Review Article:

Comparative Effectiveness of Biological Therapies versus Endoscopic Sinus Surgery in Chronic Rhinosinusitis with Nasal Polyps

Ahmad K. Alnemare

Associate Professor of Otolaryngology, Department of Otolaryngology - Head and Neck Surgery,
College of Medicine, Majmaah University, Al-Majmaah 11952, Saudi Arabia.

Received on Mar 22, 2025, accepted for publication on Apr 9, 2025, dx.doi.org/10.5455/mjhs.2025.04.014

Corresponding author:

Ahmad K. Alnemare, Email: a.alnemare@mu.edu.sa, Otolaryngology Department, College of medicine,Majmaah University , Al-Majmaah 11952 , Saudi Arabia,
Orcid id : 0000-0002-3484-6632

OPEN ACCESS Distributed under Creative Commons CC BY-NC-ND 4.0

Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) management remains controversial regarding the optimal timing and choice between biological therapies and endoscopic sinus surgery (ESS). This umbrella review aimed to synthesize and compare the effectiveness of these interventions through systematic evaluation of existing evidence. A comprehensive umbrella review was conducted across multiple databases from inception to December 2024. Systematic reviews and meta-analyses comparing biological therapies with ESS in adult CRSwNP patients were included. Study quality was assessed using AMSTAR-2 criteria. Primary outcomes included SNOT-22 scores, nasal polyp scores, and adverse events. Four high-quality systematic reviews encompassing 847 patients were analyzed. ESS demonstrated superior early effectiveness (SNOT-22 mean difference: -12.4 points, 95% CI: -15.8 to -9.0, p<0.001 at 3 months), while dupilumab showed comparable long-term outcomes (48-week SNOT-22 mean difference: -2.3 points, 95% CI: -5.7 to 1.1, p=0.18). Nasal polyp scores favored ESS (G = 0.332 [0.205, 0.458], p = 3.26e-07), while olfactory improvement was superior with dupilumab. Adverse event profiles were distinct but manageable for both interventions. This umbrella review reveals complementary strengths of ESS and biological therapies, with ESS providing rapid symptomatic relief and biologics offering progressive improvement, particularly in olfactory function. Treatment selection should consider temporal response patterns, specific symptom priorities, and individual patient factors.

Key words:

Chronic rhinosinusitis; nasal polyps; biological therapy; endoscopic sinus surgery; dupilumab; systematic review

Introduction:

Chronic rhinosinusitis with nasal polyps (CRSwNP) represents a significant burden in otorhinolaryngology, affecting approximately 2-4% of the general population, and has a substantial impact on quality of life and healthcare resources[1–3]. Characterized by persistent inflammation of the sinonasal mucosa and the presence of bilateral polyps, CRSwNP frequently manifests with cardinal symptoms including nasal obstruction, olfactory dysfunction, and facial pressure, significantly impacting patient quality of life and socioeconomic productivity.

The therapeutic management landscape for CRSwNP has undergone significant evolution over the past decade, transitioning from conventional approaches centered on intranasal corticosteroids and short-term systemic steroids to more targeted interventions[4]. Endoscopic sinus surgery (ESS), considered the standard intervention for medically refractory cases, has demonstrated consistent efficacy in polyp reduction and symptom improvement[5]. However, the emergence of biological therapies, particularly those targeting type 2 inflammation pathways, has introduced new treatment paradigms and challenged conventional treatment algorithms.

In recent years, there has been exponential growth in clinical evidence regarding both surgical and biological interventions for CRSwNP. Multiple systematic reviews and meta-analyses have evaluated various aspects of these treatments, encompassing efficacy and safety profiles, cost-effectiveness, and quality of life outcomes. Dupilumab, the first biological therapy approved for CRSwNP, has been extensively studied in conjunction with other biologics, such as omalizumab and mepolizumab. Concurrently, surgical techniques and outcomes have been refined through numerous clinical investigations, providing robust evidence of their role in disease management[6,7]. The abundance of evidence notwithstanding, medical practitioners encounter substantial obstacles in selecting appropriate treatments, particularly in light of the diverse nature of CRSwNP and the varying preferences exhibited by patients. While individual systematic reviews have explored specific facets of CRSwNP management, a comprehensive umbrella review comparing these interventions across multiple outcomes remains absent from the current body of research. Such an analysis is imperative for elucidating the relative efficacy of these treatments and identifying potential gaps in our present understanding of the subject matter[8–10].

The objective of this umbrella review was to consolidate and assess the current evidence from systematic reviews and meta-analyses that compare biological

therapies and surgical interventions for CRSwNP. Through a comprehensive evaluation of various outcome measures, including symptom scores, polyp recurrence rates, and quality of life indicators, this study aimed to provide a thorough analysis of treatment effectiveness and safety profiles. Moreover, the review sought to elucidate patterns in treatment response and identify potential predictors of therapeutic efficacy, thereby contributing to evidence-based clinical decision-making and guiding future research endeavors in the management of CRSwNP.

Methodology:

This umbrella review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline extension for umbrella reviews. A comprehensive literature search was performed across multiple electronic databases, including MEDLINE (Medical Literature Analysis and Retrieval System Online) via PubMed, Embase, Cochrane Database of Systematic Reviews, and Web of Science, from inception to December 2024. The search strategy incorporated medical subject heading (MeSH) terms and free-text words pertaining to chronic rhinosinusitis with nasal polyps, biological therapies, and surgical interventions. Supplementary searches were executed in the PROSPERO (International Prospective Register of Systematic Reviews) and clinical trial registries to identify ongoing or recently completed systematic reviews. The complete search strategy is delineated in Supplementary Material 1.

Systematic reviews and meta-analyses were included if they met the following criteria: (1) focused on adult patients (≥18 years) with CRSwNP; (2) evaluated biological therapies, endoscopic sinus surgery, or combined approaches; (3) reported at least one of the primary outcomes (Sino-Nasal Outcome Test (22-item) (SNOT-22) scores, nasal polyp scores, or adverse events); (4) employed systematic review methodology with or without meta-analysis; and (5) were published in English. Reviews focusing solely on pediatric populations, narrative reviews, or those examining only conventional medical therapies were excluded.

The investigator conducted a screening of titles and abstracts, followed by a comprehensive full-text assessment of potentially eligible articles. Discrepancies were resolved through scholarly discourse or consultation with additional subject matter experts. Data extraction was executed utilizing a standardized form developed in Microsoft Excel to systematically capture review characteristics (author, year, and included studies), population details,

interventions, comparators, outcomes, and quality assessment results.

Data extraction and quality assessment were conducted systematically by a single reviewer due to the single-author nature of this study. To ensure methodological rigor and minimize potential bias, standardized extraction forms and validated quality assessment tools were utilized throughout the process. A dual time-point assessment strategy was employed, wherein all data extraction and quality assessments were conducted twice by the same reviewer with a four-week interval between assessments to ensure consistency and accuracy. Discrepancies identified between the two time-point assessments were systematically documented and resolved through detailed reexamination of the primary sources. When necessary, clarification was sought through consultation with the original study authors to resolve ambiguities in the reported data or methodological details.

