases

We planned a funnel plot analysis to assess possible publication bias.

Data synthesis

We used the fixed-effect model for combining study data.

GRADE and 'Summary of findings' table

We created Summary of findings for the main comparison table using the outcome proportion of participants with any adverse event. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses according to the treatment in the control group to assess the impact of this possible source of heterogeneity. We included only two studies in the review, and both used placebo in the control group.

Sensitivity analysis

We planned to use the random-effects model to test the robustness of results when heterogeneity was present. We detected no

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heterogeneity between the studies. We performed a sensitivity analysis to check the robustness of the result by imputing data, considering best-case scenario (assuming none of the dropouts in the intervention group had an adverse event and all dropouts in the control group had an adverse event) and worst-case scenario (assuming all dropouts in the intervention group had an adverse event and none of the dropouts in the control group had an adverse event), as Ponikau 2012 had a high dropout rate.

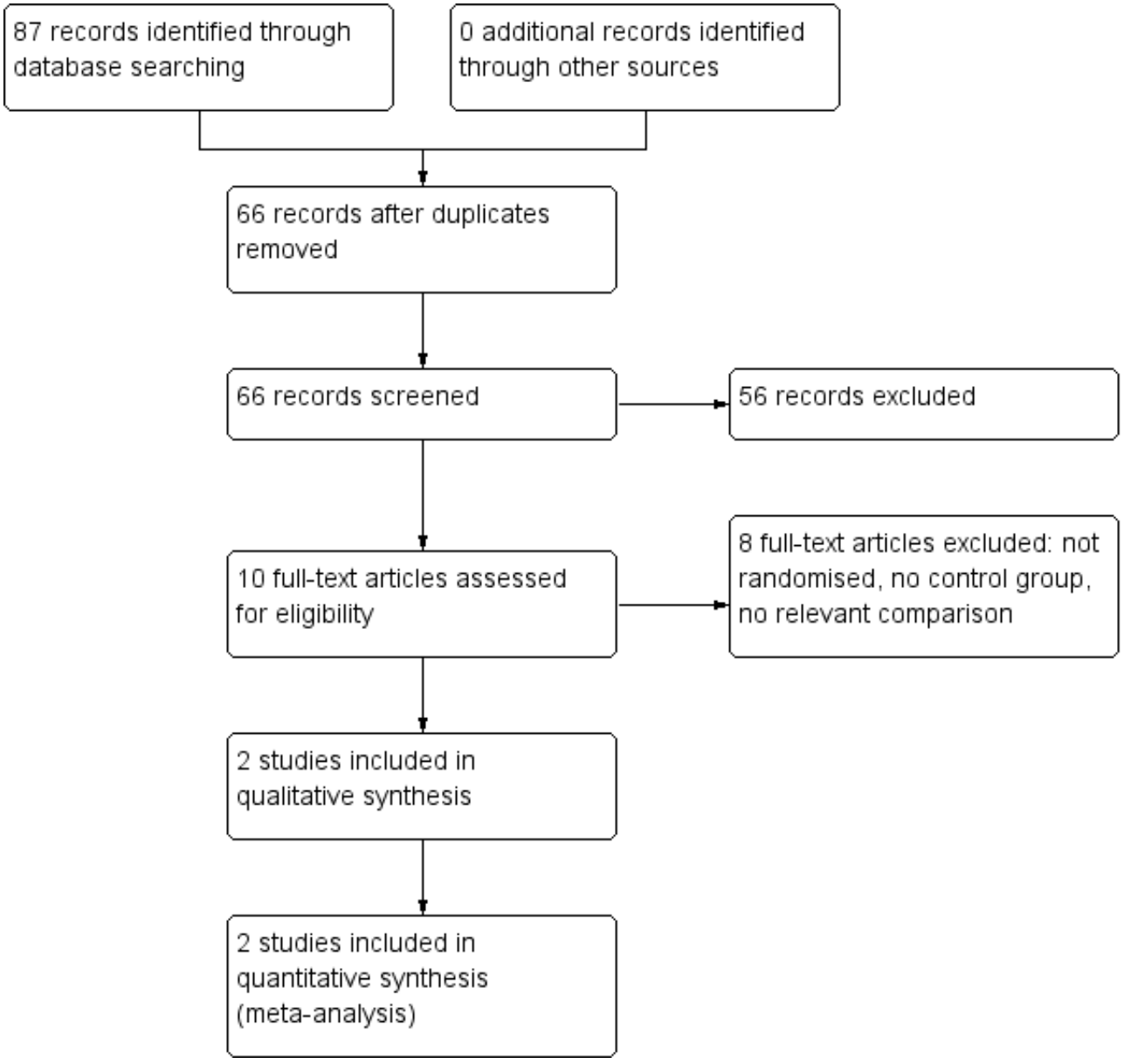
RESULTS

Description of studies

Results of the search

We identified 87 references from the electronic searches. After removing 21 duplicates, two review authors (AZT, AB) inspected 66 abstracts. We excluded 56 abstracts for the following reasons: not acute sinusitis, not randomised, observational study, intervention of interest not used, no relevant outcomes, review articles. We considered 10 studies for inclusion after inspecting the abstracts and obtaining full-text reports (Figure 1). We excluded eight studies which did not meet the inclusion criteria for this review.

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies table.

Two studies (147 participants) met the inclusion criteria and were included in the review. Participants were assigned to nasal *Cyclamen europaeum* spray or placebo. The studies were

