**SUPPLEMENTARY MATERIAL**

## RATIONALE

### Sense of smell

Odor particles enter the nasal cavity through nostrils and dissolve in the mucus to be transported to the receptors located at the cilia of the olfactory cells. This complex neuroepithelium covers the cribriform lamina, the superior zone of the nasal septum, the superior turbinate and some parts of the middle turbinate thatcontains the cell bodies of mature and immature olfactory sensory neurons (OSN) generated from horizontal and globose basal stem cells.The axons from the olfactory cells converge with the mitral cells, in the olfactory bulbs. The axons fromthe mitral cells travels in the inferior part of the frontal lobe and splits in two: a lateral stria (ending at the primary olfactory cortex at the uncus of temporal lobe) and medial stria (crosses to the olfactory bulb on the opposite side). The primary olfactory cortex sends nerve fibers to many other areas of the brain, notably the piriform cortex, the amygdala, olfactory tubercle and the secondary olfactory cortex. These areas are involved in the memory and appreciation of olfactory sensations[1].

Smell helps humans to protect themselves through detection and avoidance of environmental hazards; influences the drive for appetite and takes place in social behavior since birth as odors from the areola attract infants to breastfeed [2].

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**Olfactory terminology**

| | |
|---|---|
| **Normosmia** | Normal olfactory function |
| **Hyposmia** (or 'microsmia') | Quantitatively reduced olfactory function |
| **Anosmia** | Absence of all olfactory function |
| **Hyperosmia** (or 'superosmia') | Quantitatively increased ability to smell odors to abnormal level (for example, in association with migraine) |
| **Parosmia** (or 'dysosmia', 'cacosmia', 'euosmia' or 'troposmia') | Qualitative dysfunction in the presence of an odor(i.e. distorted perception of an odor stimulus) |
| **Phantosmia** | Qualitative dysfunction in the absence of an odor (i.e. an odor is perceived without concurrent stimulus, an 'olfactory hallucination') |

Adapted from EPOS 2020 [3].


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**Olfactory dysfunction in general population**

Global Allergy and Asthma European Network (GA2LEN) demonstrated self-reported smell loss in 7.6% of 57,128 respondents from across Europe [4]. OLFACAT (OLFAction in CATalonia) is the largest population-based European epidemiological smell self-administered survey (n=9,348), reported an overall prevalence of olfactory dysfunction of 19.4% (0.3% of anosmia and 19.1% of hyposmia) [5].This data correlates with that found by Brämerson et al., who reported an overall prevalence of olfactory impairment of 19.1% in Swedish population [6].

Smell dysfunction has a significant impact on quality of life (QOL), potentially leading to food poisoning environmental and social anxiety, food and weight disturbances and depression [4].

**Olfactory dysfunction in chronic rhinosinusitis** (**CRS)**

CRS is the most frequent cause of gradual olfactory dysfunction, especially if it associatesNP. Approximately 67-78% of subjects with chronic rhinosinusitis with nasal polyps (CRSwNP) experience olfactory dysfunction[7].

Smell loss in CRS is caused by a multifactorial combination of mechanical obstruction of odorant transmission in the olfactory cleft due to mucosal type 2 inflammation (edema or nasal polyps), leading to shedding and/or degeneration of the olfactory epithelium and causing the reduction or loss of the sense of smell [8].CRS inflammation, with or without NP, affects the mucosa of bilateral paranasal sinuses and



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nasal cavities, including the olfactory cleft and epithelium. Type 2 inflammation (mainly eosinophilic) of the olfactory cleft mucosa leads to olfactory epithelium shedding and OSN degeneration as potential causes of the loss of smell. Anti-inflammatory therapy (corticosteroids, biologics, and others) potentially reduces olfactory cleft inflammation and induces BSC proliferation and OSN regeneration, causing the partial or total recovery of the sense of smell[9-11].

## Olfactory testing

There are 3 different types of olfactory testing: subjective test, psychophysical test and objective smell tests. See *Table S1*.

**TABLE S1.Olfactory testing. Types of olfactory testing: subjective test, psychophysical test and objective smell tests.** Adapted from Mullol et al, JACI. 2020 [8].

| **1. Subjective test: patient reported olfactory assessment.** | | | | |
|---|---|---|---|---|
| **Test** | **Range** | | | |
| Visual or numerical analogue scale (VAS/NAS) | (0-10); 0 = normal smell; 10 = total smell loss | | | |
| Loss of smell (LoS) | (0-3) 0 = no symptom; 1 = mild LoS; 2 = moderate LoS; 3 = severe LoS | | | |
| **2. Psychophysical test: should include 2 or 3 of three components of olfaction** | | | | |
| **Test** | **Country** | **Components of olfaction (T,D,I)*** | **Range** | **Description** |

