International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	BIOLOGIC THERAPY AND QUALITY OF LIFE IN NSAID-EXACERBATED RESPIRATORY DISEASE: A SYSTEMATIC REVIEW OF SNOT-22 PATIENT-REPORTED OUTCOMES
DOI	https://doi.org/10.31435/ijitss.1(49).2026.5420
RECEIVED	29 January 2026
ACCEPTED	23 March 2026
PUBLISHED	30 March 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

BIOLOGIC THERAPY AND QUALITY OF LIFE IN NSAID-EXACERBATED RESPIRATORY DISEASE: A SYSTEMATIC REVIEW OF SNOT-22 PATIENT-REPORTED OUTCOMES

Alicja Laske *(Corresponding Author, Email: laske.a.j@gmail.com)*
4th Military Clinical Hospital with Polyclinic, Independent Public Health Care Centre, Wrocław, Poland
ORCID ID: 0009-0000-3690-4659

Antoni Majda
Provincial Specialist Hospital in Wroclaw, Wroclaw, Poland
ORCID ID: 0009-0006-4357-513X

Natalia Sitko
Lower Silesian Specialist Hospital T. Marciniak – Emergency Medicine Center, Wroclaw, Poland
ORCID ID: 0009-0002-4128-134X

Paulina Makowska
Voivodeship Specialist Hospital in Wrocław, Wroclaw, Poland
ORCID ID: 0009-0009-1279-5422

Joanna Gontarczyk
University Hospital in Wroclaw, Wroclaw, Poland
ORCID ID: 0009-0002-7512-8853

Martyna Sowa
Independent Public Healthcare Facility in Bochnia "District Hospital", Bochnia, Poland
ORCID ID: 0009-0003-7152-5787

Julia Pająk
4th Military Clinical Hospital with Polyclinic, Independent Care Institution, Wroclaw, Poland
ORCID ID: 0009-0007-0882-9365

Kacper Kucharski
Jan Mikulicz Radecki University Clinical Hospital, Wroclaw, Poland
ORCID ID: 0009-0004-5709-8974

Anna Kamosińska
4th Military Clinical Hospital with Polyclinic, Independent Care Institution, Wroclaw, Poland
ORCID ID: 0009-0005-0718-2112

Adam Kowal
Jan Mikulicz Radecki University Clinical Hospital, Wroclaw, Poland
ORCID ID: 0009-0007-7779-598X

Julia Sokołowska
Lower Silesian Centre for Oncology, Pulmonology and Hematology, Wrocław, Poland
ORCID ID: 0000-0002-7042-0348

Marcel Dawidowicz
Lower Silesian Centre for Oncology, Pulmonology and Hematology, Wrocław, Poland
ORCID ID: 0009-0000-5297-3507

ABSTRACT

Background: Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) is a severe, refractory phenotype of chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma. Traditional treatments, including repeated endoscopic sinus surgeries and aspirin therapy after desensitization (ATAD), are frequently limited by high recurrence and discontinuation rates, leaving a critical unmet need for durable symptom control.
Objective: To systematically evaluate the impact of targeted biologic therapies on patient-reported quality of life in the N-ERD population, utilizing the 22-item Sino-Nasal Outcome Test (SNOT-22).
Methods: A systematic literature search of PubMed and Scopus was conducted between January and March 2026. Eligibility criteria strictly isolated studies reporting longitudinal, continuous SNOT-22 data for adult N-ERD cohorts treated with monoclonal antibodies.
Results: Eight studies met the inclusion criteria. Pre-treatment SNOT-22 scores confirmed severe baseline disability across all cohorts.Treatment with the anti-IL-4Rα agent dupilumab rapidly transformed patient outcomes, yielding clinically meaningful SNOT-22 score reductions ranging from 27 to 48 points, which were sustained for up to two years.Dupilumab demonstrated robust efficacy in restoring olfactory function and improving asthma control. While anti-IL-5 therapies (mepolizumab) provided clinical benefit, comparative data indicated they were less consistently effective at normalizing olfaction and achieving comprehensive symptom resolution than dupilumab.
Conclusion: Targeted biologic therapies, particularly dupilumab, deliver significant improvements in quality of life for patients with N-ERD. They represent a highly effective, non-surgical step-up therapy capable of halting the surgical cycle and achieving profound symptom relief in treatment-refractory patients.

KEYWORDS

NSAID-Exacerbated Respiratory Disease (N-ERD), Aspirin-Exacerbated Respiratory Disease (AERD), Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), Biologics, Dupilumab, Mepolizumab, SNOT-22; Quality of Life

CITATION

Alicja Laske, Antoni Majda, Natalia Sitko, Paulina Makowska, Joanna Gontarczyk, Martyna Sowa, Julia Pająk, Kacper Kucharski, Anna Kamosińska, Adam Kowal, Julia Sokołowska, Marcel Dawidowicz. (2026) Biologic Therapy and Quality of Life in NSAID-Exacerbated Respiratory Disease: A Systematic Review of SNOT-22 Patient-Reported Outcomes. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.5420

1. Introduction

1.1. Evolution of the Concept and Clinical Phenotype of N-ERD

First described by Widal et al. in 1922 and subsequently fully characterized by Samter and Beer in 1968, the clinical syndrome historically referred to as Samter's triad or Morbus Widal is now formally recognized as nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) or aspirin-exacerbated respiratory disease (AERD) (Bertlich et al., 2021; Ley-Tomas et al., 2024). The condition is classically defined by the clinical triad of adult-onset asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), and respiratory reactions induced by exposure to cyclooxygenase-1 (COX-1) inhibitors. (Ley-Tomas et al., 2024; Mullur & Buchheit, 2023).

The clinical phenotype of N-ERD typically manifests in the third or fourth decade of life and is distinguished by a uniquely severe and refractory disease trajectory (Imam & Woessner, 2023; Ley-Tomas et al., 2024). Compared to aspirin-tolerant patients, individuals with N-ERD present with a significantly greater burden of sinonasal inflammation, more severe olfactory dysfunction (anosmia), a higher reliance on systemic corticosteroids, and highly aggressive, rapid nasal polyp regrowth that frequently necessitates multiple revision surgeries (Chen et al., 2024; Imam & Woessner, 2023; Stevens & Cahill, 2023). Pathophysiologically, the N-ERD phenotypes are driven by intense type 2 (T2) inflammation, extensive tissue eosinophilia, mast cell activation, and a hallmark dysregulation of arachidonic acid metabolism (Laidlaw, 2025; Ley-Tomas et al., 2024). This metabolic impairment results in an overproduction of proinflammatory cysteinyl leukotrienes and

prostaglandin D2 (PGD2), alongside a deficient synthesis of anti-inflammatory prostaglandin E2 (PGE2) (Ley-Tomas et al., 2024; Mullur & Buchheit, 2023).

Recent advancements have further evolved the conceptual understanding of N-ERD, demonstrating that it encompasses significant inflammatory heterogeneity. While predominantly a T2-driven disease, distinct subendotypes featuring type 1 and type 3 inflammatory signatures have been identified, which may correlate with the severity and rapidity of polyp recurrence (Mullur & Buchheit, 2023; Stevens & Cahill, 2023). Furthermore, the modern clinical phenotype extends beyond the classic respiratory triad to include profound alcohol intolerance-manifesting as upper and lower respiratory symptoms after consumption in up to 75% of patients-as well as episodic extrarespiratory complications, such as cutaneous eruptions, gastrointestinal symptoms, and angina-like chest pain (Foerster-Ruhrmann et al., 2024; Hayashi et al., 2023; Ley-Tomas et al., 2024).

1.2. Failure of the Traditional Treatment Paradigm and the "Revolving Door" of Surgery

Despite maximal medical and surgical standard-of-care treatments, the disease often remains uncontrolled, establishing a critical clinical gap characterized by a high disease burden and significantly reduced patient quality of life (Van Broeck et al., 2023).

In the management of N-ERD, standard surgical interventions frequently fail to provide complete or sustained resolution of symptoms (Patel et al., 2022). Patients with AERD are at a significantly higher risk of rapid and aggressive nasal polyp recurrence following endoscopic sinus surgery (ESS) compared to aspirin-tolerant CRSwNP patients (Chen et al., 2024). Post-operatively, nasal polyps regrow within two years in up to 85% of AERD patients (Patel et al., 2022). This refractory disease trajectory forces patients into a "revolving door" of multiple revision surgeries, with clinical cohorts reporting an average of 3.1 ±1.3 (range 1–6) previous sinus surgeries per patient (Bertlich et al., 2021). The persistent burden of the disease, including debilitating loss of smell, profoundly impacts patients' overall quality of life (Laidlaw, 2025; Patel et al., 2022).