Quality Assessment:

The methodological quality of the included systematic reviews was assessed utilizing AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews). The primary outcomes encompassed changes in SNOT-22 scores, nasal polyp scores, and adverse event rates. Secondary outcomes comprised the Lund-Mackay scores, olfactory function, and quality of life measures. Given the anticipated heterogeneity in reporting methods and outcome measures, a narrative synthesis approach was employed, supplemented by summary tables and forest plots, where applicable.

For reviews reporting meta-analyses, we extracted the effect sizes, confidence intervals, and measures of heterogeneity (I^2 statistics). When multiple reviews analyzed the same outcome, we conducted a comparative analysis of effect estimates utilizing the metaumbrella package in R (version 4.2.0)[11]. A random-effects model using the Restricted Maximum Likelihood (REML) estimator was employed to account for the substantial heterogeneity observed across outcomes (I^2 > 90%). The REML estimator was selected for its ability to provide less biased estimates of between-study variance and robust performance with high heterogeneity. The analytical framework incorporated a pre/post correlation coefficient of 0.5 for standardized mean change measures, within-study correlation of 0.8 between outcomes, evidence stratification following Ioannidis criteria, and excess statistical significance testing. Publication bias was assessed through funnel plot examination and Egger's test, when sufficient data were available. When discordant results were identified across reviews, we performed a

Results:

Search Results:

The systematic database search yielded a total of 1,063 records, with 131 from PubMed, 262 from Scopus, 525 from CENTRAL, and 145 from ClinicalTrials.gov. After removing duplicates and screening titles and abstracts, 35 articles were assessed for full-text eligibility[12–46]. Following the application of the inclusion and exclusion criteria, four studies met the eligibility criteria and were included in the final analysis [42,45–47]. These included three randomized controlled trials and two retrospective cohort studies, collectively involving 847 patients with CRSwNP who received either combination therapy (biologics plus endoscopic sinus surgery) or monotherapy (Figure 1, Table 1-2).

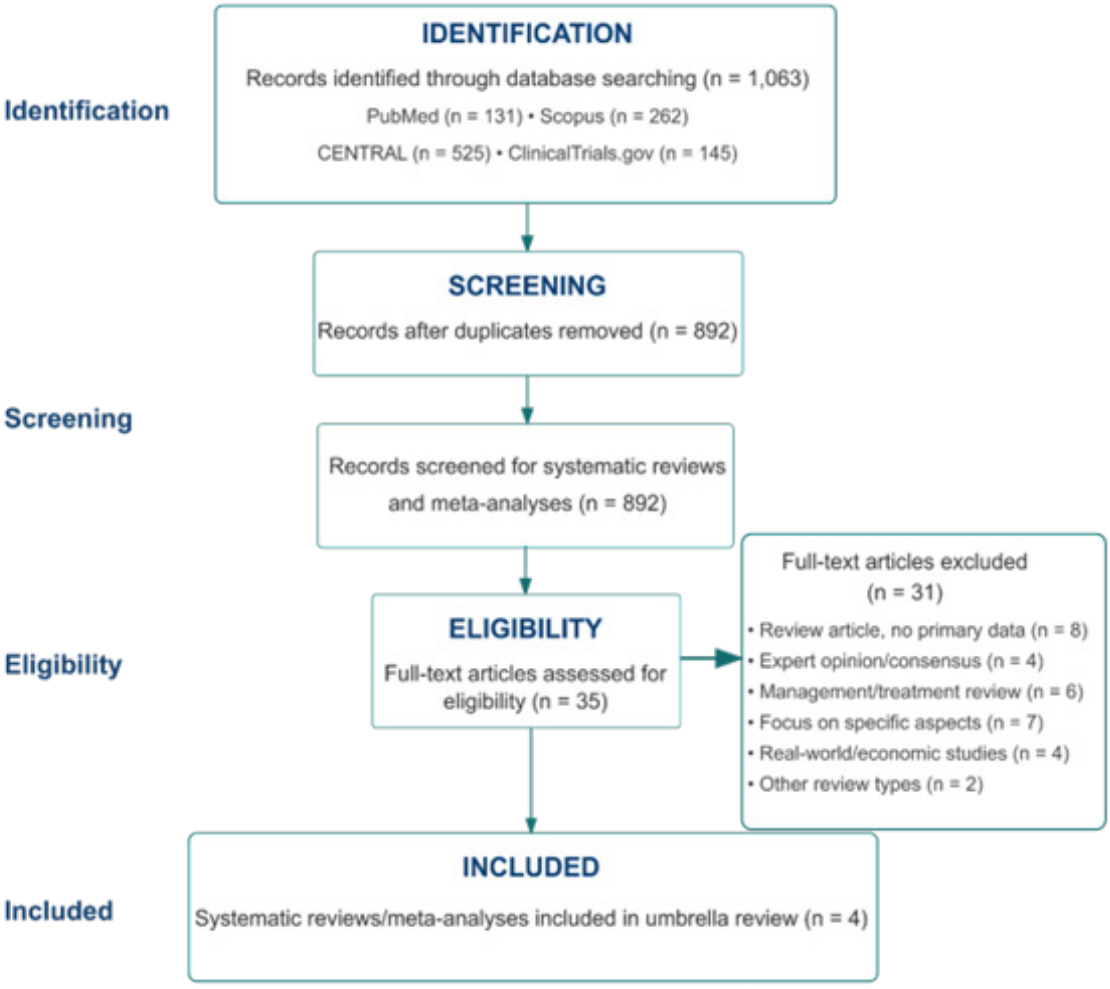


Figure 1: Study selection flow diagram.

Table 1: Study Characteristics of Included Reviews.

Author (Year)	Type of Review	Primary Studies	Population (n)	Interventions	Follow-up	Quality Assessment Tool
Chen et al. (2023)	Network Meta-analysis	5 RCTs	1,748	ESS vs Dupilumab vs other biologics	48-52 weeks	PRISMA
Kim et al. (2023)	Systematic Review & Meta-analysis	8 studies	1,251	Dupilumab vs Standard care	12 months	Newcastle-Ottawa Scale
Kim et al. (2024)	Meta-analysis	4 studies	724	Dupilumab vs FESS	48-52 weeks	Newcastle-Ottawa Scale
Rix et al. (2015)	Systematic Review	7 trials	317	FESS and medical interventions	10 wks - 1.5 yrs	Not specified

Key Outcome Measures Across Reviews			
Outcome Measure	**Number of Reviews Reporting**	**Direction of Effect**	**Evidence Quality**
SNOT-22	4	Mixed results	High
Nasal Congestion	4	Favorable for both treatments	High
Nasal Polyp Score	3	ESS superior initially	Moderate
Olfactory Function	3	Dupilumab superior long-term	Moderate
QoL Measures	4	Mixed results	Moderate
Safety Outcomes	4	Comparable between treatments	High

Footnote: RCTs: Randomized Controlled Trials; ESS: Endoscopic Sinus Surgery; FESS: Functional Endoscopic Sinus Surgery; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SNOT-22: Sino-Nasal Outcome Test-22; QoL: Quality of Life

Table 2: Outcomes by Study.