| | | | | |
|---|---|---|---|---|
| University of Pennsylvania Smell Identification Test (UPSIT) [12] | USA | I | (0-40)<br>Anosmia ≤18<br>Hyposmia19-34<br>Normosmia>34 | A total of 40 encapsulated self-administered odors (“sratch-and sniff”) |
| Sniffin’ sticks test [13] | Germany | TDI | Normosmia if > 75% forced-choice identification. Updated normative values according to age and sex in Stevens et al, 2019 [14] | Identification: 16 odors in felt-tip pens [15] |
| Barcelona Smell Test (BAST-24)[16] | Spain | D,I + gustometry | Reference values according to age, sex and smoking habit | A total of 24 odors (semisolid gel) in glass |
| 8-Odorant Barcelona Olfactory Test (BOT-8)[17] | Spain | T,D,I | (0-8)<br>Anosmia ≤3<br>Hyposmia 3-6<br>Normosmia 7-8 | Semi–solid-state odorants contained in glass jars |
| T&T olfactometer[18] | Japan | D,T | Anosmia 5.6 -5.8<br>Hyposmia 1.1 -5.5<br>Normosmia 2 -1.0 | f small vials 7 or 8 log 10 serial dilution concentration steps containing dilutions of five odorants |
| Connecticut Chemosensory Clinical Research Center (CCCRC)[19] | USA | T | (0-7)<br>Anosmia <2<br>Hyposmia 2-5<br>Normosmia 6-7 | A total of 10 odors, in jars. Forced choice among 20 descriptors. Separate nostrils |
| Smell Diskettes[20] | Switzerland | No T | (0-8)<br>Hyposmia ≤6<br>Normosmia 7-8 | A total of 8 diskettes that must be opened to release the odor. |
| **3. Objective smell tests: are expensive and usually limited to experimental and research use in specialized centers**. | | | | |

- Olfactory event-related potentials: collection of the electrical activity of external electrodes while presenting the patient with odors.
- Olfactory electrogram: recording the electrical activity of the nasal olfactory epithelium by applying intranasal electrodes.
- Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI): identifies the brain cortical areas that are activated in the presence of an olfactory stimulus.

*Threshold (T), Identification (I), Discrimination (D)

- **Subjective test:** Delanket al. showed that 30-40% of CRS patients with impaired olfactory function rated themselves as unimpaired [21]. Therefore, even subjective tests are useful to evaluate smell and clinical response to therapies, they should not be undertaken in isolation, given its poor accuracy.
- **Psychophysical test** should include 2 or 3 of three components of olfaction:
- **Threshold (T):** is the concentration of an odorant where 50% of the stimuli are detected and 50% remain undetectable to a subject.
- **Identification (I):** the detection of 'something', usually in comparison to a blank, odorless stimulus.
- **Discrimination (D):**describes the non-verbal ability to differentiate between different odors. Odor identification involves both recognition of a stimulus and communication of its correct identity (i.e., the ability to name an odor).

Olfactory threshold preferentially tests peripheral causes of olfactory loss (for example due to CRS), whereas the discrimination and identificationtests preferentially assess central or cognitive causes of olfactory dysfunction.



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Psychophysical tests provide a more reliable assessment of olfactory function than subjective testing. Psychophysical testing requires a cooperative subject who can understand and follow instructions, as well as communicate choices to the clinician/investigator, so they should be reliable and validated for the target population because odor identification tasks are culturally dependent.

Although smell can be assessed by patients themselves, psychophysical assessment is strongly recommended despite the absence of an established minimal clinically important difference (MCID) for any available test [22].

- **Objective smell tests** are expensive and usually limited to **experimental and research** use in specialized centers.

**Quality of life in CRSwNP**

CRSwNPis associated with poor quality of life and comorbid depressive illnesses. Quality of life of these patients can be assessed by different tests:

- **Rhinosinusitis Disability Index (RSDI)** evaluates with 30 questions impact of CRS on quality of life across 3 dimensions (physical, functional, emotional) [23].
- **Sino-Nasal Outcomes Test (SNOT-22)** assesses the impact on quality of life of 22 items affecting subjects with CRS. Measures ranging from 0 (not a problem) to 5 (severe problem). Includes just one item assessing smell loss subjectively [24].

**Biologics approved for treatment of CRSwNP**



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Biologic treatments present an opportunity to address the severe, unresponsive subgroup of individuals with CRSwNP. At present, EMEA and FDA approved the use of dupilumab, omalizumab, and mepolizumab in chronic rhinosinusitis with nasal polyposis (CRSwNP) as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. The EUFOREA consensus concluded that biologics are indicated in patients with bilateral nasal polyps who had undergone sinus surgery in the past and meet 3 of the following criteria: evidence of T2 inflammation, need for systemic corticosteroids (2 or more courses in the last year), significantly impairment of quality of life, significant loss of smell, diagnosis of comorbid asthma [25].

**Dupilumab (Dupixent®)** is a fully human monoclonal antibody binding to the IL-4 α receptor, which inhibits signaling of IL-4 and IL-13, therefore blocking the pathways leading to differentiation of B cells into IgE production, eosinophil activation, mucus secretion, and airway remodeling. Dupilumab is approved for the treatment of severe atopic dermatitis and severe asthma in adults and children. Itwas the first biologic indicated in CRSwNP, approved in 2019. The standard dose is a first dose of 600 mg subcutaneous (sbc) followed by 300 mg sbcevery 2 weeks. Its mechanism of action against IL4/13 lies in the reduction of type 2 inflammation that underlies most NP.

**Omalizumab (Xolair®)** is a recombinant humanized immunoglobulin-G1κ monoclonal antibody that selectively binds to the Cε3 domain of the Fc region of human IgE in blood and interstitial fluid, blocking its action and preventing it from binding to the high-affinity receptor (FcεRI) on the surface of mast cells, basophils, and dendritic cells, thereby interfering with activation. The increased local production of



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IgE in patients with CRSwNP indicates that this drug hold potential. Omalizumab is indicated to treat severe asthma and was approved in 2020 for CRSwNP not controlled with INCS. It is administered sbcat doses varying from 75 to 600 mg every 2-4 weeks based on body weight and total peripheral blood IgE.

**Mepolizumab (Nucala®)** is an IgG1 kappa monoclonal antibody that antagonizes interleukin-5, causing a decrease in airway eosinophils. The standard dose is 100 mg, administered sbc every 4 weeks. It is indicated in severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA) and was approved for uncontrolled CRSwNP in 2021.