Due to the aggressive recurrence of upper and lower airway symptoms, patients with N-ERD exhibit a greater reliance on rescue therapies, including chronic systemic oral corticosteroids (OCS) (Mullur & Buchheit, 2023; Van Broeck et al., 2023). However, the cumulative toxicity of long-term or repeated systemic corticosteroid bursts imposes a severe iatrogenic burden on patients, exposing them to a wide array of well-documented adverse effects and long-term complications (Bachert et al., 2022).

While aspirin treatment after desensitization (ATAD) has been utilized following ESS to delay polyp regrowth and improve symptoms, its clinical utility is significantly hindered by treatment-limiting adverse effects (Patel et al., 2022). Real-world observational data indicate that ATAD discontinuation rates are remarkably high, exceeding 60% in some cohorts (Lyly et al., 2021). The primary barriers to adherence include burdensome gastrointestinal intolerances-such as gastritis and abdominal pain-alongside respiratory and cutaneous side effects (Kumar et al., 2026; Van Broeck et al., 2023). Furthermore, long-term high-dose aspirin therapy carries increased risk of major gastrointestinal bleeding, which limits its viability for some patients (Van Broeck et al., 2023). Ultimately, a substantial proportion of patients discontinue ATAD due to safety concerns, unmanageable side effects, or changes in risk-benefit stratification rather than a lack of initial efficacy (Mullur et al., 2022).

1.3. The Role of SNOT-22 as the Gold Standard for Patient-Reported Outcome Measures (PROMs)

While objective endoscopic assessments, such as the Nasal Polyp Score (NPS), are routinely utilized to quantify disease severity, physician-reported outcomes and impressions of disease control do not always perfectly correlate with patient-reported outcomes (Fokkens et al., 2023). The clinical evaluation of polyp size has inherent shortcomings related to logistical and interpretational challenges, and a consensus on the most effective endoscopic grading system remains lacking (Fokkens et al., 2023). Furthermore, whereas physicians objectively measure polyp burden, patients with N-ERD experience a profound impairment in health-related quality of life (HRQoL) driven by severe subjective symptoms, including facial pain or pressure, sleep disruption, and fatigue (Domínguez-Sosa et al., 2023; Mullol et al., 2024).

1.4. Definition of the SNOT-22 Instrument

The SNOT-22 is a disease-specific questionnaire designed to measure HRQoL and symptom severity in patients with chronic rhinosinusitis (CRS) (Domínguez-Sosa et al., 2023). The instrument evaluates 22 different CRS-related items categorized into five distinct domains: nasal, ear/face, sleep, function, and emotion (Garvey et al., 2024). Patients rate each item on a scale from 0 (representing "no problem at all") to 5 (representing the "worst possible symptom"), generating a cumulative score ranging from 0 to 110. Higher scores indicate worse symptoms and a greater overall disease burden (Domínguez-Sosa et al., 2023; Grose et al., 2023).

The tool was structurally refined to assess not only cardinal sinonasal symptoms but also the broader multi-systemic effects of the disease (Garvey et al., 2024; Mullol et al., 2024). It is considered a highly reliable and validated measurement tool, widely recognized for possessing proven quality of developmental methodology and psychometric performance in rhinology (Domínguez-Sosa et al., 2023; Grose et al., 2023). The reliability of the SNOT-22 is further reinforced by the establishment of a Minimal Clinically Important Difference (MCID). Most frequently established at 8.9 points, the MCID provides clinicians with a standardized threshold to confirm whether a specific medical or surgical intervention has produced a genuinely meaningful clinical improvement for the patient (Grose et al., 2023; Mullol et al., 2024).

1.5. Rationale for the Study

Despite the expanding use of targeted monoclonal antibodies, patients with N-ERD have typically constituted only a minority-often less than 30%-of the overall CRSwNP populations analyzed in large phase III clinical trials (Van Broeck et al., 2023). The existing literature assessing biologic therapies in this specific, difficult-to-treat phenotype is largely restricted to small case series, retrospective cohorts, and post-hoc subgroup analyses rather than dedicated, large-scale investigations (Lyly et al., 2025; Tepetam et al., 2023). Therefore, more specific studies and real-world data evaluating the efficacy of biologics directly in the N-ERD population are urgently needed (Çelik Tuğlu et al., 2025). To address this critical gap, this systematic review was conducted to strictly isolate continuous SNOT-22 data exclusively for the severe N-ERD cohort, aiming to conclusively define the impact of biologic therapies solely on patient-reported quality of life in the modern treatment era.

2. Methodology

2.1. Search Strategy

A systematic literature search was conducted to identify relevant studies evaluating the impact of biologic therapies on patient-reported outcomes in patients with Non-steroidal-Drug Exacerbated Respiratory Disease (N-ERD/AERD). The primary electronic databases utilized for this search were PubMed and Scopus. The search was conducted up to March 2026, with a strict five-year publication date filter applied (January 2021 to March 2026) to ensure the captured literature reflects the most current, modern era of biologic interventions.

For PubMed, the search strategy employed the following combination of keywords and Boolean operators: ("AERD" OR "Aspirin-Exacerbated Respiratory Disease" OR "Samter's Triad" OR "N-ERD" OR "Aspirin-Induced Asthma") AND ("biologics" OR "biological therapy" OR "monoclonal antibodies" OR "dupilumab" OR "omalizumab" OR "mepolizumab" OR "benralizumab" OR "reslizumab" OR "tezepelumab").

For Scopus, the search was restricted to English-language publications between 2021 and 2026 using the string: TITLE-ABS-KEY

(("AERD" OR "Aspirin-Exacerbated Respiratory Disease" OR "Samter's Triad" OR "N-ERD" OR "Aspirin-Induced Asthma") AND ("biologics" OR "biological therapy" OR "monoclonal antibodies" OR "dupilumab" OR "omalizumab" OR "mepolizumab" OR "benralizumab" OR "reslizumab" OR "tezepelumab")).

The complete screening and selection process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram included in this manuscript.

2.2. Eligibility Criteria

Study selection was governed by a strict set of predefined parameters to ensure the isolation of continuous, high-quality data specific to the N-ERD phenotype.

Inclusion Criteria To be included in the review, studies were required to meet all of the following criteria:

- **Population:** Adult patients with a confirmed diagnosis of N-ERD (AERD). If the study included a broader group (e.g., the general CRSwNP population), the data for the N-ERD subgroup had to be completely isolated.
- **Intervention:** Monotherapy with a biologic agent (e.g., Dupilumab, Mepolizumab, Omalizumab, Benralizumab).
- **Endpoints:** The study must report longitudinal, continuous numerical data for the total SNOT-22 questionnaire score (scale 0-110) before treatment (Baseline) and at the end of the follow-up period (Post-treatment).
- **Data Format:** SNOT-22 results must include measures of central tendency and dispersion: Mean and Standard Deviation (SD) OR Median and Interquartile Range (IQR) / Min-Max Range OR Mean change with a reported p-value or confidence interval (95% CI).

Exclusion Criteria Studies were excluded from the synthesis if any of the following conditions were present:

- Lack of isolated data for the N-ERD cohort (results mixed with the general population).
- Reporting SNOT-22 solely in a graphical format (charts) without exact numerical values in the text or tables.
- Reporting results exclusively for SNOT-22 subdomains (e.g., only the sleep domain, only the otologic domain), without reporting the total score.
- Confounded intervention: administration of a biologic agent strictly perioperatively, which prevents the separation of the pharmacological effect from the surgical effect.
- Salvage therapy: studies solely evaluating the switch from one biologic to another (biologic switching) in patients unresponsive to first-line treatment.
- Lack of any measures of dispersion for the reported continuous values (e.g., only the median is reported without the IQR, preventing statistical transformation).
- Cross-sectional survey studies assessing only drug utilization patterns without hard pre/post continuous endpoints.

2.3. Quality Assessment and Risk of Bias

The methodological quality and risk of bias of the included studies were systematically evaluated using the National Institutes of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group. This 12-item tool assesses study quality across multiple domains, including the clarity of the study objective, explicit definition of the study population, description of the intervention, use of validated outcome measures, and appropriate statistical analyses. Studies were ultimately categorized as "Good," "Fair," or "Poor" based on the presence of methodological flaws, susceptibility to bias, and the transparency of the reported data.

2.4. Study Selection

The systematic literature search across the selected databases yielded a total of 420 initial records, comprising 144 records from PubMed and 276 from Scopus. Prior to the screening phase, 134 duplicate records were identified and removed.

The remaining 286 unique records underwent title and abstract screening. During this phase, 230 records were excluded mostly for failing to align with the primary research objectives or reported as wrong study type. Subsequently, full-text retrieval was sought for the remaining 56 reports; however, 15 of these could not be retrieved.