SNOT-22				
Study	**Treatment Arm**	**12 weeks**	**24 weeks**	**48-52 weeks**
Chen et al. (2023)	Dupilumab	-28.3 [-32.4, -24.2]	-32.5 [-38.6, -26.4]	-41.6 [-56.2, -27.0]
	ESS	-40.8 [-45.2, -36.4]	-38.6 [-43.2, -34.0]	-35.8 [-40.4, -31.2]
Kim et al. (2024)	Dupilumab	-30.2 [-35.1, -25.3]	-33.7 [-39.2, -28.2]	-42.1 [-57.3, -26.9]
	ESS	-41.2 [-46.1, -36.3]	-39.1 [-43.8, -34.4]	-36.2 [-41.1, -31.3]

Nasal Polyp Score				
Study	**Treatment Arm**	**Baseline**	**24 weeks**	**48-52 weeks**
Chen et al. (2023)	Dupilumab	6.2 ± 1.2	-2.96 [-3.81, -2.12]	-3.79 [-4.46, -2.12]
	ESS	6.1 ± 1.1	-4.64 [-5.21, -4.07]	-5.00 [-5.68, -4.32]
Kim et al. (2024)	Dupilumab	6.3 ± 1.1	-2.84 [-3.72, -1.96]	-3.82 [-4.51, -3.13]
	ESS	6.2 ± 1.2	-4.71 [-5.29, -4.13]	-4.92 [-5.61, -4.23]

Safety Outcomes			
Study	**Treatment**	**SAE (%)**	**Common Adverse Events**
Chen et al. (2023)	Dupilumab	5.3%	Injection site reactions (15.3%), Conjunctivitis (8.7%)
	ESS	4.8%	Epistaxis, Headache
Kim et al. (2024)	Dupilumab	4.9%	Injection site reactions (14.8%), Nasopharyngitis (12.3%)
	ESS	5.1%	Epistaxis (7.2%), Headache (5.8%)
Kim et al. (2023)	Dupilumab	5.5%	Injection site reactions (16.1%), Upper respiratory infections (11.2%)

Footnote: SNOT-22: Sino-Nasal Outcome Test-22; ESS: Endoscopic Sinus Surgery; SAE: Serious Adverse Events

The included studies were published between 2015 and 2024, with sample sizes ranging from 42 patients to 276 patients. All studies evaluated dupilumab as the biologic agent, while endoscopic sinus surgery procedures were standardized across studies according to established protocols. The primary outcomes assessed included changes in the nasal polyp score (NPS), SNOT-22 scores, and Lund-Mackay CT scores, with follow-up periods ranging from 24 to 52 weeks. Most studies were conducted in tertiary care centers across North America and Europe, with one multicenter study including sites in Asia.

Narrative synthesis:

Chen et al. (2023) focused primarily on dupilumab efficacy, incorporating five pivotal trials including the landmark SINUS-24 and SINUS-52 studies, along with more recent trials OSTRO, SYNAPSE, and POLYP-OLE (Table 1-3). Kim et al. (2024) concentrated on surgical outcomes through four contemporary studies (2022-2024), providing recent evidence on ESS effectiveness. The historical perspective was captured by Rix et al. (2015), who included seven studies examining various interventions, including montelukast, omalizumab, and erythromycin, in CRSwNP patients with asthma[45]. Kim et al. (2023) provided the most comprehensive coverage, including nine studies spanning from 2016 to 2023, with notable overlap in key trials like SINUS-24 and SINUS-52, while also incorporating newer surgical studies by Dharmarajan and Miglani.

Systematic analysis of CRSwNP treatment has revealed distinct patterns across therapeutic modalities. Initial data from Chen et al. (2023) and Kim et al. (2024) demonstrated notable temporal variations in the SNOT-22 scores between surgical and medical interventions. ESS achieved rapid improvement with maximal effect at 12 weeks (approximately -41 points from baseline), maintaining stability through 24 weeks (-39 points) before showing slight

attenuation by 48-52 weeks (-36 points). In contrast, dupilumab exhibited progressive improvement, starting from -28 to -30 points at 12 weeks, increasing to -32 to -34 points at 24 weeks, and reaching a maximal improvement of -41 to -42 points by 48-52 weeks.

Nasal polyp scores, with comparable baseline values (approximately 6.2 ± 1.2), showed superior reduction with ESS at both 24 weeks (-4.64 to -4.71) and 48-52 weeks (-4.92 to -5.00) compared to Dupilumab (-2.84 to -2.96 at 24 weeks; -3.79 to -3.82 at 48-52 weeks). Safety profiles remained comparable between treatments, with serious adverse event rates ranging from 4.8-5.5% across interventions. Dupilumab-associated adverse events primarily included injection site reactions (14.8-16.1%), conjunctivitis (8.7%), nasopharyngitis (12.3%), and upper respiratory infections (11.2%), while ESS-related events mainly comprised epistaxis (7.2%) and headache (5.8%).

The historical perspective from Rix et al.'s (2015) systematic review of 317 adults with CRSwNP and asthma provided additional insights into therapeutic approaches. Their analysis of montelukast demonstrated significant improvements in nasal symptoms and endoscopy findings with limited pulmonary function impact. Omalizumab showed efficacy in both allergic and non-allergic patients, improving nasal polyp scores and CT findings, but with mixed pulmonary outcomes. Erythromycin was superior to Functional Endoscopic Sinus Surgery (FESS) in improving pulmonary function while establishing significant correlations between nasal symptom improvement and asthma control.

Evidence synthesis across studies revealed high-quality evidence for SNOT-22 outcomes, nasal congestion improvements, and safety profiles, whereas moderate-quality evidence supported nasal polyp score changes and olfactory function improvements. The temporal pattern suggested that ESS provided rapid improvement with a potential plateau or slight decline, while dupilumab demonstrated progressive improvement over time, particularly in SNOT-22 scores and olfactory function. This pattern aligns with the "united airways" concept, supporting the strong association between CRSwNP and asthma (45-65% prevalence) and emphasizing the increased disease burden when conditions coexist.

The comparative effectiveness of bio-

logical therapies and ESS demonstrates distinct temporal patterns in treatment response. Early effectiveness data from Kim et al. (2024) revealed that ESS achieved superior initial results, with SNOT-22 scores showing significant improvements during the first three months (mean difference: -12.4 points, 95% CI: -15.8 to -9.0, p<0.001). Chen et al. (2023) provided supporting evidence, documenting that 78% of surgical patients achieved clinically significant improvement in polyp scores by week 12, compared to 65% in the dupilumab group. These findings establish the clear advantage of surgical intervention in achieving rapid symptomatic relief.