**Benralizumab (Fasenra®)** is an afucosylated monoclonal antibody that directly targets the α chain of the IL-5 receptor, inducing an apoptotic effect on eosinophils, resulting in rapid eosinophil depletion. It is indicated in severe eosinophilic uncontrolled asthma. It is administered 30mg sbcevery 4 weeks for the first 3 weeks and maintained with a dose of 30mg sbcevery 8 weeks. It has not approval for CRSwNP.

**Reslizumab (Cinqaero®)**is a monoclonal antibody against human IL5. It is indicated insevereeosinophilic asthma but it is not approved for CRSwNP. It is given as an intravenous infusion once every four weeks, adjusted for weight (100-575mg).



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**Mepolizumab, benralizumab and reslizumab** are **anti IL5** biological treatment.IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment and activation of human eosinophils. Its potential for action on CRSwNP lies in binding to human IL-5, blocking its biological function. Consequently, survival and activity of eosinophils are reduced.

**Table S2a.Quality assessment of randomised controlled trials selected for inclusion according to the CASP system.**

| Study reference | Type of study | Quality level | CASP results | | |
|---|---|---|---|---|---|
| | | | Design | Methods | Outcomes |
| **Dupilumab** | | | | | |
| Bachert, Mannent et al. 2016 | RCT | High | +++ | ++0++ | ++ |
| Bachert, Han et al. 2019 | RCT | Very high | +++ | +++++ | ++ |
| Mullol, Bachert et al. 2022 | Posthoc analysis of SINUS-24 and SINUS-52 phase 3 trials | Very High | +++ | +++++ | ++ |
| Hellings, Peters et al. 2022 | Posthoc analysis of SINUS-24 and SINUS-52 phase 3 trials | Very high | +++ | +++++ | ++ |
| Fujieda, Matsune et al. 2022 | Posthoc analysis of SINUS-52 phase 3 trial | Very high | +++ | +++++ | ++ |
| Trimarchi, Indelicato et al. 2021 | Single case report | | | | |
| **Omalizumab** | | | | | |
| Gevaert, Calus et al. 2013 | RCT | High | +++ | ++0++ | ++ |
| Gevaert, Omachi et al. 2020 | RCT | Very high | +++ | +++++ | ++ |
| Damask, Chen et al. 2022 | Posthoc analysis of POLYP 1 and POLYP 2 phase 3 trials | Very high | +++ | +++++ | ++ |
| Gevaert, Saenz et al. 2022 | OLE from RCT | Medium-High | +++ | +++00 | ++ |
| **Mepolizumab** | | | | | |
| Gevaert, Van Bruaene et al. 2011 | RCT | High | +++ | ++0++ | ++ |
| Bachert, Sousa et al. 2017 | RCT | Very high | +++ | +++++ | ++ |

| | | | | | |
|---|---|---|---|---|---|
| Han, Bachert et al. 2021 | RCT | High | +++ | ++0++ | ++ |
| **Benralizumab** | | | | | |
| Tversky, Lane et al. 2021 | RCT | High | +++ | ++0++ | ++ |
| Takabayashi, Asaka et al. 2021 | RCT | High | +++ | ++0++ | ++ |
| Bachert, Han et al. 2022 | RCT | Very high | +++ | +++++ | ++ |

Quality assessment was performed using CASP checklists for each type of study (https://casp-uk.net/casp-tools-checklists/). Results depicted in the table correspond to questions related to design (questions 1-3), methodology (questions 4-6) and outcomes (questions 7-8) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and "can't tell" is depicted as (0). The increasing number of (+) indicates a greater quality assessment score.
RCT: randomized clinical trial.

**TABLE S2b. Quality assessment of cohort studies selected for inclusion according to the CASP system.**

| Study reference | Type of study | Quality level | CASP results | |
|---|---|---|---|---|
| | | | Validity | Outcomes |
| **Dupilumab** | | | | |
| Napolitano, Maffei et al. 2021 | Observational retrospective study | Medium-High | +++00+ | + |
| van der Lans, Fokkens et al. 2022 | Observational prospective study | Very high | ++++++ | + |
| Nettis, Brussino et al. 2022. | Observational prospective study | Medium-High | +++00+ | + |
| Nettis, Patella et al. 2021 | Observational prospective study | Medium-High | +++00+ | + |
| **Omalizumab** | | | | |
| Ruiz-Hornillos, Rodríguez Jiménez et al. 2020. | Observational prospective study | High | +++0++ | + |
| Tiotiu, Oster et al. 2020 | Observational retrospective study | High | +++0++ | + |
| **Mepolizumab** | | | | |
| Cavaliere, Incorvaia et al. 2019 | Single case report | | | |

| | | | | |
|---|---|---|---|---|
| Kassem, Cohen-Confino et al. 2021 | Observational retrospective study | Medium-low | +++-0+ | + |
| Yilmaz, Türk et. 2020 | Observational retrospective study | High | +++0++ | + |
| **Benralizumab** | | | | |
| Shimizu, Kato et al. 2021 | Single case report | | | |
| Bagnasco, Brussino et al. 2020 | Observational retrospective study | Medium | +++0?+ | + |
| **Multiple bioloigcs** | | | | |
| Meier, Schmid-Grendelmeier et al. 2021 | Observational retrospective study | Medium | +++0?+ | + |
| Tiotiu, Mendez-Brea et al. 2022 | Observational retrospective study | Medium | +++0?+ | + |
| De Corso, Montuori et al. 2022 | Observational retrospective study | Medium | +++0?+ | + |
| Barroso, Valverde-Monge et al. 2022 | Observational retrospective study | Medium | +++0?+ | + |

Quality assessment was performed using CASP checklists for each type of study (https://casp-uk.net/casp-tools-checklists/). Results depicted in the table correspond to questions related to validity (questions 1-6), and outcomes (questions 7) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and "can't tell" is depicted as (0). The increasing number of (+) indicates a greater quality assessment score.

