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A systematic review and meta-analysis of the role of doxycycline in chronic rhinosinusitis

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Abstract

Objective. The objective of this systematic review and meta-analysis was to evaluate the role of doxycycline in the management of chronic rhinosinusitis.

Method. This was a systematic review using Ovid Medline, Cinahl, Scopus and Cochrane and was limited to meta-analyses, systematic reviews and randomised, clinical trials. A combination of the following search terms was used: 'sinusitis', 'nasal polyps', 'doxycycline' and 'tetracycline'. Raw means and standard deviations were extracted from the included studies. The meta-analysis was performed using mean differences of pre- versus post-doxycycline treatment.

Results. A total of 279 studies were screened, of which 5 studies met the criteria (all randomised, controlled trials published between 2010 and 2021). The interventions, endpoints and measured outcomes varied across all studies. Meta-analysis performed on pre- versus post-doxycycline treatment for Sino-Nasal Outcome Test-22, nasal polyp scores and symptom scores did not yield statistically significant results.

Conclusion. This review identified a small number of high-quality studies on the use of doxycycline in chronic rhinosinusitis. There does not seem to be convincing evidence for the routine use of doxycycline in patients with chronic rhinosinusitis. Further research may try to identify certain phenotypes of chronic rhinosinusitis that may better respond to doxycycline.

Review Article

Dr D Chan takes responsibility for the integrity of the content of the paper

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Introduction

Chronic rhinosinusitis with or without nasal polyps is defined as the presence of two or more symptoms of nasal obstruction, nasal discharge, congestion, facial pain or reduction of smell that lasts for equal to or more than 12 weeks.[1] There should be confirmed evidence of inflammation on endoscopy or imaging. Although symptoms can be mild, chronic rhinosinusitis can have a significant negative impact on a person's quality of life, sleep and productivity. Chronic rhinosinusitis also has a large economic burden on the healthcare system and society overall. In Australia, chronic rhinosinusitis has been estimated to cost an overall annual productivity of AUD $10 893.84 per patient.[2] In the USA, the overall direct healthcare cost related to chronic rhinosinusitis is estimated to range between US $10 and $13 billion per year, and the indirect cost related to loss of work productivity is estimated to be more than US $20 billion.[3]

There are an array of different medical therapies for chronic rhinosinusitis. Several guidelines recommend saline sprays or rinses, intranasal or oral corticosteroids, and short or prolonged courses of antibiotics for the treatment of chronic rhinosinusitis depending on the clinical context.[1,4,5] The effectiveness and choice of antibiotics has been controversial. A 2016 Cochrane review of 5 randomised, controlled trials (293 participants) found very little evidence that systemic antibiotics are effective in the treatment of patients with chronic rhinosinusitis.[6] However, in that review, there was only one trial that investigated the effects of doxycycline in chronic rhinosinusitis (Van Zele *et al.*[7]) in 2010. This randomised, placebo-controlled, multicentre trial found that a 20-day course of doxycycline had a moderate effect in reducing polyp size with persistent effects for 12 weeks.[7]

Doxycycline is a tetracycline that targets the 30S ribosomal subunit and thereby blocks protein synthesis. It is used to treat a variety of infections, but it also has several anti-inflammatory properties that make it suitable for non-infectious conditions as well. It has been found to inhibit matrix metalloproteinase, neutrophil migration and activation, mast cell activation, interleukin 8, and T-cell proliferation.[8,9] Doxycycline's role in chronic rhinosinusitis may therefore be through its anti-inflammatory effect, rather than as an antibiotic, because chronic rhinosinusitis is more an inflammatory process of the sinuses and upper airways rather than an infection.[10]

The objective of this current study was to perform an updated systematic review and meta-analysis to investigate the highest-quality evidence on the role of doxycycline in the management of chronic rhinosinusitis with or without nasal polyps.

Materials and methods

Relevant articles were identified through a literature search of the following databases: Ovid Medline, Cinahl, Scopus and Web of Science. In order to identify relevant literature,

a combination of the following search terms was used: 'sinusitis', 'nasal polyps', 'doxycycline' and 'tetracycline'. The search was combined to limit manuscripts to randomised, controlled trials, systematic reviews and meta-analyses. Animal studies were excluded. References from the identified studies were reviewed for additional relevant articles. The search strategy was developed by a medical research librarian at Flinders University, Adelaide, Australia.

Article selection

Only randomised, clinical trials, systematic reviews and meta-analyses were accepted. Inclusion criteria were: studies that were conducted on adults above the age of 16 years who were considered to have chronic rhinosinusitis with or without nasal polyps and had been treated with a course of doxycycline.

Selected studies were chosen only if there were clinical and/or radiological outcomes. Diagnostic criteria for chronic rhinosinusitis were allowed to vary across individual studies. Any studies involving children, acute sinusitis, allergic fungal sinusitis, cystic fibrosis, primary ciliary dyskinesia, aspirin-exacerbated respiratory disease, sarcoidosis, immunodeficiency or rheumatological diagnoses were excluded.