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multicentre trials: one was conducted in 13 centres in Germany (Pfaar 2012), and one study involved outpatients in 25 centres in the USA (Ponikau 2012).

Participants were adults with a documented episode of acute sinusitis confirmed by radiology or nasal endoscopy. The entry criteria and participants in the trials were similar.

Both studies used a placebo in the control group and the same dose of *Cyclamen europaeum* lyophilised extract, 1.3 mg once daily in each nostril, in the treatment group. Pfaar 2012 used concomitant amoxycillin in both arms or an alternative for participants who were allergic to penicillin. Treatment duration in the studies was 15 days in Pfaar 2012 and seven days in Ponikau 2012.

The outcomes in the included studies reported change from baseline in mean total symptom score, individual symptom scores, endoscopic changes, treatment failure or need for additional treatment, complications, sleep quality, and overall treatment satisfaction in Pfaar 2012; and change from baseline in sinus opacification on computed tomography (CT) scans, reduction in total symptom score, other symptom scores changes from baseline, and endoscopic inflammation in Ponikau 2012.

Information on adverse events that occurred during the trials is presented in Table 1. The studies described participants who dropped out before the end of the study, and their reasons for leaving.

Excluded studies

See Characteristics of excluded studies table.

We excluded eight studies for the following reasons: not randomised, control group not used, intervention of interest not used (Bogomil'skii 2010; Ianov 2007; Kriukov 2007; Mashkova 2010; Ovchinnikov 2009; Rybak 2008; Semenov 2011; Svistushkin 2013). We contacted one author to ask if the study was randomised; we subsequently excluded this study because quasi-randomisation was used (Ovchinnikov 2009). All excluded studies were published in the same journal between 2007 and 2013.