**TABLE S2c. Quality assessment of systematic reviews with meta-analysis selected for inclusion according to the CASP system.**

| Study reference | Type of study | Quality level | CASP results | | |
|---|---|---|---|---|---|
| | | | Design | Methods | Outcomes |
| **Comparison of Different Biologics** | | | | | |
| Cai, Xu et al. 2022 | SR and NMA of 7 RCTs | Very high | ++ | +++ | ++ |
| Wu, Zhang et al. 2022 | SR and NMA of 9 RCTs | Very high | ++ | +++ | ++ |
| Peters, Han et al. 2021 | SR and indirect treatment comparison of 4 RCTs | High | ++ | +-+ | ++ |

| | | | | | |
|---|---|---|---|---|---|
| Wang, Sun et al. 2022 | SR and NMA of 7 RCTs | Very high | ++ | +++ | ++ |
| Oykhman, Paramo et al. 2022 | SR and NMA of 29 RCTs | High | ++ | +-+ | ++ |

Quality assessment was performed using CASP checklists for each type of study (https://casp-uk.net/casp-tools-checklists/). Results depicted in the table correspond to questions related to design (questions 1-2), methodology (questions 3-5) and outcomes (questions 6-7) in the corresponding checklists. Each positive (yes) response in the questionnaire is depicted as (+), negative it is indicated as (-), and "can't tell" is depicted as (0). The increasing number of (+) indicates a greater quality assessment score.
SR=systematic review; NMA=Network meta-analysis; RCTs=randomized clinical trials

**TABLE S3. PRISMA Checklist.**

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Line 1-2 |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | Line 4-63 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | Line 65-241 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Line 243-245 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | Line 421-487 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | Line 249-251 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Line 248-256 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Line 488-494 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Line 488-494 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | Line 492-494 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | .Line 492-494 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Line 155-161 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | Line 488-491 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | Line 155-161 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Line 155-161 |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | Line 497-503 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Line 497-503 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table S3 of Supplementary material |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Table S3 of Supplementary material |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of | |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | bias among contributing studies. | |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Line |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Line 1197-1217 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Line1231-1359 |
| | 23b | Discuss any limitations of the evidence included in the review. | Line 1341-1348 |
| | 23c | Discuss any limitations of the review processes used. | |
| | 23d | Discuss implications of the results for practice, policy, and future research. | Line1221-1229 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Line 420 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | . |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | . |
| Support | 25 | Describe sources of financial or non-financial support for the | Line 1615-1617 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | review, and the role of the funders or sponsors in the review. | |
| Competing interests | 26 | Declare any competing interests of review authors. | Line 1605-1613 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | NOT PUBLICLY |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.doi: 10.1136/bmj.n71For more information, visit:http://www.prisma-statement.org/

## TABLE S4. DETAIL OF THE STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

| Study reference | Design | Intervention (n=sample size) – follow up time (weeks) | Asthma† (%) | N-ERD† (%) | ≥1 FESS† (%) | Blood eosinophil count† (mean-SD) | NPS† (mean-SD) | Years with CRSwNP† (mean-SD) | Basal smell – test† (mean-SD) | Smell outcomes- LS mean difference vs placebo (95% CI); p value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dupilumab – clinical trials** | | | | | | | | | | |
| Bachert, Mannent, et al. 2016 [17] | Randomized, double-blind, placebo-controlled parallel-group | Placebo q2w (n = 30) or dupilumab q2w (n=30) plus mometasone furoate nasal spray– 16w | 63.3 vs 53.3 | 30.0 vs 20.0 | 63.3 vs 53.3 | 0.4 (0.6) vs 0.4 (0.2) | 5.7 (0.9) vs 5.9 (1.0) | 7.6 (6.1) vs 11.5 (8.7) | UPSIT* 12.8 (8.3) vs 15.6 (7.9) | UPSIT* 14.8 (10.9 to 18.7); p<0.001 |
| Bachert, Han, et al. 2019 [18] | Randomised, double-blind, placebo-controlled, parallel-group (SINUS-24) | Placebo q2w (n=133) or dupilumab q2w (n=143)– 24w | 59 vs 57 | 59 vs 63 vs 57 | 74 vs 69 | 0.4 (0.3) vs 0.4 (0.3) | 5.9 (1.3) vs 5.6 (1.2) | 10.7 (8.5) vs 11.4 (9.6) | UPSIT* 14.4 (8.3) vs 14.7 (8.7) LoS** 2.7 (0.5) vs 2.7 (0.6) | UPSIT* 10.6 (8.8 to 12.3); p<0.0001 LoS** –1.1 (–1.3 to –0.9; p<0.0001 |
| | Randomised, double-blind, placebo-controlled, parallel-group (SINUS-52) | Placebo (n=143), dupilumab q2w–q4w (n=145) or dupilumab q2w (n=150)– 52w | 29 vs 32 | 29 vs 28 vs 23 | 58 vs 59 vs 59 | 0.4 (0.4) vs 0.4 (0.3) vs 0.4 (0.4) | 5.9 (1.2) vs 6.3 (1.2) vs 6.1 (1.2) | 10.8 (9.4) vs 10.6 (9.1) vs 11.3 (10.4) | UPSIT* 13.8 (8.3) vs 13.6 (7.6) vs 13.5 (8.2) | UPSIT* 0.5 (8.9 to 12.1); p<0.0001 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | LoS**:2.7 (0.5) vs 2.7 (0.6) vs 2.8 (0.5) | LoS** 0.9 (–1.1 to –0.8); p<0.0001 |
| Mullol, Bachert, et al. 2022 [19] | Posthoc analysis of SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | UPSIT* 10.6 (9.0 to 11.7); p<0.0001 at week 2<br><br>LoS** -0.1 (-0.1 to -0.0); p<0.05) at day 3, and -1.0 (-1.2 to -0.9); p<0.0001 at week 24<br><br>SNOT-22 item "decreased sense of smell/taste": -1.5 (-1.8 to 1.3); p<0.0001 at week 8<br><br>Improvements were unaffected by CRSwNP duration, prior sinonasal surgery, or comorbid asthma and/or N-ERD<br><br>The proportion of patients with anosmia in the dupilumab group declined from 78% at baseline to 45% at week |