Article review

Our review process involved two stages. In stage one, two of the authors (DSC and OHK) screened the titles and abstracts of each article independently. If there were any disagreements between the reviewers, there was a discussion among them. If there was still a disagreement at that point, then the article was included in stage two of the review process.

In the second stage, the complete manuscripts of the selected studies were independently reviewed by the two authors using standardised critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (Appendix 1). If there were disagreements between them for a given article, a third senior author (EO) arbitrated for further inclusion. We also reviewed the bibliographies from all the included studies to incorporate additional relevant articles. There was no blinding to authors, affiliations or publishing journal.

Data extraction and analysis

Raw means and standard deviations were extracted from the included studies. Because of the gross heterogeneity of the data, we decided to perform the meta-analysis using mean differences of pre- versus post-doxycycline treatment that were recorded using the same measurement tool pre- and post-treatment to report the effects.

The Comprehensive Meta-Analysis software (Biostat, Englewood, USA) was used to compute the data and generate the result using the random effects model. In situations wherein statistical pooling was impractical, the findings were represented in a narrative format with relevant tables to assist in representation of data.

Risk of bias

Each included randomised, clinical trial was assessed for potential risk of bias using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0 tool) by the two authors.[11] The assessment was made on the randomisation processes, deviation from the intended intervention arising from effect to intervention and effect of adhering to intervention (if adherence was studied), missing outcomes, measurement in outcome, and selection of reported results. Results were classified to be low potential, some potential or high potential for risk of bias. The final risk of bias assessment for each study was equated as a combination of assessment in each domain as per instructions given in the tool. Discrepancies were resolved through discussion (Table 1).

The overall risk of bias assessment reported one study as a high risk of bias,[7] three studies with some concern related to risk of bias (Pinto Bezerra Soter *et al.*, 2017[12]; Siu *et al.*, 2021[13]; Parasher *et al.*, 2019[14]), and only one study that had a low risk of bias (Cherian *et al.*, 2020[15]). Across all five domains of assessment, all studies had low risk of bias on measurement of outcome as these were measured objectively using validated tools. There was some concern in three studies related to randomisation as there was no random sequence generation or allocation concealment (Pinto Bezerra Soter *et al.*[12]; Siu *et al.*[13]; Parasher *et al.*[14]). In the study conducted by Van Zele *et al.*,[7] many of the patients in the placebo group dropped out as there was no progress in the outcome associated with the disease. This was not accounted for and was therefore graded as high risk of bias in missing outcome data.

Results

A total of 279 studies were screened, of which 5 studies met our inclusion and exclusion criteria. All the five included studies were randomised, controlled trials (Table 2).

Sample characteristics

The sample size of the included studies ranged from 31 to 60 participants. The total sample size of all the included studies combined was 235 participants. The inclusion criteria for three studies were that the patients had a primary diagnosis of chronic rhinosinusitis (Cherian *et al.*[15]; Parasher *et al.*[14]; Pinto Bezerra Soter *et al.*[12]). Among these, the study by Pinto Bezerra Soter *et al.*[12] included only those patients who had nasal polyps, whereas Cherian *et al.*[15] and Parasher *et al.*[14] included participants either with or without nasal polyps. Two studies included only those participants who had been or were about to undergo surgery for chronic rhinosinusitis with nasal polyps (Siu *et al.*[13]; Van Zele *et al.*[7]). In all the included studies, the ratio of men to women was almost equal except for one study in which the number of men was significantly greater (Van Zele *et al.*[7]). The age in the included studies ranged from 35–57 years.

Intervention characteristics

All the included studies had unique study designs with different doxycycline doses, comparators, length of follow up and outcome measures. Pinto Bezerra Soter *et al.*[12] and Parasher *et al.*[14] compared two study arms. The former study consisted of one arm that was treated with saline nasal irrigations, nasal steroids and doxycycline versus a control arm that was treated with only saline irrigations and topical nasal steroids. The latter study compared a study arm with topical steroids, saline nasal sprays and doxycycline to a control arm that was treated

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Table 1. Assessment of risk of bias

Author, year	Randomisation	Effect of assignment to intervention	Missing outcome data	Bias in measurement of outcome	Selection of reported results	Overall assessment
Van Zele *et al.*,[7] 2010	LR	LR	HR	LR	LR	HR
Pinto Bezerra Soter *et al.*,[12] 2017	SC	LR	LR	LR	LR	SC
Siu *et al.*,[13] 2021	SC	LR	LR	LR	SC	SC
Parasher *et al.*,[14] 2019	SC	LR	LR	LR	LR	SC
Cherian *et al.*,[15] 2020	LR	LR	LR	LR	LR	LR

LR = low risk of bias; HR = high risk of bias; SC = some concern

with a similar regimen where doxycycline was replaced with a placebo.

Van Zele *et al.*[7] and Siu *et al.*[13] had a study design with three arms each. Van Zele *et al.*[7] compared the effects of doxycycline, methylprednisolone and placebo separately in different arms. Similarly, Siu *et al.* compared the effects of doxycycline and roxithromycin in different arms to another arm that was not treated with any antibiotics.