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

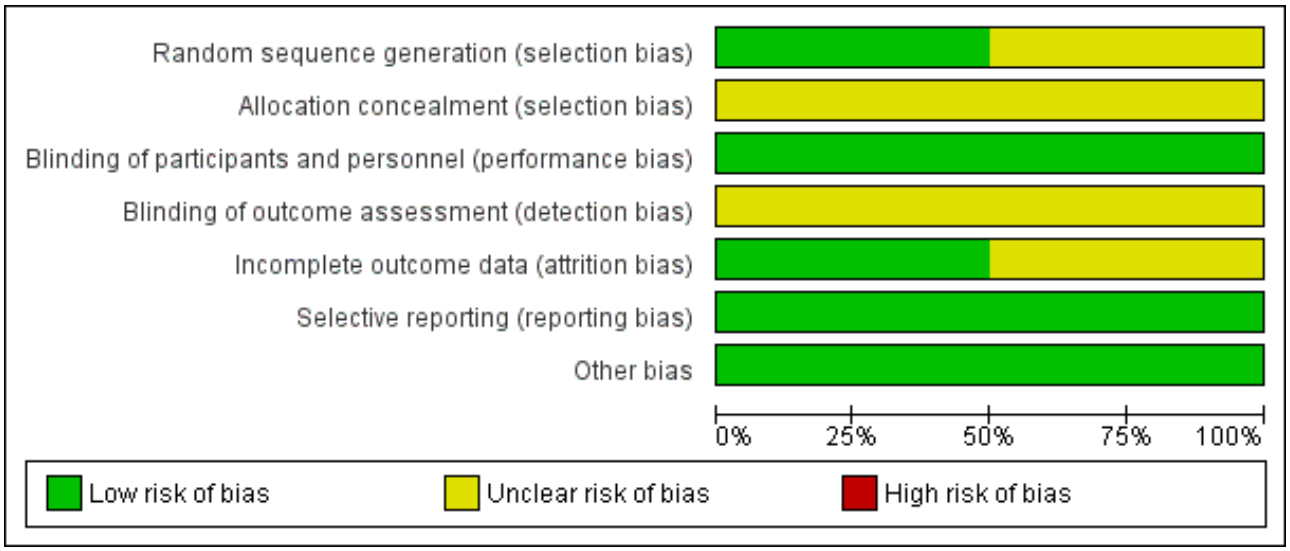

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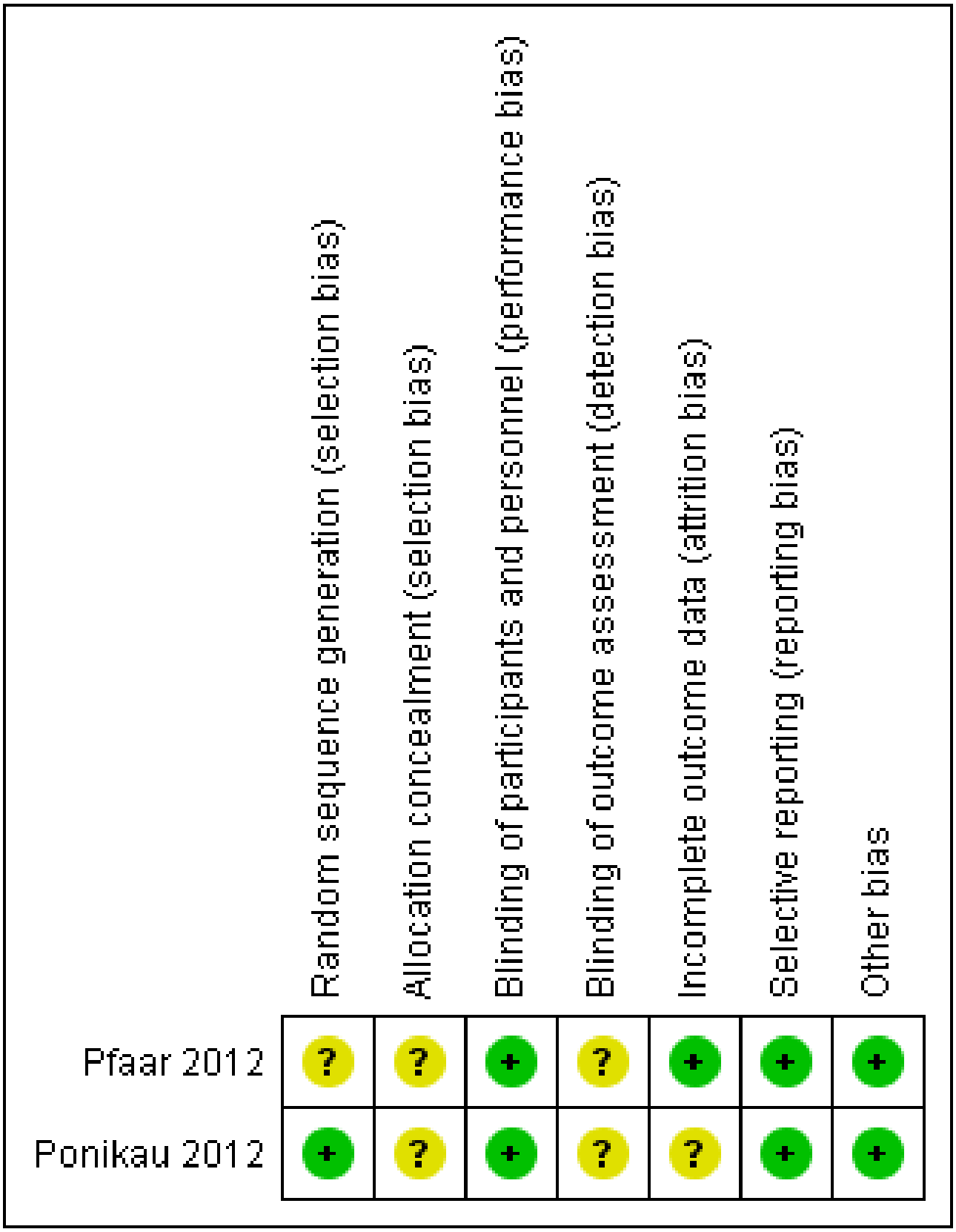
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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The studies were randomised, double-blind, placebo-controlled trials.