The 41 successfully retrieved full-text reports were then rigorously assessed for eligibility against the strict predefined inclusion and exclusion criteria. During this full-text evaluation, 33 reports were excluded for the following specific reasons:

- Wrong outcomes (n = 10)
- Wrong study design (n = 9)
- Unextractable data (n = 6)
- Wrong patient population (n = 4)
- Confounded intervention / Biologic switching (n = 4)

Following this selection process, a final total of 8 distinct studies successfully met all criteria and were included in the systematic review for data extraction and synthesis. Retrieved data are presented in *Table 1* in Results section.

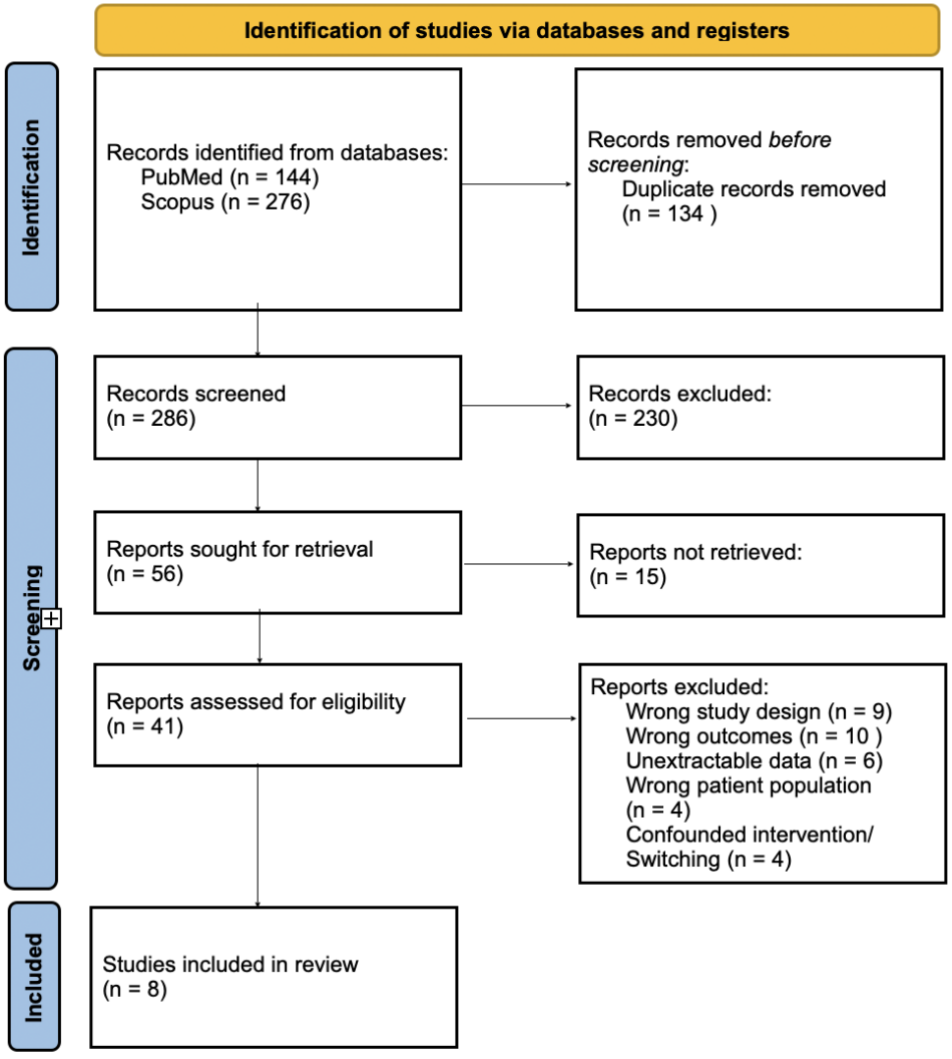

Fig. 1. PRISMA flow diagram of the literature search and study selection process. *> Note. A total of 420 initial records were identified through PubMed and Scopus searches (January–March 2026). Following the removal of duplicates and initial title/abstract screening, 41 full-text articles were rigorously assessed for eligibility. Thirty-three articles were excluded based on predefined criteria (wrong outcomes, wrong study design, unextractable data, wrong patient population, or confounded interventions). A final total of 8 studies met all inclusion criteria and were included in the systematic review*

3. Results

3.1. Risk of Bias and Study Quality

The methodological quality of the eight included studies was assessed using the NIH Quality Assessment Tool. No studies exhibited "fatal flaws" or were rated as "Poor." All eight studies successfully met the criteria for clearly defining their primary objectives, utilizing strict eligibility criteria to isolate the N-ERD population, precisely describing the pharmacological intervention, and employing appropriate statistical tests. Furthermore, all studies consistently utilized a validated, objective instrument (SNOT-22) to measure patient-reported outcomes.

Two studies (Elzinga et al., 2025; Schneider et al., 2023) were rated as "Good." These studies were distinguished by their high methodological rigor, characterized by their prospective or registry-based designs, the consecutive inclusion of all eligible patients, and the utilization of multiple time-series measurements (e.g., at 24 weeks and 2 years), which allowed for a robust evaluation of treatment durability.

The remaining six studies (Bavaro et al., 2021; Bertlich et al., 2022; Buchheit et al., 2022; Grose et al., 2023; Ozuna et al., 2022; Wangberg et al., 2022) were rated as "Fair." The primary factors lowering the quality scores across these cohorts were the inherent limitations of retrospective observational designs. Specifically, these studies lacked blinding of the outcome assessors-a limitation expected in real-world clinical effectiveness research-and did not perform *a priori* sample size or power calculations. The small sample sizes observed in these studies reflect the rarity of the specific N-ERD phenotype treated with biologics at individual tertiary centers rather than fundamental flaws in the experimental design.

3.2 Baseline Characteristics and Disease Burden

Across the evaluated studies, patients with Non-steroidal-Drug Exacerbated Respiratory Disease (N-ERD), also referred to as Aspirin-Exacerbated Respiratory Disease (AERD), exhibited a substantial baseline impairment in quality of life prior to the initiation of biologic therapies. This burden was primarily quantified utilizing the 22-item Sino-Nasal Outcome Test (SNOT-22).

Pre-treatment SNOT-22 scores demonstrated severe baseline symptomatology across all cohorts. Bertlich et al. (2022) reported the highest mean baseline SNOT-22 score of 68.1 ±13.9 in a cohort of 17 refractory patients. Similarly, Elzinga et al. (2025) noted a median baseline score of 60 (IQR 43–67) for N-ERD patients, which was notably higher than the comparative chronic rhinosinusitis with nasal polyps (CRSwNP-NOS) cohort (median 53, IQR 39–65). Other studies reported mean baseline scores ranging from 41.43 ±23.27 (Schneider et al., 2023) to 56.5 ±14.4 (Grose et al., 2023), confirming a consistently high level of sinonasal disease burden prior to biological intervention.

Table 1.

Study Details (Drug, Follow-up)	Population (N)	SNOT-22 Baseline	SNOT-22 Post-Treatment	SNOT-22 Change	Additional Data
Schneider et al., 2023 Dupilumab, 24 weeks	31 (n=30 for SNOT-22)	41.43 (SD 23.27)	Derived: 14.70	-26.73 (SD 23.49), p < 0.001	TPS: Base 3.58 (SD 2.42), Change -2.68 (SD 1.84), p < 0.001. UPSIT: Base 14.70 (SD 8.68), Change +11.16 (SD 9.54), p < 0.001.
Bertlich et al., 2021 Dupilumab, 6.4 ± 2.7 months	17	68.1 (SD 13.9, Range 50–86)	20.1 (SD 13.9, Range 11-60)	Mean change not reported, p < 0.001	NPS: No isolated data. B-SIT: Base 3.5 (SD 2.6, Range 0-8), Post 8.6 (SD 2.4, Range 4-12)
Wangberg et al., 2022 Multiple Biologics, Median 458 days	74 Total IL-4Rα: 49 IgE: 17 IL-5: 9	Total: 53.5 (IQR 24.75 - 72.25) IL-4Rα: 51 (IQR 27-76.5) IgE: 56 (IQR 31.5-58.5) IL-5: 35.5 (IQR 24.25-46.75)	Total: 16.5 (IQR 7.5-32.12) IL-4Rα: 19 (IQR 7.5-29.75) IgE: 13 (IQR 8.5-26.5) IL-5: 27.5 (IQR 14.25-49.75)	Total: p = 0.0002 IL-4Rα: p = 0.0002 IgE: p = 0.6286 IL-5: p > 0.9999	NPS: No isolated data. Smell: Base 5 (IQR 4-5), Post 1 (IQR 0-3.75), p < 0.0001.
Ozuna et al., 2022 Dupilumab, 2 to 22 months	8	55.8 (SD 23.6)	20.5 (SD 18.7)	p = 0.003	No isolated data for NPS or olfaction.
Grose et al., 2023 Dupilumab, Mean 10.8 months	11	56.5 (SD 14.4)	15.2 (SD 17.8) after 12 months	-46.0 (SD 18.9), p-value not reported	No isolated data.
Elzinga et al., 2025 Dupilumab, 2 years	105 (67 at 2 years)	60 (IQR 43-67)	18 (IQR 10-25) at 24 wks; 19 (IQR 8-31) at 2 yrs	Significant change over study period (p < 0.001)	NPS: Base 6 (IQR 5-6), Post 2 (IQR 0-3) at 24 wks, 0 (IQR 0-2) at 2 yrs. Sniffin' Sticks: Base 3 (IQR 2-4), Post 6.5 (IQR 4-9) at 24 wks, 7 (IQI 4.5-9) at 2 yrs.
Buchheit et al., 2022 Dupilumab, 3 months	22	48.7 (SD 22.3)	Derived: 14.2	-34.5, p < 0.0001	NPS: Significant reduction (p < 0.0001). UPSIT: Base 15.5 (SD 9.6), Change +11.9, p < 0.0001.
Bavaro et al., 2021 Mepolizumab, 40.8 ± 8.6 months	14	47.8 (SD 14)	27.8 (SD 20.1)	-20.0, p = 0.007	No isolated data.