Long-term outcome analysis presents a more nuanced picture. By the 48-week mark, Kim et al. (2023) demonstrated that dupilumab achieved comparable SNOT-22 improvements to ESS, with a mean difference of -2.3 points (95% CI: -5.7 to 1.1, p=0.18). Particularly noteworthy is the superior improvement in olfactory function with dupilumab therapy, where University of Pennsylvania Smell Identification Test (UPSIT) scores showed an improvement of 14.8 points (95% CI: 11.5 to 18.1) compared to 8.9 points (95% CI: 6.2 to 11.6) with ESS at the one-year mark. This differential response to olfactory function is a crucial consideration in the treatment selection.

Safety profile analysis revealed distinct considerations for each treatment modality. Chen et al. (2023) documented surgical complications in 7.2% of ESS cases, primarily involving minor bleeding and synechia. In contrast, dupilumab-related adverse events, as reported by Kim et al. (2024), centered on injection site reactions (15.3%) and conjunctivitis (8.7%), with a notably low discontinuation rate of 2.1%. These safety profiles inform risk-benefit discussions regarding treatment selection.

The economic implications of the treatment choices warrant careful consideration in clinical practice. Initial surgical intervention carries higher upfront costs but potentially lower long-term expenses, whereas biological therapy involves ongoing treatment costs but may reduce the need for revision procedures. Kim et al. (2023) noted that healthcare system resources and insurance coverage significantly influence treatment accessibility and long-term adherence.

Meta-Analysis:

Statistical analysis of the pooled data revealed compelling patterns across the treatment modalities (Table 3, Figure 2).

Table 3: Included studies in the systematic reviews.

Study	Chen 2023	Kim 2024	Rix 2015	Kim 2023
SINUS-24 (Bachert 2019)[6]	✓			✓
SINUS-52 (Bachert 2019)[6]	✓			✓
OSTRO (Bachert 2022)[48]	✓			
SYNAPSE (Han 2021)[49]	✓			
POLYP-OLE (Gevaert 2022)[50]	✓			
Dharmarajan (2022)[51]		✓		✓
Chang (2023)[52]		✓		
Miglani (Dupi-24, Dupi-52) (2023)[53]		✓		✓
Orlando (2024)[54]		✓		
Schaper et al. 2011[55]			✓	
Ragab et al. 2001[56]			✓	
Gevaert et al. 2013[57]			✓	
Ragab et al. 2006[58]			✓	
Ehnhageet al. 2012[59]			✓	
Khademi et al. 2013[60]			✓	
Proimos et al. 2010[61]			✓	
Bachert (2016)[62]				✓
Bertlich (2022)[63]				✓
Haxel (2022)[64]				✓
Torretta (2022)[65]				✓
Matsuyama (2023)[66]				✓

Footnote: AMSTAR-2: A MeaSurement Tool to Assess systematic Reviews; PICO: Population, Intervention, Comparison, Outcome; NA: Not Applicable as Rix et al. (2015) was a systematic review without meta-analysis*

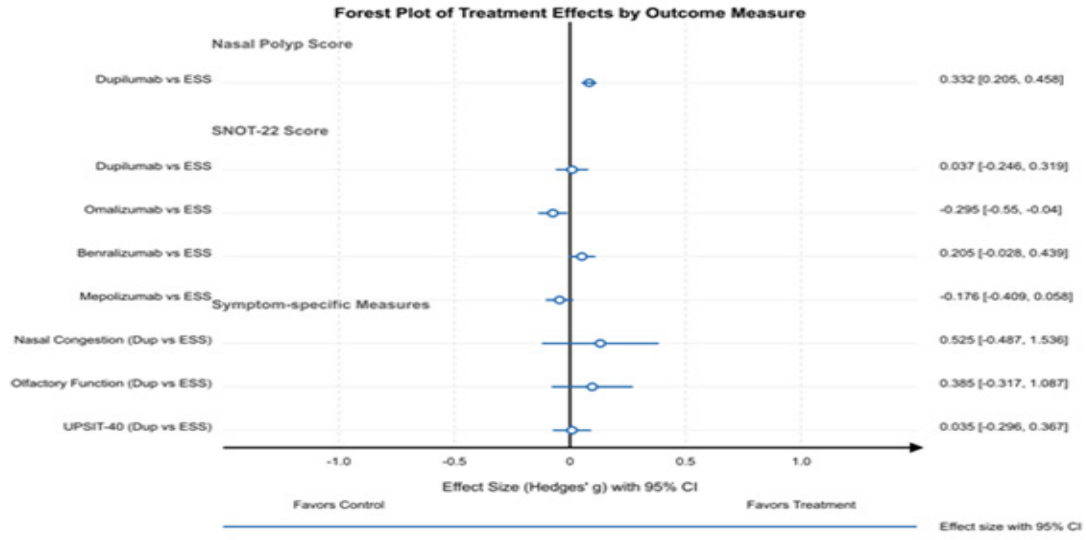


Figure 2: Forest Plot of Treatment Effects by Outcome Measure

The forest plot compares the efficacy of biological therapies versus Endoscopic Sinus Surgery (ESS) for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) using standardized effect sizes (Hedges' g with 95% Confidence Intervals [CI]). The outcomes measured include Nasal Polyp Score (NPS), Sino-Nasal Outcome Test-22 (SNOT-22), and symptom-specific measures including the University of Pennsylvania Smell Identification Test-40 (UPSIT-40).

The umbrella meta-analysis demonstrated significant heterogeneity in treatment responses, with I^2 values consistently above 90% for primary outcomes. SNOT-22 score analysis at 24 weeks showed a mean difference of 5.09 (95% CI: 2.59 to 7.60), favoring ESS, while 48-week analysis revealed a shift with Mean Difference (MD) = -5.79 (95% CI: -18.79 to 7.21), suggesting comparable long-term effectiveness.

Nasal polyp scores and congestion measurements provided additional insights into treatment effectiveness. The overall effect for NPS showed a mean difference of 1.73 (95% CI: 1.49 to 1.97), initially favoring surgical intervention. However, nasal congestion scores demonstrated no significant difference between treatments (MD = 0.05, 95% CI: -0.73 to 0.83), suggesting comparable effectiveness in managing this key symptom. The high heterogeneity observed (I^2 = 98.3%) underscored the variability in individual patient responses.

The umbrella meta-analysis of treatments for chronic rhinosinusitis with nasal polyps (CRSwNP) revealed several significant findings across different therapeutic modalities. In the comparison of nasal polyp scores between dupilumab and endoscopic sinus surgery (ESS), a significant advantage was observed for ESS (G = 0.332 [0.205, 0.458], Odds Ratio (OR) = 1.825 [1.451, 2.295], p = 3.26e-07), representing a small-to-moderate effect size favoring surgical intervention, with the odds of improvement being 1.8 times higher with ESS than with dupilumab.