Allocation

Pfaar 2012 did not report randomisation methods (unclear risk of bias). Ponikau 2012 adequately reported generation of the allocation sequence (low risk of bias). Neither study reported concealment of allocation to treatment (unclear risk of bias).

Blinding

The trials were double-blinded, and the method of blinding was described (low risk of bias). Blinding of outcome assessors was not reported in the studies (unclear risk of bias).

Incomplete outcome data

Both studies described dropouts before the end of the study and provided reasons (low risk of bias). Total losses to follow-up were 17% in Pfaar 2012 and 60% in Ponikau 2012. Dropouts were balanced between study arms.

Selective reporting

The studies reported outcomes and results as prespecified in their protocols (low risk of bias).

Other potential sources of bias

We did not identify possible sources of bias. The studies were small and were assessed as moderate quality for the only outcome assessed (adverse events), with similar direction of results for the outcome included in our meta-analysis. Both studies were supported by pharmaceutical companies, but funding sources did not seem to influence results.

Effects of interventions

See: **Summary of findings for the main comparison** *Cyclamen europaeum* compared to placebo for acute sinusitis

We included two studies (147 participants) (Pfaar 2012; Ponikau 2012). See Summary of findings for the main comparison.

Primary outcomes

1. Proportion of participants with resolution or improvement of symptoms up to 14 days

No studies reported this outcome. One study reported changes in mean total symptom score up to seven days and a trend toward greater symptomatic relief in the *Cyclamen europaeum* group, although this was not clear (P = 0.64) (Pfaar 2012). Uncertainty in results was observed for improvement of nasal obstruction and oedema. Improvement in facial pain up to seven days was observed, and this was obvious (mean difference -1.20, 95% confidence interval (CI) -2.32 to -0.08; P = 0.04) (Pfaar 2012). There was no clear difference between treatment and control groups for total or individual symptom scores in Ponikau 2012.

2. Proportion of participants with resolution or improvement of symptoms up to 30 days

No studies reported this outcome.

Secondary outcomes

1. Proportion of participants with any adverse event

Both studies reported data for this outcome (Table 1). More adverse events were reported in the *Cyclamen europaeum* group than in the placebo group during the treatment period, and we are confident in the result (risk ratio (RR) 2.11, 95% CI 1.35 to 3.29; risk difference 0.26, 95% CI 0.13 to 0.40; Analysis 1.1). We assessed the quality of the evidence as moderate (Summary of findings for the main comparison).

We performed sensitivity analysis by imputing data to check the robustness of the result, considering best-case scenario (assuming none of the dropouts in the intervention group had an adverse event and all dropouts in the control group had an adverse event) (RR 0.94, 95% CI 0.68 to 1.30; Analysis 1.2), and worst-case scenario (assuming all dropouts in the intervention group had an adverse event and none of the dropouts in the control group had an adverse event) (RR 3.49, 95% CI 2.30 to 5.30; Analysis 1.3).

2. Proportion of participants who developed complications

Only one study reported this outcome; no complications were reported (Pfaar 2012).

3. Days off school or work

No studies reported this outcome.

We did not perform planned funnel plots and subgroup analyses due to the small number of included studies and because both used a placebo in the control group.

DISCUSSION

Rhinosinusitis is one of the most common upper respiratory diseases treated in general practice (Marple 2006; Schappert 2006). The condition is associated with significant economic burden, which includes reduced productivity and absenteeism, as well as medical costs (Fokkens 2007; Padia 2016; Rudmik 2017). Sinusitis is a common disorder that can cause further morbidity and mortality through progression of inflammation and extension of infection. It is associated with significant patient symptomatology that adversely affects quality of life (Carr 2016). Management of uncomplicated acute rhinosinusitis includes analgesics, saline irrigations and intranasal steroids. The use of antibiotics for people with acute rhinosinusitis is widespread, and there seems to be only a slight added benefit over placebo (Sng 2015). There is a need for improved antibiotic stewardship across all settings (Sharp 2015). Alternative treatments should be considered according to severity of symptoms. We aimed to investigate whether *Cyclamen europaeum* extract, a novel phytotherapeutic treatment, is an effective topical treatment for acute sinusitis.

Summary of main results

We included two small studies that involved a total of 147 adult participants who received *Cyclamen europaeum* extract as an intranasal spray versus placebo and provided moderate-quality evidence for the only outcome assessed (adverse events). We could not assess whether *Cyclamen europaeum* is effective or not for treating sinusitis. We were able to meta-analyse results for adverse events only; data for other review outcomes were not available from the included studies. Neither study showed clear differences

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for total symptom scores changes between people who received *Cyclamen europaeum* and those who received placebo, although Pfaar 2012 reported a trend toward improvement in total symptom score and obvious difference for improvement of facial pain up to seven days. More adverse events during the treatment period were found in participants in the *Cyclamen europaeum* group compared to those in the placebo group, although no serious adverse events were reported in either study (Table 1).