N-ERD: Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; SNOT-22: 22-item Sino-Nasal Outcome Test; SD: Standard Deviation; IQR: Interquartile Range.

3.3 Impact of Dupilumab on Patient-Reported Quality of Life (SNOT-22)

Treatment with the anti-IL-4 receptor alpha (anti-IL-4Rα) monoclonal antibody dupilumab consistently yielded statistically significant and clinically meaningful reductions in SNOT-22 scores across short-term, mid-term, and long-term evaluation intervals.

Short-Term Efficacy (1 to 3 Months)

Rapid improvements in quality of life were observed within the first month of dupilumab therapy. Buchheit et al. (2022) reported a mean reduction of 34.4 points in SNOT-22 scores ($P < 0.001$) after just one month of treatment in a cohort of 22 adult patients, far exceeding the minimal clinically important difference (MCID) of 8.9 points. This reduction was sustained at three months with a mean change of -34.5 points ($P < 0.001$). Grose et al. (2023) similarly documented progressive reductions, observing a mean SNOT-22 score decrease to 31.3 ±22.2 (a reduction of 28.3 ±16.2 points from baseline) by the three-month follow-up.

Mid-Term Efficacy (6 Months / 24 Weeks)

Sustained clinical benefit was documented across multiple cohorts at the six-month mark.

- **Schneider et al. (2023):** Following 24 weeks of therapy, 30 patients exhibited a mean SNOT-22 reduction of 26.73 ±23.49 points ($P < 0.001$).
- **Elzinga et al. (2025):** The median SNOT-22 score decreased from 60 to 18 (IQR 10–25) at 24 weeks.
- **Bertlich et al. (2022):** After an average treatment duration of 6.4 months, mean scores significantly decreased from 68.1 to 20.1 ±13.9 ($P < 0.001$).
- **Grose et al. (2023):** Patients demonstrated a mean SNOT-22 score of 27.4 ±21.8, reflecting a mean decrease of 40.3 ±29.0 points from baseline.

Long-Term Efficacy (12 Months to 2 Years)

Longitudinal data indicates that the clinical improvements achieved with dupilumab are highly durable. Grose et al. (2023) reported a sustained mean SNOT-22 score of 15.2 ±17.8 at 12 months, representing a total mean reduction of 46.0 ±18.9 points. Elzinga et al. (2025) confirmed long-term disease control, with N-ERD patients maintaining a median SNOT-22 score of 19 (IQR 8–31) after 2 years of continuous treatment. Furthermore, Ozuna et al. (2022) evaluated patients over intervals ranging from 2 to 22 months, reporting a mean post-treatment SNOT-22 score of 20.5 ±18.7 ($P = 0.003$), with all evaluated patients opting to remain with the same biologic agent despite isolated reports of possible dupilumab-associated arthralgias.

3.4 Subgroup Analyses in Dupilumab Therapy

Subgroup evaluations revealed that dupilumab's efficacy is largely independent of specific patient comorbidities, such as continued aspirin intolerance or the specific classification of CRSwNP.

- **Aspirin Tolerance:** Schneider et al. (2023) evaluated patients based on post-treatment aspirin tolerance. Baseline SNOT-22 scores between the aspirin-intolerant subgroup (46.85 ±22.34) and the aspirin-tolerant subgroup (37.12 ±24.54) were not statistically different ($P = 0.28$). Following 6 months of dupilumab therapy, the reduction in clinical parameters was comparable between both groups.
- **N-ERD vs. CRSwNP-NOS:** Elzinga et al. (2025) compared outcomes between patients with N-ERD and those with CRSwNP-NOS. At 24 weeks, both cohorts achieved similar SNOT-22 scores (18 vs. 19, $P = 0.27$). This parity was maintained at the 2-year follow-up (19 vs. 19, $P = 0.78$), indicating that dupilumab effectively mitigates the additional disease burden typically associated with N-ERD.

Secondary Patient-Reported and Objective Outcomes

Beyond general sinonasal symptoms, dupilumab demonstrated significant efficacy in addressing secondary clinical endpoints, including subjective discomfort, asthma control, and olfactory function.

- **Overall Discomfort:** Bertlich et al. (2022) utilized a visual analogue scale (VAS) for overall complaints, observing an improvement from a pre-treatment baseline of 8.7 ±0.9 to 2.2 ±1.5 post-treatment ($P < 0.001$), corroborating the SNOT-22 findings.

- **Asthma Control:** Buchheit et al. (2022) evaluated lower airway symptoms using the Asthma Control Questionnaire-6 (ACQ-6). The cohort achieved a mean reduction of 1.3 points from a baseline of 1.6 ±1.3 after one month ($P < 0.001$), an improvement that was sustained at three months.
- **Olfactory Function:** Sense of smell was significantly restored by anti-IL-4Rα therapy. Buchheit et al. (2022) reported that of 16 patients categorized as anosmic at baseline via the University of Pennsylvania Smell Identification Test (UPSIT), only 4 remained anosmic after one month of dupilumab therapy ($P = 0.0002$). Wangberg et al. (2022) also documented highly significant reductions in SNOT-22 domain scores for both sense of smell (median 5 to 1; $P < 0.0001$) and sense of taste (median 5 to 1; $P < 0.0001$) under anti-IL-4Rα therapy.

3.5 Comparative Efficacy Across Biologic Classes

Analyses comparing different biologic classes highlight varying degrees of efficacy in the N-ERD population, with anti-IL-4Rα (dupilumab) consistently outperforming anti-IgE and anti-IL-5 therapies in comprehensive symptom resolution.

Table 2. Summary of SNOT-22 Reductions by Biologic Class (Wangberg Data)

Biologic Class	Pre-Therapy Median	Post-Therapy Median	Statxistical Significance
Anti-IL-4Rα (Dupilumab)	51.0	19.0	$P = 0.0002$
Anti-IgE	56.0	13.0	$P = 0.6286$ (ns)
Anti-IL-5/IL-5Rα	35.5	27.5	$P > 0.9999$ (ns)

Wangberg et al. (2022) demonstrated that total cohort improvements in quality of life were primarily driven by the anti-IL-4Rα subgroup. Patients receiving anti-IgE or anti-IL-5 therapies exhibited changes in total SNOT-22 scores that failed to reach statistical significance.

Bavaro et al. (2021) evaluated 41 patients with N-ERD initially treated with anti-IL-5/IL-5Rα therapies (predominantly mepolizumab). The cohort naturally divided into two subgroups based on their clinical response.

A subgroup of 14 patients achieved adequate symptom control and was maintained on mepolizumab. In this group, continued mepolizumab therapy was associated with significant improvements in total SNOT-22 scores (mean difference of 20 points, $P = 0.007$) and the nasal congestion subdomain ($P = 0.01$). However, the treatment failed to produce a statistically significant improvement in the specific SNOT-22 smell/taste domain.

The remaining 27 patients experienced inadequate symptom control on anti-IL-5/IL-5Rα therapies, demonstrating no significant improvements in total SNOT-22 scores, smell/taste, or nasal congestion. Consequently, these non-responders were transitioned to dupilumab. Following the switch to anti-IL-4Rα therapy, this previously refractory subgroup achieved significant improvements across all evaluated metrics, including total SNOT-22, nasal congestion, and smell/taste scores.