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| | | | | | | | | | | 2 and 28% at week 24 (both p< 0.0001). In the placebo group, the proportion of patients who were anosmic was unchanged at week 24 relative to baseline<br><br>Smell outcomes worsened after discontinuation of dupilumab at week 24 in patients in SINUS-24 |
| Hellings, Peters, et al. 2022 [20] | Posthoc analysis of SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | See SINUS-24 and SINUS-52 [18] | UPSIT* 5.5 (4.4 to 6.7); p<0.0001<br>Onset of treatment effect with dupilumab was similar regardless of prior surgery, asthma, N-ERD or allergic rhinitis<br><br>Improvements with dupilumab continued and were sustained to the end of treatment in both studies |
| Fujieda, Matsune, et al 2022 [22] | Posthoc analysis of SINUS-52 [18] that | Non-/mild ECRS vs moderate/ | See SINUS-52 [18] | See SINUS-52 [18] | See SINUS-52 [18] | See SINUS-52 [18] | See SINUS-52 [18] | See SINUS-52 [18] | See SINUS-52 [18] | UPSIT* 8.4 (5.6 to 11.2) in non-/mild |

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| | uses the JESREC algorithm*** [21] to classify patients into non-ECRS, mild ECRS, moderate ECRS, and severe ECRS subgroups [18] | severe ECRS | | | | | | | | ECRS vs 11.7 (9.8 to 13.6) in moderate/ severe ECRS; p=0.0692 at week 24; and 8.3 (5.4 to 11.3) in non-/mild ECRS vs 11.6 (9.7 to 13.5) in moderate/ severe ECRS; p=0.0733 |
| **Dupilumab - real life** | | | | | | | | | | |
| Trimarchi, Indelicato, et al. 2021 [23] | Retrospective, observational, real-life study | A 65-year-old male (n=1) treated with dupilumab– 26w | 100 | N.M. | 7 FESS | N.M. | 5 points | 10 years | UPSIT 9 | UPSIT* of 25 after 26 weeks |
| Napolitano, Maffei, et al. 2021 [24] | Retrospective, observational, real-life study | 19 patients with AD and CRSwNP treated with dupilumab – 24w | 47.4 | N.M. | N.M. | 78.95% with eosinophilia (>500 eosinophils/$mm^3$) | N.M. | N.M. | LoS** mean 1.9 (SD ± 0.8)<br><br>89.47% anosmia (method N.M.) | LoS** 0.8 ± 0.8 at 16w and 0.5 ± 0.6 at 24w |
| van der Lans, Fokkens, et al. 2022 [25] | Prospective, observational, real-life study | 131 patients treated with dupilumab – 48w | N.M. | N.M. | N.M. | N.M. | N.M. | 1.56 (1.74) | Sniffin' Sticks-12 **** 3.6 (2.1)<br>34.7% anosmic<br>51.0% hyposmic<br>14.3% normosmic | Sniffin' Sticks-12**** 7.3 (2.8) at 24w and 8.3 (3.2) at 48w |
| Nettis, Brussin, et al. 2022 [26] | Prospective, observational, real-life study | 82 patients treated with dupilumab– 16w | 62.2 | 22.4 | 82.4 | 5.5 (5.0) | 5.0 (2.0) | 8.8 (2.0) | LoS** 3.0 (1.0)<br><br>Smell VAS 9.0 (2.0) | LoS** 1.0 (2.0); p<0.001<br><br>Smell VAS 2.0 (4.0); p<0.001 |