Overall completeness and applicability of evidence

The study population included in this review was diagnosed both clinically and by radiology or endoscopy and is not identical to people diagnosed in clinical practice, among whom diagnosis is usually based on clinical symptoms and signs alone.

Cyclamen europaeum extract has been available for the treatment of acute rhinosinusitis in over 20 European countries as an intranasal product. Clinical trials in people with acute rhinosinusitis suggest that *Cyclamen europaeum* reduces symptoms (Semenov 2011); improves mucociliary transport time (Lopatin 2007); and increases cure rate (Mullol 2009). The saponin fraction of *Cyclamen europaeum* immediately stimulates nasal secretions. These actions are attributable to irritation of the trigeminal nerve endings in the nasal mucous membranes through cholinergic pathways, leading to reflex discharge of inflammatory sinus exudates through the nose and subsequent decongestion (Gedevanishvili 2007; Jurkiewicz 2016). One study found this treatment was as effective as traditional treatment, and when used as initial monotherapy, reduced drug loading (Svistushkin 2013). We could not assess in our review whether *Cyclamen europaeum* is effective or not.

Quality of the evidence

We included two small studies (147 participants) in this review. The studies were randomised, but neither reported concealment of allocation to treatment (Pfaar 2012; Ponikau 2012). Both studies found the same direction of effect for the outcome included in the meta-analysis, that is more adverse events in the groups receiving *Cyclamen europaeum*. Ponikau 2012 had a high dropout rate (60%), but dropouts were described and balanced between study arms, and absolute numbers of dropouts were small as sample size was small in this study; we performed a sensitivity analysis considering both extreme scenarios to test the robustness of the result and this did not change the conclusion. Both studies were funded by pharmaceutical companies, among them Hartington Pharmaceutical; *Cyclamen europaeum* nasal spray known as Sinuforte or Nasodren is a trademark and brand of Hartington Pharmaceutical. This did not seem to influence the results, as more adverse events were reported in participants who received *Cyclamen europaeum* compared to the placebo group. Using GRADE principles we assessed the evidence for the only outcome meta-analysed, that is proportion of participants with any adverse event, as of moderate quality (Summary of findings for the main comparison), downgrading quality due to lack of reporting of concealment of allocation to treatment and blinding of outcome assessors in the studies, and a small sample size with high dropouts in Ponikau 2012.

Potential biases in the review process

We conducted searches according to Cochrane Acute Respiratory Infections Group recommendations. Two review authors (AZT, AB) independently selected studies for inclusion and extracted data. Two review authors (AZT, BP) analysed data and interpreted results to prevent possible bias in the review process. We conducted this review according to the published protocol. Participants received concomitant antibiotics in Pfaar 2012; as both groups received antibiotics, the only intervention that differed between groups was *Cyclamen europaeum* or placebo, and the effect could only be attributed to *Cyclamen europaeum.* We assessed both studies as at unclear risk of bias for blinding of outcome assessors and at low risk of bias for blinding of participants and personnel.

Agreements and disagreements with other studies or reviews

The limited existing evidence for *Cyclamen europaeum* treatment, which is controversial, has not been systematically reviewed, and we found the methodology of many studies to be questionable (see Characteristics of excluded studies). One study found that monotherapy with *Cyclamen europaeum* for participants with moderately severe acute sinusitis was associated with recovery in 73% of people (Semenov 2011). Jurkiewicz 2016 reported that *Cyclamen europaeum* efficiently reduced symptoms of acute sinusitis. We could not assess the effectiveness of *Cyclamen europaeum* for acute sinusitis in our review.

The included studies reported no serious adverse events linked to *Cyclamen europaeum* treatment. This was consistent with findings reported by Kriukov 2007, Ovchinnikov 2009, and Svistushkin 2013.

AUTHORS' CONCLUSIONS

Implications for practice

The effectiveness of *Cyclamen europaeum* for people with acute sinusitis is unknown. Although no serious side effects were observed, 50% of participants who received *Cyclamen europaeum* reported adverse events compared with 24% who received placebo.