Cherian *et al.* compared treatment arms in a significantly robust manner wherein treatment arm 'A' received oral steroids in addition to placebo saline irrigation and placebo antibiotics, treatment arm 'B' received topical steroids in addition to placebo saline irrigation and placebo antibiotics, and treatment arm 'C' received oral doxycycline in addition to placebo saline irrigations and placebo for oral steroids.

All the studies used doxycycline for a minimum of 20 days except for Siu *et al.*[13] who used it for only 7 days. A detailed description of the antibiotic dosages is outlined in Table 2.

End points

The pre-treatment scores were recorded in a clinical setting across all the five studies. Siu *et al.*[13] had the shortest treatment span of 7 days prior to sinus surgery with post-treatment scores being measured on the 7th day intra-operatively after the final dose of doxycycline. On the contrary, Pinto Bezerra Soter *et al.*[12] measured their outcomes directly at the end of 12 weeks of treatment. Van Zele *et al.*[7] measured their outcomes at 1, 2, 4, 8 and 12 weeks, and Parasher *et al.*[14] measured their outcomes at 3, 8 and 12 weeks. The only study to measure the outcomes after a significant period following the end of treatment was the study by Cherian *et al.*,[15] who measured it at the cessation of therapy (three weeks) and then again three weeks after the cessation of therapy. For the purpose of our analysis, we considered their scores from the three-week time point (Table 3).

Outcomes

The measured outcomes used to record pre-treatment and post-doxycycline treatment scores varied across all the included studies. Pinto Bezerra Soter *et al.*[12] used the Sino-Nasal Outcome Test-20 (SNOT-20), Nasal Obstruction Symptom Evaluation Scale and Lund–Kennedy endoscopic scores. Similarly, Parasher *et al.*[14] used the SNOT-22, endoscopic nasal polyp score, a visual analogue scale and a subjective symptom score that reported a summative mean score for nasal congestion, rhinorrhoea and post-nasal discharge. The other study that used nasal polyp scores to report outcomes was Van Zele *et al.*[7] However, they also reported symptoms such as anosmia, nasal congestion, rhinorrhoea and post-nasal discharge in the form of a separate mean and standard deviation for each symptom. The only other study to report outcomes using SNOT-22 scores was Cherian *et al.*[15] They also reported outcomes using Lund–Kennedy, Lund–Mackay (pre-treatment only) and Adelaide Disease Severity score. Lastly, Siu *et al.*[13] used median Lund–Kennedy scores to report their pre-treatment and post-treatment outcomes (Table 2). Because of the vast variety of tools used to report the outcomes, we decided to compute the data of studies that used similar tools to record pre- and post-doxycycline treatment scores, namely SNOT-22, nasal polyp score and symptom score.

Sino-Nasal Outcome Test-22

The SNOT-22 is a validated health-related quality-of-life outcome measure that was developed to assess symptoms pertaining to chronic rhinosinusitis. It consists of 22 patient-reported signs and symptoms, each of which range from 0 to 5 (0 equates to no symptoms and 5 equates to an intolerable state). Only two studies used pre- and post-treatment means to report the outcomes (Cherian *et al.*[15] (standardised mean difference, 0.195; standard error of the mean (SEM), 0.252; *p*-value, 0.440) and Parasher *et al.*[14] (standardised mean difference, 0.160; SEM, 0.205; *p*-value, 0.435) (Figure 1a).

Nasal polyp scores

Nasal polyp score is a validated endoscopic score that was developed to assess the size of the nasal polyps. It is scored from 0 to 4 (0 equates to no polyps and 4 equates to large polyps causing complete obstruction until the level of the inferior meatus). Total endoscopic nasal polyp score is the sum of both unilateral scores.[16] Only two studies used pre- and post-treatment means to report the outcomes of nasal polyp scores: Parasher *et al.*[14] (standardised mean difference, 0.074; SEM, 0.204; *p*-value, 0.717) and Van Zele *et al.*[7] (standardised mean difference, 0.749; SEM, 0.302; *p*-value, 0.013) (Figure 1b).

Symptom scores

Although all the studies briefly mentioned the symptoms of chronic rhinosinusitis, such as congestion, nasal discharge, post-nasal drip and anosmia, only 2 studies reported both pre- and post-treatment scores for these symptoms and were compared accordingly: Van Zele *et al.*[7] (standardised mean difference, 0.574; SEM, 0.288; *p*-value, 0.046) and Cherian *et al.*[15] (standardised mean difference, −0.538; SEM, 0.267;

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Table 2. Study characteristics