4. Discussion

4.1. The Scale of Quality of Life Improvement (Clinical Significance of SNOT-22 Reduction)

Patients with N-ERD typically present with baseline SNOT-22 scores exceeding 50 to 60 points-often reaching median scores around 70 in real-world cohorts-indicative of severe otolaryngological disability and profound impairment in daily functioning (Bertlich et al., 2021; Elzinga et al., 2025; Grose et al., 2023). Following targeted biologic therapy, these scores decrease by 30 to 45 points, far exceeding the established minimal clinically important difference (MCID) of 8.9 points (Fokkens et al., 2023; Grose et al., 2023; Mieli et al., 2025). Crucially, final post-treatment SNOT-22 scores frequently fall below 20 points, reflecting a clinically meaningful resolution of the disease burden and a symptomatic state that closely approximates the healthy population (Elzinga et al., 2025; Wangberg et al., 2022).

Translating these quantitative reductions into real-world clinical benefits reveals a substantial alleviation of both the physical and emotional toll of the disease. The sharp decline in total SNOT-22 scores corresponds directly with the rapid and sustained restoration of olfactory sensation, relief from chronic facial pain and

pressure, and the resolution of severe nasal obstruction (Domínguez-Sosa et al., 2023; Laidlaw, 2025; Mieli et al., 2025). Consequently, a 30- to 40-point reduction in the SNOT-22 score represents more than a statistical milestone; it signifies a fundamental shift in the patient experience. It demonstrates the capacity of biologics to liberate individuals from the daily burden of refractory sinonasal symptoms, returning them to a quality of life that was largely unattainable under traditional surgical and medical treatment paradigms (Domínguez-Sosa et al., 2023; Laidlaw, 2025; Wangberg et al., 2022).

4.2. Multisensory Rehabilitation: Smell and Taste as Foundations of Well-being

One of the most debilitating hallmarks of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) is severe hyposmia or complete anosmia, frequently accompanied by a profound loss of taste (Buchheit et al., 2022; Laidlaw, 2025). This multisensory deficit is notably more severe in patients with N-ERD than in those with aspirin-tolerant chronic rhinosinusitis with nasal polyps (CRSwNP) (Buchheit et al., 2022). The loss of these senses profoundly impairs health-related quality of life; surveyed patients report an inability to enjoy meals, difficulty identifying spoiled food, and persistent feelings of physical vulnerability due to compromised environmental awareness (Laidlaw, 2025). Historically, the sustained restoration of normal olfactory sensation has been difficult to achieve and maintain through the traditional treatment paradigm of endoscopic sinus surgery (ESS) and systemic corticosteroid therapy (Laidlaw, 2025).

In the era of biologic therapies, the targeted modulation of type 2 inflammation has demonstrated rapid and substantial efficacy in restoring olfactory and gustatory function (Laidlaw, 2025). Real-world cohorts and clinical trials consistently reveal significant reductions in patient-reported 22-item Sino-Nasal Outcome Test (SNOT-22) smell and taste impairment scores following biologic initiation (Wangberg et al., 2022). These subjective patient-reported outcomes are corroborated by robust improvements in objective olfactory assessments, such as the University of Pennsylvania Smell Identification Test (UPSIT) and the Connecticut Chemosensory Clinical Research Center (CCCRC) test (Buchheit et al., 2022; Mieli et al., 2025; Schneider et al., 2023). While improvements in olfaction have been observed across various monoclonal antibodies-including anti-IgE (omalizumab) and anti-IL-5 agents (mepolizumab, benralizumab, reslizumab)-dupilumab specifically exhibits strong evidence for rapid and sustained olfactory recovery, often demonstrating clinically meaningful benefits within the first month of therapy (Barroso et al., 2023; Buchheit et al., 2022; Laidlaw, 2025).

Despite these biologic-driven improvements, biologic therapy generally yields a success rate of approximately 60% regarding the improvement of smell, meaning a substantial proportion of patients may not achieve complete, spontaneous sensory resolution (Fokkens et al., 2023). Consequently, expert consensus advises that active multisensory rehabilitation is a necessary adjunct to biologic treatment (Fokkens et al., 2023). Once targeted biologic therapy reduces the inflammatory burden and initiates the recovery of smell, patients are advised to commence structured olfactory training (Fokkens et al., 2023). This rehabilitation is critical to reactivate the neurogenic pathways responsible for olfactory function that remained dormant during prolonged periods of mucosal inflammation and anosmia, thereby maximizing the restoration of the patient's multisensory well-being (Fokkens et al., 2023).

4.3. Quality of Life Beyond the Nasal Cavity: Sleep, Fatigue, and Hearing

The debilitating nature of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) extends significantly beyond the cardinal sinonasal and pulmonary symptoms, profoundly impairing sleep quality, daily functioning, and otologic health. Up to 90% of patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP) experience impaired sleep, which correlates with overall disease severity and serves as a major contributor to decreased health-related quality of life, increased depression risk, impaired cognitive function, and decreased work productivity (Mullol et al., 2024). Post-hoc analyses of large clinical trials indicate that targeted biologic therapies, such as mepolizumab, significantly reduce both sleep disturbances and fatigue in patients with severe CRSwNP, irrespective of comorbid N-ERD or asthma status (Mullol et al., 2024). Specifically, biologic treatment yields clinically meaningful improvements across the SNOT-22 sleep and fatigue domains, alleviating difficulties in falling asleep, nighttime awakenings, and daytime fatigue, which directly translates to improved patient concentration and work productivity (Mullol et al., 2024).

Furthermore, the chronic type 2 inflammation and mucosal obstruction characteristic of N-ERD frequently involve the eustachian tubes, predisposing patients to eustachian tube dysfunction (ETD), recurrent ear infections, conductive hearing loss, ear fullness, and ear pain (Mullur et al., 2024). The SNOT-22 ear/facial subdomain has been validated as a strong predictor of clinically meaningful ETD in this specific patient

population (Mullur et al., 2024). Real-world observational data demonstrate that treatment with dupilumab rapidly and significantly improves these otologic symptoms-specifically reducing "ear fullness" and "ear pain/pressure" scores-within one month of treatment initiation, with sustained benefits observed at three months (Mullur et al., 2024). This rapid alleviation of ETD is hypothesized to result from the systemic immunological mitigation of type 2 inflammation, which improves sinonasal and eustachian tube patency (Mullur et al., 2024). Collectively, these findings underscore that targeted biologic therapies provide comprehensive relief from the multi-systemic burdens of N-ERD, facilitating restorative sleep and restoring otologic function that traditional therapies often fail to address.

4.4. Halting the Surgical Cycle

Historically, patients with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) have been subjected to a continuous cycle of surgical interventions due to the aggressive nature of the disease and high rates of rapid polyp regrowth following endoscopic sinus surgery (ESS) (Laidlaw, 2025). However, the advent of targeted biologic therapies has fundamentally shifted this management paradigm by offering a pharmacological mechanism to halt disease recurrence and avoid repeated surgical trauma (Domínguez-Sosa et al., 2023; Laidlaw, 2025). Clinical trials and real-world studies consistently demonstrate that biologics, including dupilumab and mepolizumab, significantly reduce the need for revision surgeries in patients with severe CRSwNP and comorbid N-ERD (Bachert et al., 2022; Domínguez-Sosa et al., 2023; Grose et al., 2023).

For example, in cohorts of AERD patients characterized by rapid polyp regrowth-often recurring within months of their initial ESS-the perioperative initiation of dupilumab successfully prevented rhinoscopic evidence of recurrence for extended periods, effectively breaking the cycle of surgical recalcitrance (Patel et al., 2022). Similarly, real-world data indicate that patients treated with mepolizumab frequently avoid the need for subsequent revision surgeries entirely during their treatment course (Domínguez-Sosa et al., 2023). For patients presenting with a substantial polyp burden, biologics now provide the option to intervene pharmacologically, reducing polyp size and relieving nasal congestion without the prerequisite of another operation (Laidlaw, 2025). The capacity of these therapies to medically control polyposis not only minimizes cumulative surgical morbidity and associated healthcare costs but also substantially enhances patient satisfaction by providing a durable, non-surgical solution to a previously refractory condition (Grose et al., 2023; Laidlaw, 2025).

4.5. Comparative Efficacy of Dupilumab and Mepolizumab on Asthma Control

Both dupilumab and mepolizumab have demonstrated clinical efficacy in reducing asthma exacerbations and improving lower airway function in patients with N-ERD (Laidlaw, 2025; Lázaro-Sastre et al., 2026). Mepolizumab, which targets the interleukin-5 (IL-5) pathway, effectively reduces the annual rate of clinically significant exacerbations and improves Asthma Control Questionnaire (ACQ-5) scores in patients with severe eosinophilic asthma and comorbid chronic rhinosinusitis with nasal polyps (CRSwNP) (Bachert et al., 2022; Laidlaw, 2025). Clinical cohorts indicate that a specific responder subset of patients achieves satisfactory and sustained asthma control on mepolizumab monotherapy, noting significant improvements in Asthma Control Test (ACT) scores and a trend toward better lung function (Lázaro-Sastre et al., 2026).