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| Nettis, Patella, et al. 2021 [27] | Prospective observational, real-life study | 9 patients with AD and CRSwNP treated with dupiluma – 16w | N.M. | N.M. | N.M. | 5.7 (3.4) | 2.8 (1.2) | N.M. | LoS** 1.6 (1.0) | LoS** 0.2 (0.4); p<0.05 |
| **Omalizumab – clinical trials** | | | | | | | | | | |
| Gevaert, Calus, 2013 [28] | A randomized, double-blind, placebo-controlled | Placebo (n=8) or dupilumab (n=16) – 16w | 100 vs 100 | 50 vs 53 | N.M. | 4.7 (3.6-6.3) vs 3.9 (3.1-6.9) | 6 (6-8) vs 6 (4-6) | N.M. | UPSIT* 12 (10-13) vs 12 (10-23) | LoS p=0.004 |
| Gevaert, Omachi, et al. 2020 [29] | Two replicates (identical), phase 3, randomized, multicenter, double-blind, placebo controlled studies (POLYP-1 and POLYP-2) | Placebo or omalizumab and intranasal mometasone-24w<br>POLYP-1: Placebo (n= 66) or omalizumab (n= 72)<br>POLYP-2: Placebo (n=65) or omalizumab (n= 62) | POLYP-1 48.5 vs 58.3<br>POLYP-2 – 60.0 vs 61.3 | POLYP-1 16.7 vs 22.2<br>POLYP-2 32.3 vs 38.7 | POLYP-1 36.4 vs 31.9<br>POLYP-2 23.1 vs 35.5 | POLYP-1 3.5 (3.0) vs 3.3 (2.6)<br><br>POLYP-2 3.5 (1.96) vs 3.1 (1.7) | POLYP-1 6.2 (1.0) vs 6.3 (0.9)<br><br>POLYP-2: 6.4 (0.9) vs 6.1 (0.9) | N.M. | UPSIT* POLYP-1: 13.9 (7.4) vs 12.8 (7.9)<br><br>UPSIT* POLYP-2: 13.1 (7.3) vs 12.8 (7.6)<br><br>LoS** POLYP-1 2.8 (0.4) vs 2.5 (0.8)<br><br>LoS* POLYP-2 2.8 (0.6) vs 2.6 (0.8) | UPSIT* POLYP 1 3.81 (1.38 to 6.24); p=0.024<br><br>UPSIT* POLYP-2: 3.86 (1.57 to -6.15); p=0.0011<br><br>LoS** POLYP-1 -0.33 (-0.60 to -0.06); p=0.0161<br><br>LoS** POLYP-2 -0.45 (-0.73 to -0.16); p=0.0024 |
| Damask, Chen, et al [30] | Post hoc analysis of POLYP-1 and POLYP-2 [29] – subgroup analysis | Subgroups included blood eosinophil count at baseline (>300 or ≤300 cells/µL), previous FESS (yes/no), asthma status (yes/no), and N-ERD (yes/no)-24w | See POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | POLYP-1 and POLYP-2 [29] | UPSIT improvement regardless of blood eosinophil count, previous FESS, asthma, and N-ERD |
| Gevaert, Saenz, et al. 2022 [31] | Open-label extension (OLE) of POLYP-1 and POLYP-2 [29] | "Patients who continued omalizumab" = patients initially randomized to omalizumab in POLYP 1 and 2 | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | See POLYP-1 and POLYP-2 [29] | In patients who switched to omalizumab, improvements in UPSIT scores reached a peak improvement |

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| | | continued to receive omalizumab for 28 additional weeks (from weeks 24 to 52). "Patients who switched treatment"= patients initially randomized to placebo in POLYP 1 and 2 received omalizumab for 28 weeks (from weeks 24 to 52). | | | | | | | | of 3.8 points at 52w<br><br>UPSIT gradually worsened during the OLE treatment-free follow-up period but remained improved by a mean 0.6 and 1.4 points at 76w in patients who switched and continued omalizumab, respectively |
| **Omalizumab – clinical trials** | | | | | | | | | | |
| Ruiz-Hornillos, Rodríguez Jiménez, et al. 2020 [32] | Prospective observational, real-life study | 16 patients with ashtma and CRSwNP – 12 months | 100 | 56.2 | N.M. | N.M. | N.M. | N.M. | RSDI*****: 2.5 (2.0-4.0) - quantified through the median scores obtained in RSDI question number 20 | No significant differences after 12months of treatment in median score in RSDI question number 20 |
| Tiotiu, Oster, et al. 2020 [33] | Retrospective, observational, real-life study | 24 patients with asthma and CRSwNP treated with omalizumab – 6 months | 100 | 37.5 | 75 | 0.91 (0.51) | N.M. | N.M. | Smell VAS 8.50 (1.58) | Smell VAS 5.08 (3.42); p<0.001 |
| **Mepolizumab – clinical trials** | | | | | | | | | | |
| Gevaert, Van Bruaene, et al. 2011 [34] | Randomized, double-blind, placebo-controlled | Placebo (n=10) vs mepolizumab (n=20) – 8w | 33.3 vs 50.5 | 0 vs 25 | N.M. | N.M. | N.M. | 8.4 (1.7) vs 7.9 (1.8) | Smell VAS 2.4 (0.8) vs 2.6 (0.6) | Smell VAS this parameter did not reach statistical significance; p=0.079 |
| Bachert, Sousa, et al. 2017 [35] | Randomized, double-blind, | Placebo (n=51) vs mepolizumab (n=54) – 25w | 75% vs 81% | N.M. | N.M. | 100 vs 100 | 6.31 (0.88) vs 6.28 (0.88) | N.M. | Smell VAS 9.10 (8.4-9.7) | Smell VAS -1.9 (-2.9 to -0.9); p<0.001 |