Author, year	Aim	Sample	Sample characteristics		Intervention characteristics		Follow up	Primary outcomes	Tools used	Results
			Experimental group	Control group	Experimental group	Control group				
Van Zele *et al.*,[7] 2010	To evaluate the impact of oral doxycycline & glucocorticoids on objective biological & clinical parameters in patients with CRSwNP	CRSwNP that is recurrent after surgery or severe CRSwNP	1) Doxycycline: *n* = 14; male = 11; age (mean (SD)) = 55.04 (4.28) years. 2) Methylprednisolone: *n* = 14; male = 12; age (mean (SD)) = 48.89 (3.23) years	Placebo: *n* = 19; male = 15; age (mean (SD)) = 54.67 (3.07) years	1) Oral doxycycline (200 mg on day 1, & 100 mg/day for 20 days). 2) Oral methylprednisolone (32 mg/day on days 1–5; 16 mg/day on days 6–10; & 8 mg/day on days 11–20)	Placebo	1, 2, 4, 8 & 12 weeks	Size of polyp, symptoms of post-nasal drip, eosinophilic cationic protein rhinorrhoea	NPS, postnasal drip scores, rhinorrhoea, IL-5, MMP-9	Doxycycline significantly reduced polyp size compared with placebo ($p < 0.005$). The significant reduction of polyp size remained significant even for up to 12 weeks. Doxycycline also significantly reduced rhinorrhoea ($p < 0.058$) & post-nasal drip symptoms ($p < 0.044$). Eosinophilic cationic protein levels decreased significantly in the doxycycline group at 1 month ($p < 0.032$), whereas they increased in the placebo group
Pinto Bezerra Soter *et al.*,[12] 2017	To evaluate clinical outcomes of low-dose long-term oral doxycycline therapy in difficult-to-treat CRSwNP	CRSwNP	*n* = 28; male = 13; female = 15; male: female ratio = (0.87); age (mean (SD)) = 47.50 (16) years	*n* = 30; male = 14; female = 16; mean age = 47.50 years	Saline irrigation, nasal steroids & doxycycline (200 mg on the first day, followed by 100 mg once daily) for 12 weeks	30 received only saline irrigation & nasal steroids	12 weeks after the start of treatment	Clinical improvement observed in disease-specific quality of life	SNOT-20, LKS, NOSE	There was a statistically significant improvement after 12 weeks of doxycycline on SNOT ($p = 0.002$), NOSE ($p = 0.046$) & LKS ($p = 0.004$)
Siu *et al.*,[13] 2021	To investigate the short-term impact of antibiotics on the sinus & gut microbiota	Patients set to undergo endoscopic sinus surgery for CRS	Doxycycline: *n* = 10; male = 6; female = 4; age (mean (range)) = 35 (21–73) years. Roxithromycin: *n* = 11; male = 7; female = 4; age (mean (range)) = 52 (26–72) years	Control group: *n* = 10; male = 5; female = 5; age (mean (range)) = 57 (17–74) years	(1) Doxycycline (100 mg daily for 7 days). (2) Roxithromycin (300 mg daily for 7 days)	No antibiotic given	After 7 days of treatment	Clinical improvement & comparison of scores observed by nasal endoscopy on the day of surgery (day 7)	MLK, SNOT-22 (baseline only)	There was no significant correlation between endoscopic scores (MLK) & concentration of antibiotic in the tissue, sino-nasal mucus or serum
Parasher *et al.*,[14] 2019	To understand if addition of doxycycline to the standard anti-inflammatory regimen improves patient outcomes	CRS	*n* = 24; male = 14 (58%); female = 10 (42%); age (mean ± SD) = 51.5 ± 13.8 years	*n* = 25; male = 12 (48%); female = 13 (52%); age (mean (SD)) = 44.1 ± 12.2 years	Doxycycline (200 mg orally × 1 dose on day 1, then 100 mg orally daily for days 2–20) in addition to treatment as usual	Placebo pill in addition to treatment as usual	3-, 8- & 12-week visits	Clinical improvement	SNOT-22, VAS, NPS	There was no significant difference in VAS scores, SNOT-22 scores & nasal polyp scores, between the two groups
Cherian *et al.*,[15] 2020	To investigate the impact of oral & topical corticosteroids, & antibiotics in patients	CRSsNP CRSwNP	Oral steroid: *n* = 17; male = 9; female = 7; mean age = 44.18 years.	No control groups	Oral prednisolone + 200 ml isotonic saline with water for injection as placebo + oral placebo for	No control groups	Treatment completion (3 weeks) & at 6 weeks	Patient symptom scoring, endoscopic grading & microbiome swabs	LMS, LKS, ADSS, SNOT-22	Clinically significant reduction in SNOT-22 ($p = 0.012$) & ADSS ($p = 0.008$) was observed only in the

(*Continued*)

Table 2. (*Continued.*)

Author, year	Aim	Sample	Sample characteristics		Intervention characteristics		Follow up	Primary outcomes	Tools used	Results
			Experimental group	Control group	Experimental group	Control group				
	with CRS with or without polyps		Topical steroid: $n = 17$; male = 12; female = 4; mean age = 41.25 years. Oral antibiotic, $n = 16$; male = 8; female = 5; mean age = 39.00 years		antibiotic Placebo for oral steroid + topical budesonide (0.5 mg/2 ml respules) washes of the nasal cavities & sinuses + oral placebo for antibiotic. Placebo for oral steroid + isotonic saline with water for injection as placebo + oral doxycycline (antibiotic)		(3 weeks after treatment completion)			oral & topical steroid group at the end of 3 weeks. LKS scores improved with prednisolone ($p = 0.013$) & placebo ($p = 0.025$) at the end of 3 weeks, but no significant improvement was noted with doxycycline. At the end of 6 weeks, all treatment arms did not sustain significant improvement