However, real-world observational data and sequential therapy cohorts suggest that dupilumab, targeting the interleukin-4 receptor alpha (IL-4Rα), may offer better and more consistent lower airway control for the broader, treatment-refractory N-ERD population (Bavaro et al., 2021; Mullur & Buchheit, 2023). While mepolizumab provides a clinical benefit, a substantial proportion of patients with N-ERD continue to experience inadequate control of their lower airway symptoms (Bavaro et al., 2021; Lázaro-Sastre et al., 2026). In patients exhibiting an inadequate response to mepolizumab switching to dupilumab yields robust clinical salvage (Bavaro et al., 2021). Following the transition to dupilumab, these previously refractory patients demonstrate rapid and significant improvements in ACT scores, increased FEV1 percent predicted, and a significantly lower annualized asthma exacerbation rate compared to their time on anti-IL-5 therapy (Bavaro et al., 2021; Lázaro-Sastre et al., 2026).

Ultimately, while both biologics successfully modulate lower airway inflammation, indirect comparisons and real-world transition data suggest that dupilumab provides a more robust and consistent therapeutic benefit for achieving optimal asthma control in the severe N-ERD phenotype (Bavaro et al., 2021; Mullur & Buchheit, 2023).

4.6. Comparative Efficacy of Biologics and Aspirin Desensitization on SNOT-22 Outcomes

Currently, there are no direct head-to-head randomized controlled trials comparing the efficacy of aspirin therapy after desensitization (ATAD) versus targeted biologic therapies for the management of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) (Mullur & Buchheit, 2023). Both therapeutic modalities have been shown to improve health-related quality of life, reduce nasal polyp size, and decrease sinonasal symptoms (Mullur & Buchheit, 2023). However, network meta-analyses evaluating multiple treatments demonstrate that biologics-particularly dupilumab-provide superior clinical benefit across a wider spectrum of outcomes when compared to ATAD (Lyly et al., 2025; Mullur & Buchheit, 2023). Beyond efficacy, the overall safety profile of biologics is notably more favorable than that of aspirin desensitization, as the latter is frequently limited by treatment-disrupting gastrointestinal adverse effects and has demonstrated lower relative efficacy in indirect comparisons (Foerster-Ruhrmann et al., 2024; Mullur & Buchheit, 2023).

In real-world retrospective assessments, biologic-treated patients demonstrated approximately a 50% improvement in SNOT-22 scores within the first year of therapy, achieving greater improvements in both nasal and asthma outcomes than those treated with ATAD (Lyly et al., 2025). Furthermore, survey data reveal that patients requiring concurrent biologic and ATAD therapy are significantly less likely to report that aspirin is effective for their N-ERD symptoms compared to individuals managed on ATAD alone (Mullur et al., 2022). This suggests that concurrent users represent a more treatment-refractory phenotype where ATAD monotherapy is insufficient (Lázaro-Sastre et al., 2026; Mullur et al., 2022). For patients experiencing an inadequate symptom response to initial ATAD, the subsequent addition of targeted biologics-such as dupilumab-yields significant improvements in upper and lower airway symptoms, highlighting the critical role of biologics as a necessary escalation of therapy for patients with refractory quality-of-life impairment (Achanta et al., 2025; Mullur & Buchheit, 2023).

4.7. Real-World Treatment Adherence and Safety Profiles of Biologic Therapies

In the real-world management of N-ERD, targeted biologic therapies demonstrate highly favorable adherence rates and safety profiles, particularly when contrasted with the high dropout rates historically associated with aspirin therapy after desensitization (ATAD) (Mullur et al., 2022; Wangberg et al., 2022). While ATAD discontinuation is frequently driven by intolerable gastrointestinal side effects and bleeding risks, patients prescribed biologics exhibit strong long-term persistence. This adherence is largely motivated by significant subjective symptom relief and a consistently low incidence of severe adverse events (Mullur et al., 2022; Wangberg et al., 2022).

Despite this overall tolerability, specific safety considerations must be monitored depending on the monoclonal antibody utilized. Dupilumab, an anti-IL-4Rα therapy, is uniquely associated with the development of transient hypereosinophilia (Fokkens et al., 2023; Galletti et al., 2024). This occurs because dupilumab inhibits eotaxin-3, effectively blocking the migration of eosinophils from the peripheral blood into the nasal polyp tissue (Galletti et al., 2024). Although this systemic increase in eosinophils is typically asymptomatic and temporary, expert consensus advises monitoring blood eosinophil counts at one and three months post-initiation, particularly in patients with high baseline counts (exceeding 500 cells/μL) or those transitioning off chronic systemic corticosteroids (Fokkens et al., 2023). Additionally, new-onset arthralgia has been reported as a limiting adverse effect in a subset of patients receiving dupilumab, which can occasionally necessitate treatment cessation (Ozuna et al., 2022; Supron et al., 2023).

For patients who experience such adverse effects or demonstrate inadequate symptomatic control on an initial biologic-most commonly anti-IL-5 agents like mepolizumab-real-world evidence supports the safety and efficacy of switching biologic classes (Brkic et al., 2023; Matsumoto-Sasaki et al., 2022). Studies indicate that transitioning between biologics, such as moving from an anti-IL-5 to an anti-IL-4Rα agent, is well-tolerated and can often be performed successfully without a prolonged washout period (Brkic et al., 2023). This therapeutic flexibility provides a critical pathway to achieve optimal disease control in refractory N-ERD populations without proportionately increasing the risk of adverse events (Brkic et al., 2023).

4.8. Limitations and the Strength of Current Evidence

Despite the transformative impact of targeted biologics in the management of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD), the current body of evidence presents several critical limitations. A primary shortcoming is the notable lack of large-scale, head-to-head randomized controlled trials (RCTs) specifically designed to evaluate and compare different biologic therapies, or to compare biologics directly against aspirin therapy after desensitization (ATAD) in this specific patient population (Lázaro-Sastre et al., 2026; Mullur & Buchheit, 2023). In major phase 3 clinical trials for chronic rhinosinusitis with nasal polyps (CRSwNP)-such as the SINUS-24, SINUS-52, and SYNAPSE studies-patients with N-ERD constituted only a subgroup, typically comprising less than 30% of the overall study populations (Lyly et al., 2025; Van Broeck et al., 2023).

Consequently, much of the current knowledge regarding biologic efficacy in N-ERD is derived from post-hoc subgroup analyses, small case series, and retrospective real-world observational cohorts (Achanta et al., 2025; Lázaro-Sastre et al., 2026). These study designs are inherently susceptible to selection and information biases. For instance, data originating from specialized tertiary AERD referral centers often capture patients with exceptionally severe and refractory disease, which may limit the generalizability of the findings to the broader, less severe N-ERD population (Achanta et al., 2025; Mullur et al., 2022). Furthermore, while a formal quality assessment confirmed that no studies possessed fatal methodological flaws, the majority of the included evidence was rated as "Fair" due to its retrospective nature, lack of blinding, and absence of *a priori* power calculations, necessitating a cautious interpretation of the aggregated observational data.

A further methodological limitation of this review is the absence of a formal meta-analysis. Although continuous SNOT-22 data were systematically extracted, a quantitative statistical synthesis was deemed inappropriate due to the high degree of clinical and methodological heterogeneity across the included studies. The selected cohorts exhibited significant variations in follow-up durations (ranging from 4 weeks to 2 years), the specific biologic agents utilized, and the statistical reporting formats of the primary outcomes, with studies alternately presenting data as means with standard deviations or medians with interquartile ranges. In accordance with standard systematic review guidelines, pooling such heterogeneous data from small, uncontrolled observational cohorts carries a high risk of generating misleading pooled effect estimates. Consequently, a descriptive synthesis was adopted to provide a more transparent and accurate reflection of the individual study outcomes.

5. Conclusions

The introduction of targeted biologics, particularly dupilumab, has revolutionized N-ERD management by significantly reducing nasal polyp burden, restoring olfaction, and decreasing reliance on systemic corticosteroids and revision surgeries (Laidlaw, 2025; Lázaro-Sastre et al., 2026; Schneider et al., 2023; Wangberg et al., 2022). Rather than acting as standalone interventions, biologics serve as a highly effective step-up therapy that should be integrated with surgery and aspirin desensitization (ATAD) into a personalized, multidisciplinary approach (Kumar et al., 2026; Ley-Tomas et al., 2024; Mullur et al., 2022).