Implications for research

Additional large, high-quality randomised controlled trials in adults and children comparing *Cyclamen europaeum* intranasally versus placebo are needed to evaluate if this treatment is effective or not for improving symptoms of acute sinusitis and adverse events. Observational studies should improve data on safety.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Pfaar 2012

Methods	Randomised, parallel, double-blind; intention-to-treat
Participants	Age: 18 to 65 years, N = 99

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Pfaar 2012 *(Continued)*

	Inclusion criteria: men/women, moderate or severe acute rhinosinusitis symptoms > 7 days and < 12 weeks, at least 2 of: nasal obstruction, nasal secretion, facial pain/tension/pressure, impaired or loss of smell and mucus oedema, nasal obstruction or mucopurulent secretion on nasal endoscopy Exclusion criteria: chronic rhinosinusitis, nasal polyposis, severe mechanical nasal obstruction, severe asthmatic patients, intolerance to acetylsalicylic acid, treatment with anticoagulants or anticholinergic drugs, topical nasal corticosteroids within 72 hours of study start, or antibacterial agent within 48 hours
Interventions	1. Treatment: *Cyclamen europaeum* nasal spray, lyophilised extract, 1.3 mg once daily each nostril, N = 48 2. Control: placebo matching, once daily, N = 51 Concomitant amoxycillin 500 mg 3 times daily for 8 days or alternative if allergic to penicillin in both groups Treatment duration: 15 days Follow-up: 15 days
Outcomes	Change from baseline in mean total symptom score on days 5 to 7 Individual symptoms scores on days 5 to 7 and 15 Total symptom score at day 15, endoscopic findings on days 5 to 7 and 15 Treatment failure/need for additional treatment Complications Sleep quality Overall treatment satisfaction
Notes	Similar baseline characteristics, 13 centres in Germany, informed consent, intensity of rhinosinusitis symptoms assessed by visual analogue scale (0 to 10 cm). Subjective assessment; no concomitant treatment with corticosteroids or decongestants was allowed; symptom diaries completed by participants; endoscopic findings assessed by 4-point Likert scales from 0 to 3; adverse events and complications of rhinosinusitis were monitored. Grant from Hartington Pharmaceutical Spain. We tried to contact trial authors for more information regarding the randomisation method and for data on participants, i.e. whether participants were inpatients, outpatients, or both, as this was not mentioned in the paper, but did not receive a reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo matching
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned

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Pfaar 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts described. Treatment group 8 total: 2 adverse events, 3 discontinued treatment, 1 immunosuppressive treatment, 2 other. Placebo group 9 total: 1 adverse event, 2 discontinued treatment, 1 consent withdrawal, 5 other. Dropouts balanced between study groups, reasons reported, analyses by intention-to-treat.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

Ponikau 2012

Methods	Randomised, parallel, double-blind; intention-to-treat
Participants	Age: 18 to 70 years, N = 48 Inclusion criteria: men/women, outpatients with symptoms and endoscopy + radiology acute rhinosinusitis or acute exacerbation of chronic rhinosinusitis, total symptom score ≥ 3 (nasal obstruction/congestion, facial pain/fullness/pressure), endoscopy - mucopurulence and inflammation, CT scan - air fluid levels and/or air bubbles in at least 1 maxillary sinus Exclusion criteria: pregnant, hypogammaglobulinaemia, immotile cilia syndrome, cystic fibrosis, atrophic rhinitis, rhinitis medicamentosa, hypersensitivity to Primulaceae, serious comorbidity, expansile mass or bony erosion on radiologic examination, viral upper respiratory tract infection in past 2 weeks, high fever, facial or periorbital oedema or local complications, recent nasal/sinus surgery within 3 months, radiation treatment or chemotherapy within 1 year, intranasal antibiotics within 30 days, systemic antibiotics within 15 days, oral/topical nasal decongestants within 7 days
Interventions	1. Treatment: *Cyclamen europaeum* nasal spray, 10% lyophilised (Sinuforte), 1.3 mg (0.13 mL) once daily each nostril, N = 24 2. Control: placebo spray sterile water, once daily, N = 24 Treatment duration: 7 days Follow-up: 90 days
Outcomes	Change from baseline in % sinus opacification on CT scans at days 15, 29 or endpoint Reduction in total symptom score (6-point scale: nasal obstruction, congestion, facial pain, pressure, fullness) Other symptoms scores changes from baseline Endoscopic inflammation at day 8
Notes	Similar baseline characteristics; outpatients 25 US centres; November 2007 to September 2008; intranasal/systemic antibiotics, oral/inhaled steroids, decongestants were not allowed. Visit 1: randomisation, visit 2: 7 days, follow-up visit 3: 15 days, visit 4: 29 days, telephone follow-up: 90 days; participants' diaries for symptoms, adverse events, concomitant medication. CT scans at visits 1, 3, 4, endoscopy at visits 1, 2, no serious adverse events. Funded by Hartington Pharmaceutical, Spain and Dey Pharma, LP, Napa, CA, USA
Risk of bias	