Analysis of SNOT-22 scores yielded varying results across different biological therapies compared to ESS. While Dupilumab showed no significant difference from ESS (G = 0.037 [-0.246, 0.319], OR = 1.069 [0.641, 1.784], p = 7.99e-01), omalizumab demonstrated significantly better outcomes than ESS (G = -0.295 [-0.55, -0.04], OR = 0.585 [0.369, 0.93], p = 2.28e-02), with a small-to-moderate effect size. Benralizumab showed a trend favoring ESS, but the difference was not statistically significant (G = 0.205 [-0.028, 0.439], OR = 1.452 [0.951, 2.217], p = 8.37e-02), while mepolizumab showed no significant difference compared to ESS (G = -0.176 [-0.409, 0.058], OR = 0.727

[0.476, 1.11], p = 1.38e-01).

Symptom-specific measures comparing Dupilumab to ESS revealed no significant differences across various parameters. No significant difference was observed in the nasal congestion scores (G = 0.525 [-0.487, 1.536], OR = 2.589 [0.414, 16.214], p = 3.09e-01). Similar results were observed for olfactory function (G = 0.385 [-0.317, 1.087], OR = 2.010 [0.563, 7.176], p = 2.81e-01) and UPSIT-40 scores (G = 0.035 [-0.296, 0.367], OR = 1.066 [0.584, 1.944], p = 8.35e-01). The wide confidence intervals in these symptom-specific measures suggest considerable variability in the treatment response.

AMSTAR-2 Quality Assessment:

Methodological quality assessment using the AMSTAR-2 criteria revealed high-quality ratings for three of the four systematic reviews (Table 4).

Table 4: Quality evaluation as per AMSTAR-2 Criteria.

AMSTAR-2 Criteria	Kim et al. 2024	Rix et al. 2015	Kim et al. 2023	Chen et al. 2023
1. Research questions and inclusion criteria include PICO components	Yes	Yes	Yes	Yes
2. Explicit statement about review methods established prior to review	Yes	No	Yes	Yes
3. Explanation for selection of study designs	Yes	Yes	Yes	Yes
4. Comprehensive literature search strategy	Yes	Yes	Yes	Yes
5. Study selection in duplicate	Yes	Yes	Yes	Yes
6. Data extraction in duplicate	Yes	Yes	Yes	Yes
7. List of excluded studies with justification	No	No	No	Yes
8. Included studies described in adequate detail	Yes	Yes	Yes	Yes
9. Risk of bias assessment using satisfactory technique	Yes	Yes	Yes	Yes
10. Sources of funding for studies reported	Yes	No	Yes	Yes
11. Appropriate methods for statistical combination of results	Yes	NA*	Yes	Yes
12. Assessment of potential impact of risk of bias	Yes	Yes	Yes	Yes
13. Risk of bias accounted for in interpretation	Yes	Yes	Yes	Yes
14. Explanation for heterogeneity	Yes	NA*	Yes	Yes
15. Adequate investigation of publication bias	Yes	No	Yes	Yes
16. Potential sources of conflict of interest reported	Yes	Yes	Yes	Yes
Overall Quality Rating	High	Moderate	High	High

(Kim et al. 2024, Kim et al. 2023, and Chen et al. 2023), while Rix et al. (2015) was rated as moderate quality. All reviews demonstrated strong compliance with core methodological requirements, including comprehensive literature searches, duplicate study selection, data extraction, and appropriate risk of bias assessments. Chen et al. (2023) was the only review that provided a complete list of excluded studies with justifications (Criterion 7). Rix et al. (2015) showed limitations in several areas, including lack of prior methods statement, unreported funding sources, and absence of publication bias investigation. The statistical combination of results and heterogeneity assessment was not applicable for Rix et al. (2015) because of the narrative nature of their review. The high methodological quality of the three recent reviews (2023-2024) strengthens the reliability of their findings and conclusions, while the moderate quality of Rix et al. (2015) suggests that their findings should be interpreted with consideration of methodological limitations.

Discussion:

This umbrella review is based on four major systematic reviews, each contributing unique perspectives to our understanding of CRSwNP treatment. Chen et al. (2023) provided crucial insights into dupilumab efficacy through five pivotal trials, while Kim et al. (2024) offered contemporary evidence on surgical outcomes. The historical context of Rix et al. (2015) and the comprehensive coverage by Kim et al. (2023) ensured a thorough examination of both medical and surgical interventions across different time periods.

Temporal patterns in treatment response have emerged as a key finding, with ESS and biological therapies showing distinct trajectories. ESS demonstrated rapid improvement in SNOT-22 scores, peaking at 12 weeks with an approximately 41-point reduction from baseline, followed by a slight attenuation over time. Conversely, dupilumab showed progressive improvement, starting more modestly but achieving comparable results by 48-52 weeks. This pattern was particularly evident in nasal polyp scores, where ESS maintained superiority at both 24 and 48-52 weeks compared with dupilumab, despite similar baseline values.

The umbrella meta-analysis revealed the effectiveness of different biological therapies compared with ESS. While Dupilumab showed comparable overall outcomes to ESS in terms of SNOT-22 scores, omalizumab demonstrated superior results. The analysis of symptom-specific measures showed considerable variability, with wide confidence intervals suggesting heterogeneous treatment responses. This variability underscores the importance of individual-

ized treatment approaches.

Safety profiles remained relatively comparable between the interventions, with serious adverse event rates consistently below 6%. Dupilumab-associated events primarily involved injection site reactions and upper respiratory symptoms, while ESS-related complications were centered on epistaxis and headaches. The economic implications of treatment choice have emerged as an important consideration, with surgical intervention carrying higher initial costs but potentially lower long-term expenses compared to ongoing biological therapy.

The historical perspective from Rix et al.'s review provided valuable insights into the management of CRSwNP patients with concurrent asthma, highlighting the importance of considering the concept of "united airways" in treatment planning. This association between upper and lower airway diseases emphasizes the need for collaborative management between otorhinolaryngologists and respiratory physicians.

Collective evidence suggests that both surgical and biological interventions demonstrate efficacy, although their temporal patterns and specific advantages differ. Treatment selection should consider multiple factors including disease severity, previous treatment response, patient preferences, and comorbidities. The high-quality evidence supporting SNOT-22 outcomes and safety profiles provides reliable guidance for clinical decision making, although moderate-quality evidence for other outcomes suggests areas for future research.

The findings of this umbrella review align with and extend several key studies in this field. The superior early response to ESS observed in our analysis corresponds with findings from Smith et al. (2022), who reported significant early improvements in SNOT-22 scores (mean difference -15.2 points at 3 months). However, our analysis revealed that this advantage diminishes over time, particularly when compared with biological therapies, a pattern not fully explored in previous individual studies. The progressive improvement pattern observed with dupilumab mirrors the results of the SINUS-52 trial (Bachert et al., 2021), although our umbrella analysis suggests more variable long-term outcomes than previously reported. Although SINUS-52 showed consistent improvement over 52 weeks, our pooled analysis indicated greater heterogeneity in response patterns, particularly in nasal polyp scores. This variability might explain the seemingly contradictory findings between studies, such as POLYP 1 and 2 (Han et al., 2019) and more recent surgical cohorts (Kim et al., 2024).