To optimize these care pathways, future research must address critical literature gaps (Lázaro-Sastre et al., 2026). Primary unmet needs include large-scale, head-to-head randomized trials comparing biologics against one another and ATAD in dedicated N-ERD cohorts (Lázaro-Sastre et al., 2026; Mullur & Buchheit, 2023). Additionally, advancing precision medicine will require the identification of reliable predictive biomarkers to guide treatment selection, exploration of non-type 2 inflammatory targets, and long-term real-world data to establish cost-effectiveness and protocols for dose-tapering (Elzinga et al., 2025; Fokkens et al., 2023; Laidlaw, 2025; Stevens & Cahill, 2023).

All authors have read and agreed to the published version of the manuscript.

Funding Statement: The authors received no external funding for this work.

Data Availability Statement: All data supporting the findings of this study are available in the cited literature included in this review.

Conflict of Interest Statement: The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process: During the preparation of this manuscript, Gemini was used to support language refinement and improve readability. All AI-assisted content was critically reviewed and revised by the authors. The authors take full responsibility for the content of the manuscript, including the accuracy of the data, interpretations, and conclusions presented.

REFERENCES

1. Achanta, P. M., Swirnoff, J., Parigian, R. E., Laidlaw, T. M., & Buchheit, K. M. (2025). Addition of dupilumab for patients with aspirin-exacerbated respiratory disease who have poor response to aspirin therapy after desensitization. *The Journal of Allergy and Clinical Immunology: In Practice, 13*(12), 3425–3427.e1. https://doi.org/10.1016/j.jaip.2025.08.032
2. Bachert, C., Sousa, A. R., Han, J. K., Schlosser, R. J., Sowerby, L. J., Hopkins, C., Maspero, J. F., Smith, S. G., Kante, O., Karidi-Andrioti, D. E., Mayer, B., Chan, R. H., Yancey, S. W., & Chaker, A. M. (2022). Mepolizumab for chronic rhinosinusitis with nasal polyps: Treatment efficacy by comorbidity and blood eosinophil count. *Journal of Allergy and Clinical Immunology, 149*(5), 1711–1721.e6. https://doi.org/10.1016/j.jaci.2021.10.040
3. Barroso, B., Valverde-Monge, M., Alobid, I., Olaguibel, J. M., Rial, M. J., Quirce, S., Arismendi, E., Barranco, P., Betancor, D., Bobolea, I., Cárdaba, B., Cruz Carmona, M. J., Curto, E., Dominguez-Ortega, J., González-Barcala, F. J., Martinez-Rivera, C., Mahillo-Fernández, I., Muñoz, X., Picado, C., Plaza, V., Rodrigo Muñoz, J. M., Soto-Retes, L., Valero, A., del Pozo, V., Mullol, J., & Sastre, J. (2023). Improvement in olfaction in patients with CRSwNP and severe asthma taking anti-IgE and anti-IL-5 biologics: A real-life study. *Journal of Investigational Allergology and Clinical Immunology, 33*(1), 37–44. https://doi.org/10.18176/jiaci.0812
4. Bavaro, N., Gakpo, D., Mittal, A., Bensko, J. C., Laidlaw, T. M., & Buchheit, K. M. (2021). Efficacy of dupilumab in patients with aspirin-exacerbated respiratory disease and previous inadequate response to anti-IL-5 or anti-IL-5Rα in a real-world setting. *The Journal of Allergy and Clinical Immunology: In Practice, 9*(7), 2910–2912.e1. https://doi.org/10.1016/j.jaip.2021.02.020
5. Bertlich, M., Ihler, F., Bertlich, I., Weiss, B. G., Gröger, M., & Haubner, F. (2021). Management of chronic rhinosinusitis with nasal polyps in Samter triad by low-dose ASA desensitization or dupilumab. *Medicine, 100*(40), e27471. https://doi.org/10.1097/MD.0000000000027471
6. Bertlich, M., Freytag, S., Dombrowski, T., Jurmeister, P., Spiegel, J. L., Bertlich, I., Ihler, F., Weiss, B. G., Haubner, F., & Gröger, M. (2022). Subgroups in the treatment of nasal polyposis with dupilumab: A retrospective study. *Medicine, 101*(45), e31031. https://doi.org/10.1097/MD.0000000000031031
7. Brkic, F. F., Liu, D. T., Klimbacher, R., Campion, N. J., Bartosik, T. J., Vyskocil, E., Stanek, V., Tu, A., Arnoldner, T., Bangert, C., Gangl, K., Eckl-Dorna, J., & Schneider, S. (2023). Efficacy and safety of switching between biologics in chronic rhinosinusitis with nasal polyps or N-ERD. *Rhinology Journal, 61*(4), 320–327. https://doi.org/10.4193/Rhin22.408
8. Buchheit, K. M., Sohail, A., Hacker, J., Maurer, R., Gakpo, D., Bensko, J. C., Taliaferro, F., Ordovas-Montanes, J., & Laidlaw, T. M. (2022). Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology, 150*(2), 415–424. https://doi.org/10.1016/j.jaci.2022.04.007
9. Çelik Tuğlu, H., Aksu, K., Telli, O., Dindar Çelik, F., Yağdıran, M., Akkale, Ö., Köycü Buhari, G., Bahçecioğlu, S. N., & Vural Solak, G. T. (2025). The effect of biological agent use on symptoms in patients diagnosed with NSAID-exacerbated respiratory disease (NERD). *Revue Française d'Allergologie, 65*(4), 104219. https://doi.org/10.1016/j.reval.2024.104219
10. Chen, C. C., Buchheit, K. M., Lee, P. Y., Brodeur, K. E., Sohail, A., Cho, L., Baloh, C. H., Balestrieri, B., Derakhshan, T., Feng, C., Boyce, J. A., Dwyer, D. F., & Laidlaw, T. M. (2024). IL-4Rα signaling promotes barrier-altering oncostatin M and IL-6 production in aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology, 154*(2), 458–467.e3. https://doi.org/10.1016/j.jaci.2024.04.020
11. Domínguez-Sosa, M. S., Cabrera-Ramírez, M. S., Marrero-Ramos, M. D. C., Dávila-Quintana, D., Cabrera-López, C., Carrillo-Díaz, T., & Del Rosario, J. J. B. (2023). Real-life effectiveness of mepolizumab in refractory chronic rhinosinusitis with nasal polyps. *Biomedicines, 11*(2), 485. https://doi.org/10.3390/biomedicines11020485
12. Elzinga, H. B. E., Otten, J. J., Cornet, M. E., Rinia, A. B., Van Der Lans, R. J. L., Fokkens, W. J., Reitsma, S., & PolyREG Consortium. (2025). Two-year data of tapered dupilumab shows high effectiveness in chronic rhinosinusitis with nasal polyps with nonsteroidal anti-inflammatory drug-exacerbated respiratory disease. *Allergy, 80*(6), 1737–1745. https://doi.org/10.1111/all.16579