CRSwNP = chronic rhinosinusitis with nasal polyps; SD = standard deviation; NPS = nasal polyps score; IL = interleukin; MMP = matrix metalloproteinases; SNOT-22 = Sinonasal Outcome Test-22; LKS = Lund–Kennedy Score; NOSE = Nasal Obstruction Symptom Evaluation; CRS = chronic rhinosinusitis; MLK = Modified Lund–Kennedy score; VAS = visual analogue scale; CRSsNP = chronic rhinosinusitis without nasal polyps; LMS = Lund–Mackay score; ADSS = Adelaide Disease Severity Score

Table 3. Follow-up periods

Author, year	End points
Van Zele *et al.*,[7] 2010	At 1, 2, 4, 8 and 12 weeks' treatment
Pinto Bezerra Soter *et al.*,[12] 2017	At 12 weeks after treatment
Siu *et al.*,[13] 2021	At 7 days after treatment
Parasher *et al.*,[14] 2019	At 3, 8 and 12 weeks after treatment
Cherian *et al.*,[15] 2020	At 3 weeks of treatment and 3 weeks after completion of treatment

p-value, 0.044) (Figure 1c). It is worth mentioning that the Adelaide Disease Severity Score tool, a simple validated tool that assesses symptoms such as nasal obstruction, rhinorrhoea and post-nasal drip in chronic rhinosinusitis, was used for the latter study.[17]

Discussion

This systematic review identified five randomised, controlled trials that met our inclusion criteria. The selected studies were heterogeneous and used different controls, length of treatment with doxycycline, outcome measures and length of follow up.

From our systematic review and meta-analysis of the mean change in SNOT-22, symptom scores and nasal polyp scores, it appears that doxycycline has some initial positive effects in reducing the symptoms of chronic rhinosinusitis after three weeks of treatment when compared with baseline pre-treatment scores. However, a deeper look into the data suggests that the overall size of the effect appears insignificant.

Firstly, all the studies included in the review were underpowered except for the study by Pinto Bezerra Soter *et al.*,[12] who had the largest study of 60 participants, 28 of whom received doxycycline. In recent years, research looking at the diagnostic investigation and management of chronic rhinosinusitis has become focused on phenotypes and endotypes of chronic rhinosinusitis. Phenotyping classifies types of chronic rhinosinusitis based on endoscopic findings, imaging, patients' co-morbid medical conditions, age of onset, triggers and so on. Chronic rhinosinusitis endotypes are based on specific pathogenetic mechanisms or molecular biomarkers.[18] Pinto Bezerra Soter *et al.*[12] did identify that the patients who improved their SNOT-22 scores on doxycycline were less likely to have asthma, aspirin exacerbated respiratory disease and elevated immunoglobulin E levels prior to treatment. Van Zele *et al.*[7] evaluated specific inflammatory markers and found that the doxycycline group had significantly decreased matrix metallopeptidase-9, myeloperoxidase and eosinophilic cationic protein levels in nasal secretions. Larger sample sizes would have likely depicted more precise outcomes[19] and would possibly allow for stronger conclusions regarding which phenotypes or endotypes respond to the use of doxycycline.

Although our data compared the same outcome instruments, the dosage, drug combinations and end points in the comparison were different. For example, Parasher *et al.*[14] and Van Zele *et al.*[7] used nasal polyp scores at 12 weeks to compare their outcomes. However, although Van Zele *et al.*[7] used doxycycline alone, Parasher *et al.*[14] used doxycycline in combination with methylprednisolone daily in a tapering dose along with saline nasal sprays.