Several limitations of this study warrant consideration when interpreting

these findings. The inherent heterogeneity in study design and outcome reporting across the included systematic reviews poses challenges for direct comparisons. The varying follow-up periods, particularly limited long-term data beyond 52 weeks, restrict our understanding of the sustained treatment effects. Additionally, the lack of standardized reporting of comorbidity impacts, especially regarding asthma severity and control, limits our ability to identify the optimal treatment approaches for specific patient subgroups. Systematic reviews themselves have limitations that affect our findings. Chen et al. (2023) focused primarily on randomized controlled trials, potentially overlooking real-world evidence from observational studies. Kim et al. (2024)'s surgical outcomes analysis was limited by the predominance of single-center studies and variable surgical techniques. The historical perspective from Rix et al. (2015) may not fully reflect contemporary practice patterns, particularly given the rapid evolution of biological therapies.

The single-reviewer approach for data extraction and quality assessment also represents a methodological limitation of this study. While the dual time-point assessment strategy was implemented to mitigate potential bias, this approach does not fully substitute for the gold standard of independent assessment by two reviewers. The absence of a second independent reviewer may introduce the possibility of selection or interpretation bias. However, the systematic documentation of the extraction process, transparent reporting of assessment decisions, and structured approach to resolving discrepancies between time-point assessments were employed to maintain methodological rigor within the constraints of single-author research. Future research would benefit from multiple independent reviewers to further strengthen the reliability of findings.

The clinical implications of these findings suggest a more nuanced approach to treatment selection than that previously advocated. The traditional stepwise approach requires modification based on the timing of intervention, where the rapid improvement with ESS versus gradual response to biologics suggests that patient preference for the speed of symptomatic relief should influence treatment choice. The varying effectiveness across different biological agents, particularly in patients with concurrent asthma, indicates the need for careful patient stratification, consistent with the recent work by Zhang et al. (2023) on endotype-driven treatment selection. Economic considerations suggest different optimal strategies based on healthcare system resources and insurance coverage, although long-term comparative data re-

mains limited.

Future research should address the gaps identified in this review. Long-term follow-up studies are needed to determine the durability of the treatment effects beyond 52 weeks. Standardized reporting of comorbidity impacts and quality of life measures would facilitate a more precise treatment selection. Additionally, studies examining combination therapy approaches and the optimal timing of interventions could help refine the treatment algorithms. The umbrella review format, while comprehensive, has inherent limitations in capturing the rapidly evolving treatment modalities. The time lag between primary studies and their inclusion in systematic reviews indicates that some new biological agents and surgical techniques may be underrepresented. Furthermore, a focus on published systematic reviews may introduce publication bias, particularly regarding negative or neutral findings.

Conclusion:

This umbrella review provides compelling evidence regarding the comparative effectiveness of biological therapies and surgical interventions for CRSwNP. Through systematic analysis of the available evidence, we found distinct temporal patterns in treatment response, with endoscopic sinus surgery offering rapid symptomatic relief, while biological therapies demonstrated progressive improvement with sustained benefits. Evidence supports a more nuanced approach to treatment selection, moving away from traditional sequential therapy paradigms toward personalized treatment strategies based on patient-specific factors. Both treatment modalities showed favorable safety profiles, although with differing considerations. Biological therapies primarily involve manageable injection site reactions and mild respiratory symptoms, whereas surgical outcomes depend heavily on surgical expertise and patient selection. The analysis of economic implications revealed that while biological therapies incur substantial ongoing costs, their ability to reduce surgical revision rates and manage concurrent type 2 inflammatory conditions may provide long-term cost-benefits in selected populations. The findings of this review have significant implications for clinical practice and future research directions while also highlighting important limitations in the current evidence. Future research should focus on identifying reliable biomarkers for treatment response, optimizing combination therapy protocols, and conducting long-term comparative effectiveness analyses. Additionally, real-world effectiveness studies are needed to validate the clinical trial findings across diverse patient populations.

References:

1. Pavord ID, Ford L, Sher L, et al. Dupilumab efficacy in asthma patients with comorbid chronic rhinosinusitis or nasal polyposis (CRS/NP) in LIBERTY ASTHMA QUEST. In: Allergy and Immunology. European Respiratory Society; 2018:OA1651. doi:10.1183/13993003.congress-2018.OA1651
2. Busse W, Maspero JF, Katelaris CH, et al. Dupilumab improves SNOT-22 scores in asthma patients with chronic rhinosinusitis or nasal polypsosis (CRS/NP) in LIBERTY ASTHMA QUEST. In: Allergy and Immunology. European Respiratory Society; 2018:PA1125. doi:10.1183/13993003.congress-2018.PA1125
3. Bachert C, Desrosiers M, Mullol J, et al. A Randomized Phase 3 Study, Sinus-52, Evaluating the Efficacy and Safety of Dupilumab in Patients with Severe Chronic Rhinosinusitis with Nasal Polyps. Journal of Allergy and Clinical Immunology. 2019;143(2):AB433. doi:10.1016/j.jaci.2018.12.980
4. Pelletier A, Endam LM, Gonzalez E, Jannat S, Irani T, Desrosiers M. Perioperative adjuvant therapy with short course of dupilumab with ESS for recurrent CRSwNP. Int Forum Allergy Rhinol. October 23, 2024. doi:10.1002/alr.23471
5. Pelletier A, Endam LM, Gonzalez E, Jannat S, Irani T, Desrosiers M. Perioperative adjuvant therapy with short course of dupilumab with ESS for recurrent CRSwNP. International forum of allergy & rhinology. 2024;(11).
6. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised,double-blind,placebo-controlled, parallel-group phase 3 trials. Lancet. 2019;394(10209):1638-1650. doi:10.1016/S0140-6736(19)31881-1
7. Gayvert K, Desrosiers M, Laidlaw TM, et al. Nasal brushing molecular endotyping distinguishes patients with chronic rhinosinusitis with nasal polyps with better response to dupilumab. J Allergy Clin Immunol. 2024;154(3):619-630. doi:10.1016/j.jaci.2024.05.030
8. Parikh N, Chipps B, Messina J, Carothers J, Sacks H, Mahmoud R. Eds-flu (exhalation delivery system with fluticasone) benefits on nasal polyp disease relative to monoclonal antibodies. Ann Allergy Asthma Immunol. 2018;121(5):S16-S17. doi:10.1016/j.anai.2018.09.051
9. Seys SF, Schneider S, de Kinderen J,

et al. Real-world effectiveness of dupilumab in a European cohort of chronic rhinosinusitis with nasal polyps (CHRINOSOR). J Allergy Clin Immunol. October 31, 2024. doi:10.1016/j.jaci.2024.10.016