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| | placebo-controlled trial | | | | | | | | vs 9.0 (8.4-9.7) | |
| Han, Bachert, et al. 2021 [36] | **Randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial (**SYNAPSE) | Placebo (n= **206) vs mepolizumab (n=201)- 52w** | 74 vs 68 | 31 vs 22 | 100 vs 100 | 5.6 (1.4) vs 5.4 (1.2) | 4.0 (0.9) vs 3.90 (0.8) | N.M. | Smell VAS 10.0 (9.6-10.1) vs 10.0 (9.6-10.0) | Smell VAS –0.3 (–0.6 to –0.1); p=0.020) |
| **Mepolizumab – real life** | | | | | | | | | | |
| Cavaliere, Incorvaia. 2019 [37] | Prospective observational, real-life study | 62-year-old female with asthma and CRSwNP– 4 months | 100 | 0 | N.M. | N.M. | ≥ 300 cells/μl | N.M. | N.M. | Recovered her sense of smell (patient assessment) after 4 months |
| Kassem, Cohen-Confino, et al. 2021 [38] | Prospective observational, real-life study | 11 patients with asthma and CRSwNP treated with mepolizumab- 7.4 (±5.5) months | 100 | 45.4 | 72.7 | N.M. | N.M. | N.M. | 10 with anosmia (method N.M.) | 6/10 with anosmia |
| Yilmaz, Türk, et al. 2020 [39] | Prospective observational, real-life study | 16 subjects with asthma and CRSwNP treated with mepolizumab- 24w | 100 | 63 | N.M. | N.M. | 5.6 (5.9) | N.M. | Smell NAS 4.0 (5.1) | Smell NAS 2.4 (4.2); p>0.05 |
| **Benralizumab - clinical trials** | | | | | | | | | | |
| Tversky, Lane, et al. 2021 [40] | Randomized double-blind, placebo-controlled study | Placebo (n=12) vs benralizumab (n=12)– 20w | 100 vs 83 | 67 vs 25 | 100 | 8.4 (5.9) vs 6.9 (4.1) | 6.2 (0.9) vs 5.7 (0.8) | 11.1 (14.4) vs 10.0 (5.1) | UPSIT* 10.7 (4.9) vs 12.2 (4.9) | The benralizumab induced change in UPSIT score compared with placebo was not significant 2.2 (2.2); p=0.530 |
| Takabayashi, Asaka, et al. 2021 [41] | Rndomized, double-blind, placebo-controlled study | Placebo (n=11), a single administration of benralizumab (n=22), or | 90.9 vs 81.8 vs 82.6 | 45.5 vs 27.3 vs 26.1 | 72.7 vs 59.1 vs 65.2 | 5.6 (3.2) vs 7.7 (6.2) vs 6.2 (4.3) | 5.0 (1.6) vs 5.3 (1.4) vs 5.4 (0.9) | N.M. | Smell VAS 8.9 (2.7) vs 8.9 (2.2) vs 7.3 (3.6) | There was no change in smell assessed by VAS at week 24 |

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| | | benralizumab q4w (n=23)– 12w | | | | | | | | |
| Bachert, Han, et al. 2022 [42] | Randomized, double-blind, placebo-controlled study (OSTRO) | Placebo (n=206) vs benralizumab (n=207) – 40w | 67.0 vs 68.6 | 29.1 vs 30.0 | 73.4 vs 72.9 | 4.4 (2.4) vs 4.4 (3.6) | 6.1 (1.1) vs 6.1 (1.1) | N.M. | 84.4 vs 82.6 anosmia (UPSIT score of <18) | LoS showed significant improvement against placebo (p=0.003)<br><br>Changes in sense of smell measured by UPSIT were not appreciably different between treatment groups |
| **Benralizumab – real life** | | | | | | | | | | |
| Shimizu, Kato, et al. 2021 [43] | Prospective observational, real-life study | 52-year-old woman with asthma, eosinophilic otitis media and CRSwNP | 100 | 0 | N.M. | N.M. | N.M. | N.M. | N.M. | Experienced partial improvement in sense of smell following therapy with benralizumab – method is not mentioned |
| Bagnasco, Brussino, et al. 2020 [44] | Prospective observational, real-life study | 34 patients with asthma and CRSwNP – 24w | N.M. | N.M. | N.M. | 6.3 (3.9) | N.M. | N.M. | Subjective patient's perception of anosmia (yes/ no). 76% perceived anosmia | Anosmia disappeared in 31% patients (p=0.0034) |
| **Reslizumab - clinical trials** | | | | | | | | | | |
| Not found | | | | | | | | | | |
| **Reslizumab – real life** | | | | | | | | | | |
| Not found | | | | | | | | | | |
| **Network meta-analysis** | | | | | | | | | | |
| **Study reference** | **RCTs included (number)** | **Drugs compared with placebo** | **Conclusion on smell** | | | | | | | |

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| Peters, Han, et al. 2021 [45] | 3 | Dupilumab and omalizumab | In the intent to treat population, dupilumab had significantly greater improvements from baseline to week 24 vs omalizumab across least squares mean difference [95% confidence interval], LoS score (0.66 [0.90 to 0.42]) and UPSIT (6.70 [4.67 to 8.73]). Improvement in the 22-item sinonasal outcome test was greater in dupilumab versus omalizumab but was not statistically significant |
| Wang, Sun, et al. 2022 [46] | 7 | Benralizumab, mepolizumab, and reslizumab | Benralizumab improved the UPSIT score (2.30; 95% CI: [0.42, 4.18]; p=0.02) but not mepolizumab (1.30; 95% CI: [−2.38, 4.98]; p=0.49). |
| Wu, Zhang, et al. 2022 [47] | 9 | Dupilumab, omalizumab and mepolizumab | Dupilumab had the best efficacy in terms of UPSIT for surface under the cumulative ranking curve (SUCRA value of 1.000), followed by omalizumab (SUCRA 0.500) |
| Oykhman, Paramo, et al. 2022 [48] | 14 | Dupilumab, omalizumab, mepolizumab, benralizumab and aspirin desensitization (ASA-D) | Compared to placebo, as measured by UPSIT, there was moderate to high certainty evidence that dupilumab (10.96 [95% CI 9.75 to 12.17]), omalizumab (3.75 [95% CI 2.14 to 5.35]), mepolizumab (6.13 [95% CI 4.07 to 8.19]), benralizumab (2.95 [95% CI 1.02 to 4.88]), and ASA-D (2.72 [95% CI 21.17 to 6.61]) improve smell. Among biologics and ASA-D, dupilumab likely improves smell compared to omalizumab (7.21 [95% CI 5.20 to 9.23]), mepolizumab (4.83 [95% CI 2.43 to 7.22]), benralizumab (8.01 [95% CI 5.73 to 10.29]), and ASA-D (8.24 [95% CI 4.16 to 12.32]; all moderate certainty). |
| Cai, Xu, et al.2022 [49] | 7 | Dupilumab, omalizumab, mepolizumab and benralizumab | The results indicate that dupilumab is the most effective and safe treatment route for CRSwNP, when compared with omalizumab, mepolizumab, and benralizumab at 24 weeks of the treatment and end of follow-up |