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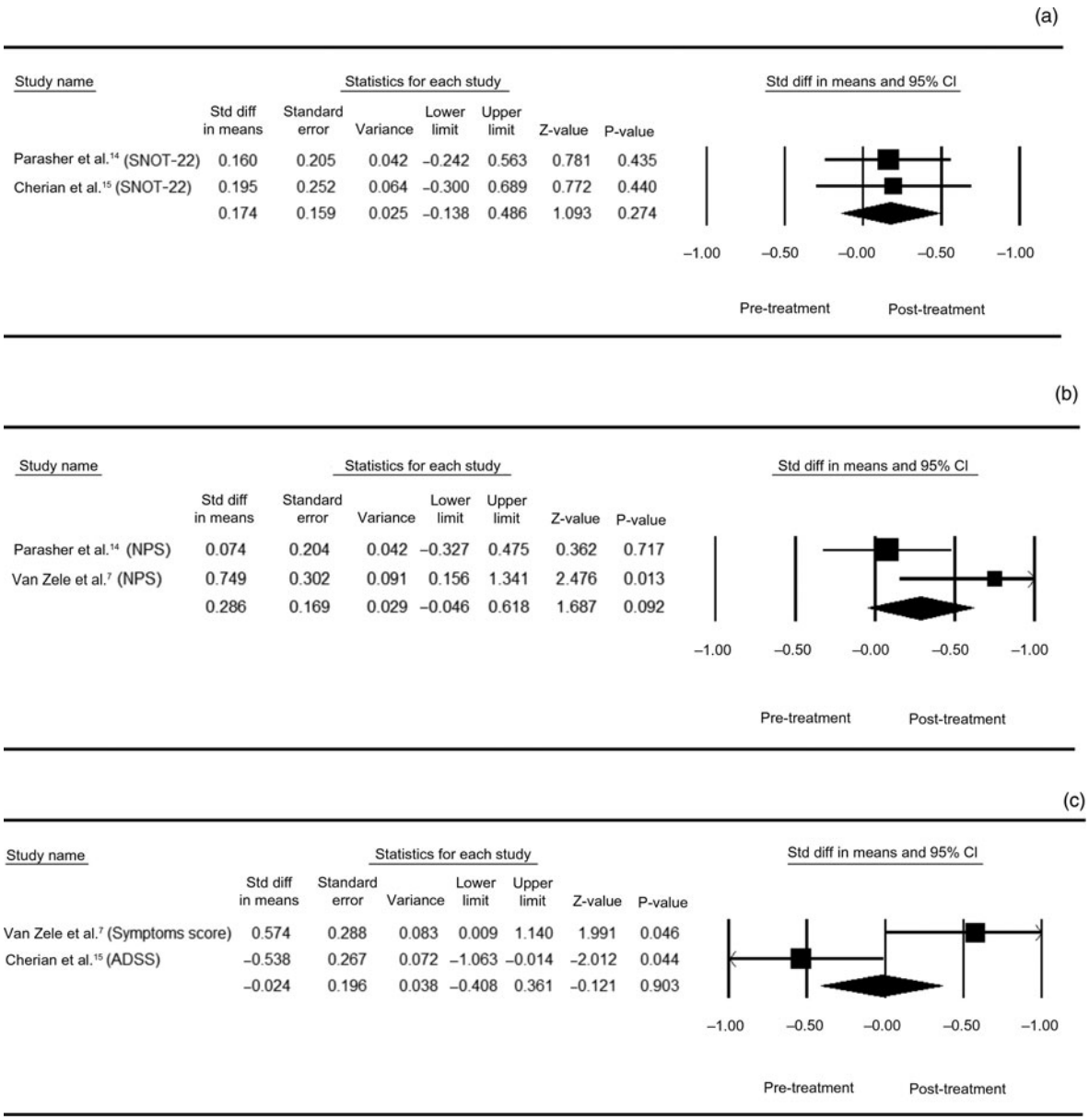

Fig. 1. (a) Forest plot for Sino-Nasal Outcome Test (SNOT)-22 scores, (b) forest plot for nasal polyp scores (NPS) and (c) forest plot for symptom scores. Std diff = ; CI = confidence interval; ADSS = Adelaide Disease Severity Score.

The length of treatment with doxycycline was variable; Siu *et al.*[13] report insignificant results with doxycycline when participants with chronic rhinosinusitis were only prescribed a short 7-day course of antibiotics one week prior to surgery. A common consensus in the current medical literature is that antibiotics are generally prescribed to regress bacterial growth and decrease inflammation in chronic rhinosinusitis.[20] However, it appears that studies in the literature suggest better outcomes in chronic rhinosinusitis when doxycycline is used for longer terms.[7,10,21–23] A common finding across all studies that used doxycycline for two weeks or more is the objective reduction in symptoms and/or a reduction in polyp size. However, it is important to follow up these cases and understand the trend following treatment cessation. Cherian *et al.*,[15] in their randomised, clinical trial, reported that the changes in the symptoms scores after a 21-day treatment of doxycycline were not sustainable beyond 3 weeks following cessation of treatment. This is in contrast to the study by Van Zele *et al.*,[7] who did identify a persistent improvement in polyp size at the 12-week follow up after treatment with a 20-day course of 100 mg doxycycline daily. Interestingly, there was no improvement in any reported symptoms with doxycycline except for post-nasal drip. Pinto Bezerra Soter *et al.*[12] had the largest study but also the longest course of doxycycline (12 weeks of 100 mg daily). They did show positive results with statistically significant improvement of SNOT-20, Nasal Obstruction Symptom Evaluation and Lund–Mackay computed tomography scan scores. Perhaps an extended course may have had superior results; however, they did not evaluate whether there was a sustained effect with their treatment regimen.

Doxycycline appears to be well tolerated by patients with chronic rhinosinusitis, and there seem to be few reported adverse events with its use. A list of adverse events was reported by Van Zele *et al.*,[7] but none of the participants randomised to the doxycycline group withdrew from the study because of adverse events. They also reported no significant differences in the number or type of adverse events between groups (methylprednisolone *vs* doxycycline *vs* placebo). Similarly, Pinto Bezerra Soter *et al.*[12] did not report any

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adverse events in their trial with the prolonged 12-week course of doxycycline.