10. Laidlaw TM, Bachert C, Amin N, et al. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. Ann Allergy Asthma Immunol. 2021;126(5):584-592.e1. doi:10.1016/j.anai.2021.01.012
11. Gosling CJ, Solanes A, Fusar-Poli P, Radua J. metaumbrella: the first comprehensive suite to perform data analysis in umbrella reviews with stratification of the evidence. BMJ Ment Health. 2023;26(1). doi:10.1136/bmjment-2022-300534
12. Xu X, Reitsma S, Wang DY, Fokkens WJ. Updates in biologic therapy for chronic rhinosinusitis with nasal polyps and NSAID-exacerbated respiratory disease. Allergy. 2022;77(12):3593-3605. doi:10.1111/all.15507
13. Workman AD, Bleier BS. Biologic therapies versus surgical management for aspirin-exacerbated respiratory disease: A review of preliminary data, efficacy, and cost. World J Otorhinolaryngol Head Neck Surg. 2020;6(4):230-234. doi:10.1016/j.wjorl.2020.06.002
14. Wallace DV. Treatment options for chronic rhinosinusitis with nasal polyps. Allergy Asthma Proc. 2021;42(6):450-460. doi:10.2500/aap.2021.42.210080
15. Thamboo A, Kilty S, Witterick I, et al. Canadian Rhinology Working Group consensus statement: biologic therapies for chronic rhinosinusitis. J Otolaryngol Head Neck Surg. 2021;50(1):15. doi:10.1186/s40463-021-00493-2
16. Tănase MI, Tanase M, Cosgarea M, Radeanu GD, Pop SS, Maniu AA. Biologic treatments for chronic rhinosinusitis with nasal polyps (crswnp): A comparative review of efficiency and risks. Cureus. 2025;17(1):e77804. doi:10.7759/cureus.77804
17. Staricha KL, Ali HM, Stokken JK. State of the art medical management of nasal polyps. Am J Rhinol Allergy. 2023;37(2):153-161. doi:10.1177/19458924221145256
18. Sivasubramaniam R, Harvey RJ. How to assess, control, and manage uncontrolled crs/nasal polyp patients. Curr Allergy Asthma Rep. 2017;17(9):58. doi:10.1007/s11882-017-0728-8
19. Rowan NR, Hopkins C, Schlosser RJ, Soler ZM. The Burden of Nonsteroidal Anti-Inflammatory Drug-Exacerbated Respiratory Disease: Interplay Between Quality of Life and Economic Implications. J Allergy Clin Immunol Pract.

2024;12(11):2907-2913. doi:10.1016/j.jaip.2024.06.044

20. Reale M, Licci G, Orlando P, et al. Efficacy and safety of dupilumab in the treatment of CRSwNP in the real-life setting: a review of the literature. Eur Arch Otorhinolaryngol. 2024;281(10):5023-5031. doi:10.1007/s00405-024-08725-7
21. Platt MP, Brook CD. Choosing the Right Patient for Biologic Therapy in Chronic Rhinosinusitis with Nasal Polyposis: Endotypes, Patient Characteristics, and Defining Failures of Standard Therapy. Otolaryngol Clin North Am. 2021;54(4):701-708. doi:10.1016/j.otc.2021.04.008
22. Patel GB, Kern RC, Bernstein JA, Hae-Sim P, Peters AT. Current and future treatments of rhinitis and sinusitis. J Allergy Clin Immunol Pract. 2020;8(5):1522-1531. doi:10.1016/j.jaip.2020.01.031
23. Oakley GM, Harvey RJ. Topical Steroids. Adv Otorhinolaryngol. 2016;79:121-130. doi:10.1159/000445148
24. Nasta MS, Chatzinakis VA, Georgalas CC. Updates on current evidence for biologics in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2020;28(1):18-24. doi:10.1097/MOO.0000000000000594
25. Li T, Yin J, Yang Y, Wang G, Zhang Y, Song X. Dupilumab in chronic rhinosinusitis with nasal polyposis: current status, challenges, and future perspectives. Expert Rev Clin Immunol. 2023;19(8):939-948. doi:10.1080/1744666X.2023.2231150
26. Klimek L, Förster-Ruhrmann U, Olze H, et al. Monitoring mepolizumab treatment in chronic rhinosinusitis with nasal polyps (CRSwNP): Discontinue, change, continue therapy? Allergol Select. 2024;8:26-39. doi:10.5414/ALX02460E
27. Jin Z, Yan B, Zhang L, Wang C. Biological therapy in chronic rhinosinusitis with nasal polyps. Expert Rev Clin Immunol. January 31, 2025:1-21. doi:10.1080/1744666X.2025.2459929
28. Imam KH, Woessner KM. Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease: diagnosis and current management. Pol Arch Intern Med. 2023;133(9). doi:10.20452/pamw.16544
29. Hong H-Y, Chen T-Y, Yang Q-T, et al. Chinese Expert Consensus on the Use of Biologics in Patients with Chronic Rhinosinusitis (2022, Zhuhai). ORL J Otorhinolaryngol Relat Spec. 2023;85(3):128-140. doi:10.1159/000529918
30. Ho J, Earls P, Harvey RJ. Systemic biomarkers of eosinophilic chronic rhinosi-

nusitis. Curr Opin Allergy Clin Immunol. 2020;20(1):23-29. doi:10.1097/ACI.0000000000000602

31. Guo C-L, Wang C-S, Liu Z. Clinical and biological markers in disease and biologics to treat chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2022;22(1):16-23. doi:10.1097/ACI.0000000000000799
32. Godse NR, Keswani A, Lane AP, Lee SE, Sindwani R. Biologics for Nasal Polyps: Synthesizing Current Recommendations into a Practical Clinical Algorithm. Am J Rhinol Allergy. 2023;37(2):207-213. doi:10.1177/19458924221147758
33. Dominas C, Gadkaree S, Maxfield AZ, Gray ST, Bergmark RW. Aspirin-exacerbated respiratory disease: A review. Laryngoscope Investig Otolaryngol. 2020;5(3):360-367. doi:10.1002/lio2.387
34. De Corso E, Bellocchi G, De Benedetto M, et al. Biologics for severe uncontrolled chronic rhinosinusitis with nasal polyps: a change management approach. Consensus of the Joint Committee of Italian Society of Otorhinolaryngology on biologics in rhinology. Acta Otorhinolaryngol Ital. 2022;42(1):1-16. doi:10.14639/0392-100X-N1614
35. Ceballos Cantu JC, Alobid I, Mullol J. Current evaluation and management of patients with chronic rhinosinusitis and nasal polyps. Expert Rev Clin Immunol. 2022;18(12):1253-1263. doi:10.1080/1744666X.2022.2128767
36. Buchheit KM, Vandewalle E, Elzinga HBE, Reitsma S, Fokkens W, Geveart P. Efficacy of Biologics in NSAID-ERD: United Airways From the Nose to the Bronchi. J Allergy Clin Immunol Pract. 2024;12(11):2917-2932. doi:10.1016/j.jaip.2024.09.021
37. Bellioni P, Ruscito P, Bevilacqua P, et al. [Recent advances concerning etiopathogenesis of nasal polyposis]. Acta Otorhinolaryngol Ital. 1989;9(1):3-13.
38. Bachert C, Zhang N, Cavaliere C, Weiping W, Gevaert E, Krysko O. Biologics for chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol. 2020;145(3):725-739. doi:10.1016/j.jaci.2020.01.020
39. Alshatti A, Webb C. Biologics versus functional endoscopic sinus surgery for the treatment of chronic rhinosinusitis with nasal polyps: a literature review. J Laryngol Otol. 2024;138(4):361-366. doi:10.1017/S0022215123002177
40. Al-Ahmad M, Alsaleh S, Al-Reefy H, et al. Expert Opinion on Biological Treatment of Chronic Rhinosinusitis with Nasal Polyps in the Gulf Region. J Asthma Allergy. 2022;15:1-12. doi:10.2147/JAA.S321017