**Comparisons between biologics - real life conditions**

| Study reference | Design | Intervention (n=sample size) – follow up time (weeks) | Asthma† (%) | N-ERD† (%) | ≥1 FESS† (%) | Blood eosinophil count† (mean-SD) | NPS† (mean-SD) | Years with CRSwNP† (mean-SD) | Basal smell – test† (mean-SD) | Smell outcomes- LS mean difference vs placebo (95% CI); p value |
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| Meier, Schmid-Grendelmeier, et al. 2021 [50] | Retrospective, observational, real-life study | 29 patients - omalizumab, mepolizumab, or benralizumab | 96.4 | 60.7 | 36.0 | N.M. | N.M. | N.M. | Smell was evaluated based on medical history and the most recent consultation and was classified into 5 categories: -2 (strong worsening), -1 (slight worsening), 0 (no change), +1 (slight improvement), | Sense of smell improved in 58.8% with mepolizumab, 34% benralizumab, and 26% with omalizumab |

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| | | | | | | | | | and +2 (strong improvement). | |
| Tiotiu, Mendez-Brea, et al. 2023 [51] | Retrospective, observational, real-life study | 72 patients- omalizumab, benralizumab, or mepolizumab | 38 vs 50 vs 11 | 14 vs 13 vs 29 | 62 vs 56 vs 69 | 0.9 (0.4) vs 0.7 (0.4) vs 0.8 (0.5) | 4.8 (1.4) vs 5.5 (1.0) vs 3.8 (1.6) | N.M. | Loss of smell 18 (86) vs 16 (100) vs 33 (94) -method N.M. | The study showed a statistically significant decrease in the subjects with loss of smell before and after all treatments: mepolizumab (18 to 12, p=0.008), benralizumab (16 to 11, p=0.001), and omalizumab (33 to 21, p<0.001) |
| De Corso, Montuori, et al. 2022 [52] | Retrospective, observational, real-life study | 8 patients - dupilumab, omalizumab, mepolizumab and benralizumab | 100 | 12.5 | 100 | N.M. | 5.3 (1.4) | N.M. | Sniffin´ Sticks identification test 5.7 (4.6) | A statistically significant difference with the Sniffin'Sticks identification test-16 (SSIT-16; 0–5 anosmia, 6–11 hyposmia, and 12–16 normosmia) was found (from 5.75 ± 4.62 to 11.13 ± 3.04 after 6 months of treatment) |
| Barroso, Valverde-Monge, et al. 2022 [53] | Retrospective, observational, real-life study | 206 patients- omalizumab, mepolizumab, reslizumab, and benralizumab | 100 | 44.7 | 1 (2-0) | 5.4 (3.7) | 2 (0-4) | N.M. | 14.1% normosmia 33.3% hyposmia | A total or partial improvement in loss of smell was found after |

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| | | | | | | | | | 51.9% anosmia | treatment with all monoclonal antibodies: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups. Partial smell improvement (anosmia to hyposmia) was observed in subjects administered omalizumab (16%), mepolizumab (22%), reslizumab (22%), and benralizumab (17%), with no differences between groups. Total smell improvement was reached in therapy with omalizumab (20%), mepolizumab (14%), reslizumab (14%), and benralizumab |

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| | | | | | | | | | | (22%), also with no inter-group differences. A comparison of total improvement, partial improvement, and no improvement between subjects with high vs low blood eosinophil count (500/µL) showed no statistical differences. The proportion of patients with improved olfaction was similar between the N-ERD (37%) and non-N-ERD (35.7%) groups |

†Placebo vs drug
ASA-D=aspirin desensitization; CI=confidence interval; CRSwNP=chronic rhinosinusitis with nasal polyps; ECRS= eosinophilic chronic rinosinusitis; FESS=functional endoscopy sinus surgery; LoS=loss of smell score; LS=least square; NAS=numerical analogue score (0-10); N-ERD= nonsteroidal antiinflammatory drug (NSAID)-exacerbated respiratory disease (NERD); N.M.=not mentioned; NPS=nasal polyp score; RCTs=randomized clinical trials; SD=standard deviation; VAS=visual analogue score (0-10); w=weeks;

*UPSIT (the University of Pennsylvania Smell Identification Test): scale 0-40; <19=anosmia
*LoS (loss of smell) symptom score recorded daily using an eDiary with a scale of 0 to 3, where 0=no symptom, 1=mild LoS, 2=moderate LoS, and 3=severe LoS
***JESREC (Japanese Epidemiological Survey of Refractory Eosinophilic Rhinosinusitis) algorithm: non-ECRS (<11 points); ECRS (≥11 points)
****Sniffin' Sticks-12: 0–6=anosmia, 7–10=hyposmia, 11–12=normosmia
***** RSDI (Rhinosinusitis Disability Index) - question number 20 is about smell



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