This review has limitations. Only level 1 evidence studies were included to try to provide adequate conclusions on the practical use of doxycycline in chronic rhinosinusitis. The inclusion and exclusion criteria restricted the authors from analysing data from other studies in the literature including case controls, case series and *in vivo* studies. In doing so, only five studies were identified, one of which had a high risk of bias. In addition, the studies may have used different diagnostic criteria for chronic rhinosinusitis, and some included mixed cohorts of chronic rhinosinusitis patients (with and without nasal polyposis). It was therefore difficult to make specific conclusions regarding the use of doxycycline in the management of chronic rhinosinusitis.

Conclusion

Doxycycline appears safe to use in patients with chronic rhinosinusitis; however, the literature is mixed regarding its efficacy. Most of the studies are underpowered, and interpretation of results must be taken with precaution. Our meta-analysis is limited by the small number of high-quality studies, the different durations of treatment, outcome measures used and follow-up periods. Based on the evidence of this review, there continues to be clinical equipoise concerning the use of doxycycline in the treatment of chronic rhinosinusitis.

There is scope for future studies to recruit a larger number of patients based on European Position Paper on Rhinosinusitis and Nasal Polyps 2020 criteria (Fokkens *et al.*[1]) for chronic rhinosinusitis and to investigate the effects of long-term doxycycline in double-blind randomised, clinical trials using placebo, saline irrigation and corticosteroids separately or in combination as comparators. Lastly, over 13 different tools have been used to report the outcomes in 5 studies alone, which made them difficult to compare. Over the last few years, patient-reported outcomes have become one of the mainstays of evaluating the effectiveness of a particular intervention. Of all the validated tools mentioned in this review, we believe that changes in SNOT-22, Lund–Mackay Score and modified Lund–Kennedy scores would give a comprehensive picture and should be used in future studies. In addition, the ability to investigate the use of doxycycline with different chronic rhinosinusitis phenotypes and endotypes with large-scale studies may allow clinicians to provide targeted therapy to those who will benefit.

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Appendix 1. Medline database

Database(s): Ovid Medline(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to November 10, 2021

Table 1. Search strategy

Number	Search	Results
1	Sinusitis/	18 786
2	Nasal Polyps/	7189
3	("Chronic Rhinosinusitis" or Rhinosinusitis or "Chronic sinusitis" or polyp* or "nasal polyp*").ti,ab,kf.	317 089
4	1 or 2 or 3	32 7658
5	Doxycycline/	10 260
6	Tetracycline/	20 521
7	(Tetracycline* or Doxycycline*).ti,ab,kf.	41 024
8	5 or 6 or 7	56 387
9	(review or meta-analysis).ti,ab,kf.	1 936 454
10	"Review Literature as Topic"/ or "Systematic Review"/ or "Review"/	2 969 768
11	clinical study/ or exp clinical trial/ or Clinical Trials as Topic/ or Randomized Controlled Trials as Topic/ or follow-up studies/ or prospective studies/ or evaluation study/ or comparative study/ or random allocation/ or single-blind method/ or Double-Blind Method/	3 936 009
12	(random* or (clinic* adj5 trial*) or ((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or placebo*).ti,ab,kf.	1 653 446
13	9 or 10 or 11 or 12	7 881 526
14	(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*).ti. or (Animal experimentation/ not (human experimentation/ or human/))	2 089 994
15	Animal/ not (Animal/ and Humans/)	4 879 634
16	14 or 15	43 917
17	4 and 8 and 13	105
18	17 not 16	92

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Table 2. Cinahl database search

Number	Query	Limiters/expanders	Results (*n*)
S21	S19 NOT S20	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	10
S20	(((MH "Animals+") OR (MH "Animal Studies") OR (TI "animal model*" OR rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*)) NOT (MH "human"))	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	259 473
S19	S4 AND S8 AND S18	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	12
S18	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	Expanders – apply equivalent subjects Search modes – Boolean/phrase	1 728 764
S17	TI ((random* or (clinic* N4 trial*) or ((singl* or doubl* or trebl* or tripl*) N4 (blind* or mask*)) or placebo*)) OR AB ((random* or (clinic* N4 trial*) or ((singl* or doubl* or trebl* or tripl*) N4 (blind* or mask*)) or placebo*))	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	480 817
S16	(MH "Double-Blind Studies")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	51 587
S15	(MH "Single-Blind Studies")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	15 201
S14	(MH "Random Assignment")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	70 821
S13	(MH "Comparative Studies")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	402 731
S12	(MH "Prospective Studies")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	481 864
S11	(MH "Clinical Trials+") OR (MH "Randomized Controlled Trials")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	326 454
S10	(MH "Literature Review") OR (MH "Systematic Review")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	108 310
S9	TI (review or meta-analysis) OR AB (review or meta-analysis)	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	606 781
S8	S5 OR S6 OR S7	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	4401
S7	TI (Doxycycline or Tetracycline*) OR AB (Doxycycline or Tetracycline*)	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	2011
S6	(MH "Tetracycline") OR (MH "Tetracyclines")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	1185
S5	(MH "Doxycycline")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	1976
S4	S1 OR S2 OR S3	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	27 724
S3	TI ("Chronic Rhinosinusitis" or Rhinosinusitis or "Chronic sinusitis" or polyp* or "nasal polyp*") OR AB ("Chronic Rhinosinusitis" or Rhinosinusitis or "Chronic sinusitis" or polyp* or "nasal polyp*")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	24 861
S2	(MH "Nasal Polyps")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	1125
S1	(MH "Sinusitis+")	Expanders – apply equivalent subjects. Search modes – Boolean/phrase	4964