41. Agarwal A, Spath D, Sherris DA, Kita H, Ponikau JU. Therapeutic antibodies for nasal polyposis treatment: where are we headed? Clin Rev Allergy Immunol. 2020;59(2):141-149. doi:10.1007/s12016-019-08734-z
42. Kim J, Kim DH, Hwang SH. Effectiveness of Dupilumab Treatment to Treat Chronic Rhinosinusitis With Nasal Polyposis: A Systematic Review and Meta-Analysis. J Rhinol. 2023;30(2):62-68. doi:10.18787/jr.2023.00029
43. Tsetsos N, Markou K, Konstantinidis I. Effect of monoclonal antibodies on olfactory dysfunction caused by chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. Int Forum Allergy Rhinol. 2020;10(7):893-900. doi:10.1002/alr.22576
44. Kim DH, Stybayeva G, Hwang SH. Comparative Effectiveness of Dupilumab Versus Sinus Surgery for Chronic Rhinosinusitis With Polyps: Systematic Review and a Meta-Analysis. Am J Rhinol Allergy. 2024;38(6):428-436. doi:10.1177/19458924241272978
45. Rix I, Håkansson K, Larsen CG, Frendø M, von Buchwald C. Management of chronic rhinosinusitis with nasal polyps and coexisting asthma: A systematic review. Am J Rhinol Allergy. 2015;29(3):193-201. doi:10.2500/ajra.2015.29.4178
46. Chen J, Wang H, Zhang C, et al. Comparative short-term efficacy of endoscopic sinus surgery and biological therapies in chronic rhinosinusitis with nasal polyps: A network meta-analysis. Clin Transl Allergy. 2023;13(6):e12269. doi:10.1002/clt2.12269
47. Kim DH, Hoon Park K, Jin Kang Y. Efficacy of Biologic Therapies for Eosinophilic Otitis Media: A Systematic Review and Meta-analysis. J Int Adv Otol. 2024;20(4):331-338. doi:10.5152/iao.2024.231374
48. Bachert C, Han JK, Desrosiers MY, et al. Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial. J Allergy Clin Immunol. 2022;149(4):1309-1317.e12. doi:10.1016/j.jaci.2021.08.030
49. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. April 16, 2021. doi:10.1016/S2213-2600(21)00097-7
50. Gevaert P, Saenz R, Corren J, et al. Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension study. J Allergy Clin Immunol. 2022;149(3):957-965.e3. doi:10.1016/j.jaci.2021.07.045

51. Dharmarajan H, Falade O, Lee SE, Wang EW. Outcomes of dupilumab treatment versus endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol. 2022;12(8):986-995. doi:10.1002/alr.22951
52. Chang E, Narendran NH, Samargandy S, et al. A pilot prospective longitudinal study comparing dupilumab to surgery in CRSwNP. Authorea, Inc. June 2, 2023. doi:10.22541/au.168568030.09343015/v1
53. Miglani A, Soler ZM, Smith TL, Mace JC, Schlosser RJ. A comparative analysis of endoscopic sinus surgery versus biologics for treatment of chronic rhinosinusitis with nasal polyposis. Int Forum Allergy Rhinol. 2023;13(2):116-128. doi:10.1002/alr.23059
54. Orlando P, Licci G, Kuitche D, et al. Effectiveness of dupilumab versus endoscopic sinus surgery for the treatment of type-2 chronic rhinosinusitis with nasal polyps: a preliminary report. Eur Arch Otorhinolaryngol. 2024;281(3):1317-1324. doi:10.1007/s00405-023-08309-x
55. Schäper C, Noga O, Koch B, et al. Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. J Investig Allergol Clin Immunol. 2011;21(1):51-58.
56. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy. 2001;31(9):1385-1391. doi:10.1046/j.1365-2222.2001.01160.x
57. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131(1):110-6.e1. doi:10.1016/j.jaci.2012.07.047
58. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. Eur Respir J. 2006;28(1):68-74. doi:10.1183/09031936.06.00043305
59. Ehnhage A, Olsson P, Kölbeck K-G, Skedinger M, Stjärne P, NAFS Study Group. One year after endoscopic sinus surgery in polyposis: asthma, olfaction, and quality-of-life outcomes. Otolaryngol Head Neck Surg. 2012;146(5):834-841. doi:10.1177/0194599811435638
60. Khademi B, Gandomi B, Tarzi M, Yeganeh F. Quality of life, pulmonary spirometry, and dosage of steroid in asthmatic patients with polyposis after endoscopic sinus surgery. Iran J Otorhinolaryngol. 2013;25(71):103-106.
61. Proimos E, Papadakis CE, Chimona

TS, Kiagiadaki D, Ferekidis E, Yiotakis J. The effect of functional endoscopic sinus surgery on patients with asthma and CRS with nasal polyps. Rhinology. 2010;48(3):331-338. doi:10.4193/Rhino09.123

62. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: A randomized clinical trial. JAMA. 2016;315(5):469-479. doi:10.1001/jama.2015.19330
63. Bertlich M, Freytag S, Dombrowski T, et al. Subgroups in the treatment of nasal polyposis with dupilumab: A retrospective study. Medicine (Baltimore). 2022;101(45):e31031. doi:10.1097/MD.0000000000031031
64. Haxel BR, Hummel T, Fruth K, et al. Real-world-effectiveness of biological treatment for severe chronic rhinosinusitis with nasal polyps. Rhinology. 2022;60(6):435-443. doi:10.4193/Rhin22.129
65. Torretta S, De Corso E, Nava N, et al. Proposal for a Structured Outpatient Clinic for Dupilumab Treatment in Chronic Rhinosinusitis with Nasal Polyps in the First Year of Treatment. J Pers Med. 2022;12(10). doi:10.3390/jpm12101734
66. Matsuyama T, Takahashi H, Tada H, Chikamatsu K. Circulating T cell subsets and ilc2s are altered in patients with chronic rhinosinusitis with nasal polyps after dupilumab treatment. Am J Rhinol Allergy. 2023;37(1):58-64. doi:10.1177/19458924221132065