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Ponikau 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned, computer-generated scheme
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, matching product vials labelled to obscure the contents
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Mentioned only for 1 outcome, central reader of CT scans was blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts described. Treatment group 16 total dropouts: 11 excluded: 9 chronic rhinosinusitis, 2 unclassified; 13 included in analyses (5 discontinued: 2 protocol violation, 3 other); 8 completed study. Placebo group 13 total dropouts: 8 excluded: 4 chronic rhinosinusitis, 4 unclassified; 16 included in analyses (1 lost to follow-up; 4 discontinued: 1 protocol violation, 3 other); 11 completed study. Reasons for dropout reported, analysis by intention-to-treat.
Selective reporting (reporting bias)	Low risk	Not observed
Other bias	Low risk	Not observed

CT: computed tomography

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bogomil'skii 2010	The comparison did not meet inclusion criteria: combined interventions were used in the control group that differed from the intervention group.
Ianov 2007	The comparison did not meet inclusion criteria: combined interventions were used in the control group that differed from the intervention group.
Kriukov 2007	The comparison did not meet inclusion criteria: combined interventions were used in the control group that differed from the intervention group.
Mashkova 2010	Not randomised, combined different treatments in the intervention and control groups.
Ovchinnikov 2009	Randomisation not clear; we contacted the author, who confirmed quasi-randomisation by odd/even numbers.
Rybak 2008	The comparison did not meet inclusion criteria: combined interventions were reported as "standard treatment" for the intervention and control groups, and the control group used punctures of the maxillary sinuses as comparison.
Semenov 2011	Not randomised, no control group

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Study	Reason for exclusion
Svistushkin 2013	Not randomised, no control group

DATA AND ANALYSES

Comparison 1. *Cyclamen europaeum* versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants with any adverse event - intention-to-treat	2	147	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.35, 3.29]
2 Proportion of participants with any adverse events - best-case sensitivity analysis	2	147	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.68, 1.30]
3 Proportion of participants with any adverse event - worst-case sensitivity analysis	2	147	Risk Ratio (M-H, Fixed, 95% CI)	3.49 [2.30, 5.30]

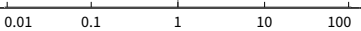
Analysis 1.1. Comparison 1 *Cyclamen europaeum* versus placebo, Outcome 1 Proportion of participants with any adverse event - intention-to-treat.

Study or subgroup	Cyclamen europaeum n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfaar 2012	32/48	15/51		82.9%	2.27[1.42,3.63]
Ponikau 2012	4/24	3/24		17.1%	1.33[0.33,5.33]
Total (95% CI)	**72**	**75**		**100%**	**2.11[1.35,3.29]**
Total events: 36 (Cyclamen europaeum), 18 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.51, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=3.28(P=0)					

Cyclamen europaeum Placebo

Analysis 1.2. Comparison 1 *Cyclamen europaeum* versus placebo, Outcome 2 Proportion of participants with any adverse events - best-case sensitivity analysis.

Study or subgroup	Cyclamen europaeum n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfaar 2012	32/48	24/51		59.26%	1.42[1,2.02]
Ponikau 2012	4/24	16/24		40.74%	0.25[0.1,0.64]
Total (95% CI)	**72**	**75**		**100%**	**0.94[0.68,1.3]**
Total events: 36 (Cyclamen europaeum), 40 (Placebo)					