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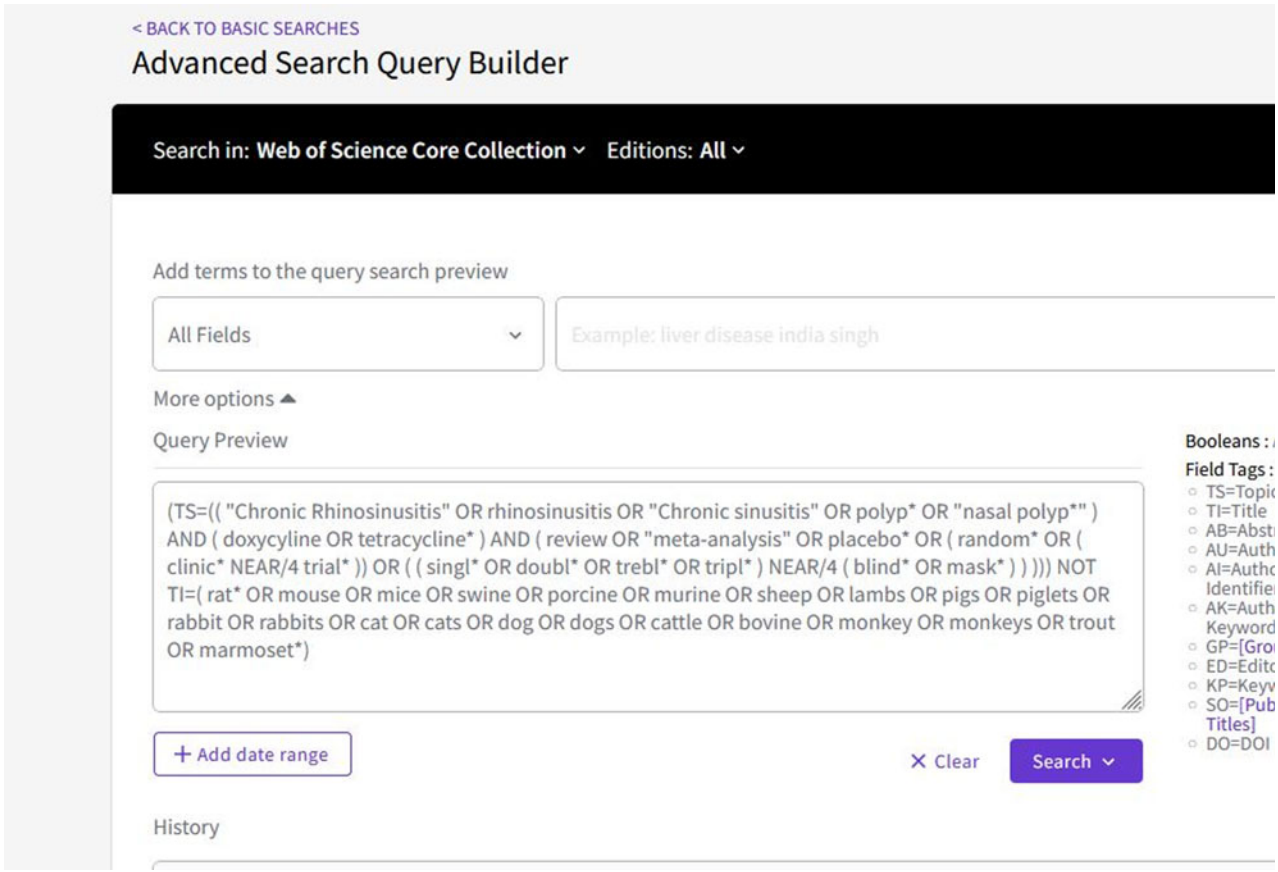
Web of Science search

(TS=((“Chronic Rhinosinusitis” OR rhinosinusitis OR “Chronic sinusitis” OR polyp* OR “nasal polyp*”) AND (doxycycline OR tetracycline*) AND ((review OR “meta-analysis” OR placebo* OR random* OR (clinic* NEAR/4 trial*)) OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/4 (blind* OR mask*))))) NOT TI=(rat* OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset*)

Screenshot below:



Scopus search

((TITLE-ABS ((“Chronic Rhinosinusitis” OR rhinosinusitis OR “Chronic sinusitis” OR polyp* OR “nasal polyp*”)) AND TITLE-ABS-KEY ((doxycycline OR tetracycline*)) AND TITLE-ABS-KEY ((review OR “meta-analysis” OR placebo* OR random* OR (clinic*W/4trial*))))) AND NOT (TITLE-ABS (rat OR rats OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset*))

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