13. Foerster-Ruhrmann, U., Jurkov, M., Szczepek, A. J., Bergmann, K.-C., Fluhr, J. W., & Olze, H. (2024). Biologics reduce symptoms of alcohol intolerance better than aspirin desensitization in patients with N-ERD and nasal polyps. *Biomedicines, 12*(5), 1025. https://doi.org/10.3390/biomedicines12051025
14. Fokkens, W. J., Viskens, A.-S., Backer, V., Conti, D., De Corso, E., Gevaert, P., Scadding, G. K., Wagemann, M., Bernal-Sprekelsen, M., Chaker, A., Heffler, E., Han, J. K., Van Staeyen, E., Hopkins, C., Mullol, J., Peters, A., Reitsma, S., Senior, B. A., & Hellings, P. W. (2023). EPOS/EUFOREA update on indication and evaluation of biologics in chronic rhinosinusitis with nasal polyps 2023. *Rhinology Journal, 0*(0). https://doi.org/10.4193/Rhin22.489
15. Galletti, C., Ragusa, M., Sireci, F., Ciodaro, F., Barbieri, M. A., Giunta, G., Grigaliute, E., Immordino, A., Lorusso, F., Dispenza, F., Freni, F., Galletti, F., Gallina, S., La Mantia, I., & Galletti, B. (2024). Dupilumab in chronic rhinosinusitis with nasal polyps: Real life data in a multicentric Sicilian experience. *American Journal of Otolaryngology, 45*(1), 104106. https://doi.org/10.1016/j.amjoto.2023.104106
16. Garvey, E., Naimi, B., Duffy, A., Hannikainen, P., Kahn, C., Farquhar, D., Rosen, M., Rabinowitz, M., Toskala, E., & Nyquist, G. (2024). Optimizing the timing of biologic and surgical therapy for patients with refractory chronic rhinosinusitis with nasal polyposis (CRSwNP). *International Forum of Allergy & Rhinology, 14*(3), 651–659. https://doi.org/10.1002/alr.23246
17. Grose, E., Li, A. Y., & Lee, J. M. (2023). Clinical outcomes of dupilumab therapy in chronic rhinosinusitis with nasal polyps in a Canadian tertiary care rhinology practice. *Allergy, Asthma & Clinical Immunology, 19*(1), 26. https://doi.org/10.1186/s13223-023-00782-7
18. Hayashi, H., Fukutomi, Y., Mitsui, C., Kajiwara, K., Watai, K., Tomita, Y., Kamide, Y., Tsuburai, T., Sekiya, K., Ishii, M., Hasegawa, Y., & Taniguchi, M. (2023). Omalizumab ameliorates extrarespiratory symptoms in patients with aspirin-exacerbated respiratory disease. *Journal of Allergy and Clinical Immunology, 151*(6), 1667–1672.e2. https://doi.org/10.1016/j.jaci.2023.03.014
19. Imam, K. H., & Woessner, K. M. (2023). Nonsteroidal anti-inflammatory drug-exacerbated respiratory disease: Diagnosis and current management. *Polish Archives of Internal Medicine*. https://doi.org/10.20452/pamw.16544
20. Kumar, N., Pace, T., Gomes, P. L., Marino, M. J., Miglani, A., & Lal, D. (2026). Real-world treatment patterns in AERD: An analysis of ATAD, biologics, and combination therapy. *International Forum of Allergy & Rhinology, 16*(1), 99–101. https://doi.org/10.1002/alr.70072
21. Laidlaw, T. M. (2025). Aspirin-exacerbated respiratory disease in the era of biologics. *Annals of Allergy, Asthma & Immunology, 135*(4), 366–373. https://doi.org/10.1016/j.anai.2025.06.001
22. Lázaro-Sastre, M., Moreno-Rodilla, E., Martín-García, C., Maza-Solano, J., Gil-Melcon, M., & Dávila, I. (2026). A systematic review of the specific role of biological therapies in aspirin-exacerbated respiratory disease. *Journal of Investigational Allergology and Clinical Immunology, 36*(1), 12–24. https://doi.org/10.18176/jiaci.1155
23. Ley-Tomas, J. J., Xicotencatl-Tellez, A. M., García-Cruz, M. L., & Jiménez-Chobillon, M. A. (2024). Nonsteroidal antiinflammatory drug-exacerbated respiratory disease: Molecular mechanism, management and treatment. *Frontiers in Allergy, 5*, 1462985. https://doi.org/10.3389/falgy.2024.1462985
24. Lyly, A., Laulajainen-Hongisto, A., Turpeinen, H., Vento, S. I., Myller, J., Numminen, J., Sillanpää, S., Sahlman, J., Kauppi, P., & Toppila-Salmi, S. (2021). Factors affecting upper airway control of NSAID-exacerbated respiratory disease: A real-world study of 167 patients. *Immunity, Inflammation and Disease, 9*(1), 80–89. https://doi.org/10.1002/iid3.347
25. Lyly, A., Sahlman, J., Pajala, K., Salminen, M., Sillanpää, S., Numminen, J., Hanif, T., Laulajainen-Hongisto, A., Mäkelä, M., Kauppi, P., Kangasniemi, I., Lilja, M., Hammaren-Malmi, S., Virkkula, P., & Toppila-Salmi, S. (2025). Study protocol for a randomized double-blinded placebo-controlled trial on mepolizumab for patients with chronic rhinosinusitis with nasal polyps, NSAID exacerbated respiratory disease and asthma. *Frontiers in Allergy, 6*, 1568081. https://doi.org/10.3389/falgy.2025.1568081
26. Matsumoto-Sasaki, M., Simizu, K., Suzuki, M., Suzuki, M., Kimura, H., Nakamaru, Y., Ito, Y. M., Homma, A., & Konno, S. (2022). Clinical characteristics of patients and factors associated with switching biologics in asthma. *Journal of Asthma and Allergy, 15*, 187–195. https://doi.org/10.2147/JAA.S348513
27. Mieli, O. M., Valera, F. C. P., Dinarte, V. R. P., De Lima, C. M. F., Nakanishi, M., Zanetti, M. E. T., Pires, F. O., Garcia, D. M., Murashima, A. D. A. B., Arruda, L. K. D. P., Romano, F. R., Lemos, J. E. S., Kosugi, E. M., Sakano, E., Tepedino, M. S., Tamashiro, E., & Anselmo-Lima, W. T. (2025). One-year efficacy of dupilumab in sense of smell, nasal polyp score and quality of life in CRSwNP patients: A real-world multicenter study in Brazil. *Brazilian Journal of Otorhinolaryngology, 91*(6), 101704. https://doi.org/10.1016/j.bjorl.2025.101704
28. Mullol, J., Fokkens, W. J., Smith, S. G., Keeley, T., Zhang, L., Howarth, P., Chan, R. H., & Bachert, C. (2024). The impact of mepolizumab on sleep impairment in CRSwNP: Post hoc analyses of SYNAPSE and MUSCA. *Rhinology Journal, 0*(0), 0–0. https://doi.org/10.4193/Rhin24.021
29. Mullur, J., Steger, C. M., Gakpo, D., Bensko, J. C., Maurer, R., Laidlaw, T. M., & Buchheit, K. M. (2022). Aspirin desensitization and biologics in aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology, 128*(5), 575–582. https://doi.org/10.1016/j.anai.2022.01.043

30. Mullur, J., & Buchheit, K. M. (2023). Aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology, 131*(3), 317–324. https://doi.org/10.1016/j.anai.2023.05.016
31. Mullur, J., Lundberg, M., Maurer, R., Laidlaw, T. M., & Buchheit, K. M. (2024). Dupilumab rapidly improves eustachian tube dysfunction and otologic symptoms in aspirin-exacerbated respiratory disease. *Allergy and Asthma Proceedings, 45*(6), 421–425. https://doi.org/10.2500/aap.2024.45.240047
32. Ozuna, L., Ryan, T., Bensko, J. C., Laidlaw, T. M., & Buchheit, K. M. (2022). Dupilumab-associated arthralgia in patients with aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology, 128*(4), 469–472. https://doi.org/10.1016/j.anai.2022.01.036
33. Patel, P., Bensko, J. C., Bhattacharyya, N., Laidlaw, T. M., & Buchheit, K. M. (2022). Dupilumab as an adjunct to surgery in patients with aspirin-exacerbated respiratory disease. *Annals of Allergy, Asthma & Immunology, 128*(3), 326–328. https://doi.org/10.1016/j.anai.2021.11.020
34. Schneider, S., Poglitsch, K., Morgenstern, C., Quint, T., Gangl, K., Sinz, C., Bartosik, T., Campion, N. J., Liu, D. T., Landegger, L. D., Tu, A., Stanek, V., Rocha-Hasler, M., Bangert, C., & Eckl-Dorna, J. (2023). Dupilumab increases aspirin tolerance in NSAID-exacerbated respiratory disease. *European Respiratory Journal, 61*(3), 2201335. https://doi.org/10.1183/13993003.01335-2022
35. Stevens, W. W., & Cahill, K. N. (2023). Mechanistic and clinical updates in AERD: 2021-2022. *Journal of Allergy and Clinical Immunology, 151*(6), 1448–1456. https://doi.org/10.1016/j.jaci.2023.03.015
36. Supron, A. D., Bergmark, R. W., Roditi, R. E., & Buchheit, K. M. (2023). Perioperative mepolizumab in aspirin-exacerbated respiratory disease does not prevent nasal polyp regrowth. *Annals of Allergy, Asthma & Immunology, 131*(3), 384–386. https://doi.org/10.1016/j.anai.2023.06.017
37. Tepetam, F. M., Özden, Ş., Kılıç, F. K., Örçen, C., & Yakut, T. (2023). Does NSAID exacerbated respiratory disease (N-ERD) accompanying severe asthma affect biological treatment response? Efficacy of omalizumab and mepolizumab in N-ERD. *World Allergy Organization Journal, 16*(9), 100817. https://doi.org/10.1016/j.waojou.2023.100817
38. Van Broeck, D., Steelant, B., Scadding, G., & Hellings, P. W. (2023). Monoclonal antibody or aspirin desensitization in NSAID-exacerbated respiratory disease (N-ERD)? *Frontiers in Allergy, 4*, 1080951. https://doi.org/10.3389/falgy.2023.1080951
39. Wangberg, H., Spierling Bagsic, S. R., Osuna, L., & White, A. A. (2022). Appraisal of the real-world effectiveness of biologic therapies in aspirin-exacerbated respiratory disease. *The Journal of Allergy and Clinical Immunology: In Practice, 10*(2), 478–484.e3. https://doi.org/10.1016/j.jaip.2021.09.030