Cyclamen europaeum Placebo

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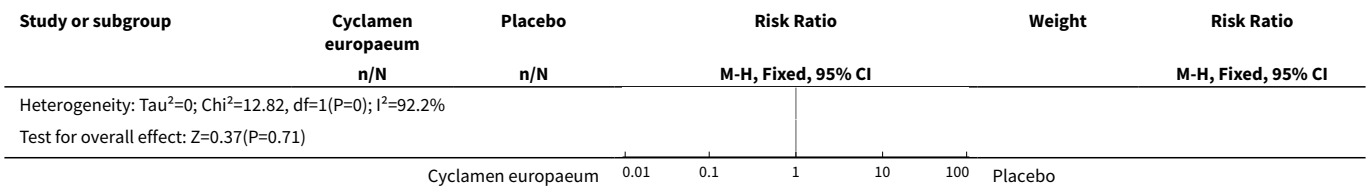
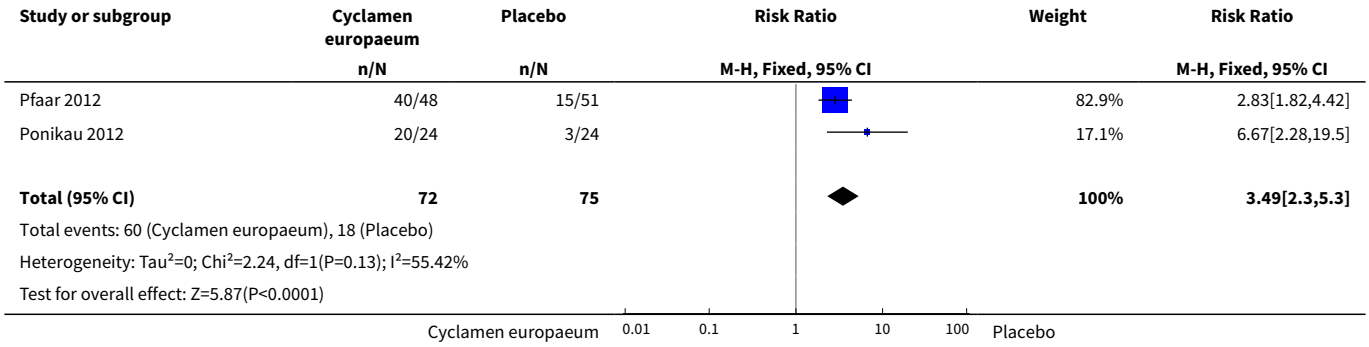


Analysis 1.3. Comparison 1 *Cyclamen europaeum* versus placebo, Outcome 3 Proportion of participants with any adverse event - worst-case sensitivity analysis.



ADDITIONAL TABLES

Table 1. Adverse events

Study ID	*Cyclamen europaeum*	Placebo
Pfaar 2012	**67% total**	**29% total**
	50% nasal irritation mild/moderate	4% nasal irritation
	27% mild epistaxis	14% mild epistaxis
	4% sneezing	4% vertigo
	3 discontinued treatment	2 discontinued treatment
Ponikau 2012	**15.4% total**	**12.5% total**
	Influenza, throat irritation, migraine, sneezing	Headache, ear pain, gastritis, back pain, conjunctival haemorrhage
	No serious adverse events	No serious adverse events
	Did not discontinue treatment	Did not discontinue treatment

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APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1 primulaceae/ or cyclamen/
2 cyclamen*.tw,nm.
3 ("c. europaeum" or "c. purpurescens").tw.
4 sinuforte.tw,nm.
5 nasodren.tw,nm.
6 or/1-5

Appendix 2. Embase (Elsevier) search strategy

#8 #6 AND #7
#7. #7('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti) NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp))
#6. #1 OR #2 OR #3 OR #4 OR #5
#5. nasodren:tn,ab,ti
#4. sinuforte:tn,ab,ti
#3. 'c. europaeum':ab,ti OR 'c. purpurescens':ab,ti
#2. cyclamen:ab,ti
#1. 'primulaceae'/de OR 'cyclamen'/de

Appendix 3. WHO International Clinical Trials Registry Platform (ICTRP) search strategy

primulaceae OR cyclamen* OR c europaeum OR c purpurescens OR sinuforte OR nasodren

Appendix 4. ClinicalTrials.gov search strategy

primulaceae OR cyclamen OR "c europaeum" OR "c purpurescens" OR sinuforte OR nasodren

WHAT'S NEW

Date	Event	Description
19 August 2019	Amended	Lead author's contact details have been updated.

CONTRIBUTIONS OF AUTHORS

Anca Zalmanovici Trestioreanu wrote the protocol, entered data into Review Manager 5, and wrote the review.
Ankur Barua signed off on the protocol and participated with Anca in study selection, quality assessment, and data extraction.
Barak Pertzov participated in data analysis, Summary of findings for the main comparison, and the interpretation of results.

DECLARATIONS OF INTEREST

Anca Zalmanovici Trestioreanu: None known.
Ankur Barua: None known.
Barak Pertzov: None known

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added a post hoc best-case/worst-case sensitivity analysis to the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Inflammatory Agents [*therapeutic use]; Cyclamen [*chemistry]; Nasal Polyps [drug therapy]; Plant Extracts [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Rhinitis [drug therapy]; Sinusitis [*drug therapy]

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MeSH check words

Adult; Humans

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