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Research Article

ARIA-EAACI 2024-2025 Guidelines on Intranasal Treatments: Where do Substantiation and Recommendations Still need to Align?

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Abstract

The ARIA-EAACI 2024-2025 Guidelines on intranasal treatments for allergic rhinitis recommend azelastine–fluticasone (AF) over olopatadine-mometasone (OM) for adult patients. This editorial examines whether the available evidence sufficiently supports this preferential recommendation. Particular focus is placed on interpretation of network meta-analysis (NMA) findings, internal consistency of effect estimates, heterogeneity and incoherence within the evidence network, application of the GRADE framework, and incorporation of patient-reported and long-term clinical data.

The NMA underpinning the recommendation reports posterior probabilities of 23% for non-trivial improvement in nasal symptoms and 56% for ocular symptoms and quality-of-life outcomes in favour of AF. These estimates indicate substantial uncertainty and proximity to equipoise rather than convincing superiority. Internal analyses reveal inconsistent direction of effect, with treatment differences frequently crossing zero and sensitivity analyses favouring neutrality or OM. The evidence base further demonstrates substantial heterogeneity ($I^2 > 50\%$) and statistically significant incoherence, limiting confidence in treatment ranking and indirect comparisons.

Despite these limitations, the certainty of evidence was graded as "moderate," a designation that appears difficult to reconcile with established GRADE principles for indirect, heterogeneous, and incoherent evidence. Additional reliance on app-based patient-reported outcomes is constrained by marked sample imbalance and potential selection bias. Furthermore, long-term randomised evidence supporting OM in perennial allergic rhinitis remains underrepresented in the guideline narrative.

Collectively, the current evidence does not substantiate a clear directional preference between AF and OM. Reconsideration of certainty grading and adoption of a conditional, no-preference recommendation may more accurately reflect the available data and support balanced clinical decision-making.

Keywords: Allergic rhinitis; ARIA–EAACI guidelines; Azelastine-fluticasone; Network meta-analysis; Olopatadine-mometasone

The recently published ARIA–EAACI 2024–2025 Guidelines on Intranasal Treatments for Allergic Rhinitis (AR) represent an important effort to synthesise contemporary evidence and guide clinical decision-making in allergic rhinitis [1]. Among the recommendations, the preferential positioning of azelastine-fluticasone (AF) over olopatadine-mometasone (OM) for adult patients with AR requires scrutiny. After careful synthesis of the available evidence, we believe that the data presented do not sufficiently support a clear directional preference between these two intranasal combination therapies.

Interpretation of Network Meta-analysis Probabilities

In the guideline, the preference for AF is largely informed by probabilistic outputs derived from a network meta-analysis (NMA), reporting a 23% probability of non-trivial improvement in nasal symptoms and a 56% probability for ocular symptoms and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) outcomes in favour of AF over OM [2]. These posterior probabilities, however, do not constitute evidence of superiority. A 23% probability necessarily implies a 77% likelihood of no clinically meaningful advantage, while a 56% probability reflects uncertainty and proximity to equipoise rather than a decisive benefit [2]. Importantly, posterior probabilities should not be interpreted as p-values nor as patient-level likelihoods of benefit [3]. On their own, such probabilistic estimates do not justify a directional clinical recommendation. Surface under cumulative ranking (SUCRA) values, if reported, often mislead without credible intervals, further inflating perceived differences (e.g., 56% probability ignoring wide uncertainty) [4].

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Contradictory direction of effect in the NMA

In the NMA internal results of Seasonal Allergic Rhinitis (SAR) trials show that AF-OM mean differences for total nasal symptom score consistently cross zero in primary and sensitivity analyses, indicating no meaningful difference. When high-risk-of-bias trials were excluded, the point estimate favoured OM over AF. Thus, the NMA provides contradictory direction of effect [2]. These probabilistic signals driving the AF preference contrast sharply with direct head-to-head evidence, such as the Patel et al., [5], environmental exposure chamber study demonstrating equivalent OM efficacy. This tension underscores deeper NMA flaws, including.

Substantial Heterogeneity and Incoherence in the NMA

The NMA demonstrates substantial heterogeneity ($I^2 \approx 66\%$), which remains elevated even after excluding high-risk-of-bias studies ($I^2 \approx 58\%$). The included trials span more than three decades and exhibit considerable variation in study design, patient populations, comparators, and baseline characteristics. In addition, statistically significant incoherence ($p < 0.001$) suggests discordance between direct and indirect evidence. Together, these features indicate that the evidence base is too inconsistent to support firm treatment ranking or preferential positioning [2]. Further, meta-regression (e.g., by trial era or population) to explore persistent heterogeneity is not found in the publication [6].

Concerns Regarding the Application of the GRADE Framework

Despite the indirect nature of the comparison, persistent heterogeneity, and significant incoherence, the certainty of evidence supporting the AF preference was graded as "moderate." Established GRADE methodology generally recommends downgrading certainty under such circumstances, often to low or very low quality. GRADE methodology explicitly recommends downgrading 1-2 levels for inconsistency (I^2>50%) and indirectness ("often to low/very low"). Retaining "moderate" certainty without rationale misaligns with these principles, justifying at most a "low" rating and no preference [6-9].

Limitations in App-Based Patient-Reported Data

Patient preference data derived from the MASK-Air application were also cited in support of the recommendation. However, these data are characterised by marked imbalance in sample size (AF n = 2694 vs OM n = 140), plus selection bias toward severe AR cases in MASK-Air, which substantially limits comparative interpretability. Moreover, higher rates of co-medication use among AF users may reflect suboptimal symptom control rather than treatment superiority [10]. Such app-based observational data should therefore be interpreted with caution and should not meaningfully influence certainty ratings or guideline recommendations.

Evidence in Perennial Allergic Rhinitis (PAR)

The guidelines state that insufficient evidence exists to offer a preference in perennial allergic rhinitis (PAR). However, a 52-week randomised, double blind, placebo-controlled trial demonstrated clinically meaningful efficacy and safety of OM in PAR [11]. These findings contribute relevant long-term data and merit explicit acknowledgment within the evidence synthesis, rather than omission.

Conclusion

The preferential recommendation for AF over OM appears to rest primarily on a weak indirect comparison with substantial methodological limitations and without adequate integration of direct clinical evidence. The probability estimates do not demonstrate superiority, and the sensitivity analyses favour neutrality. The guidelines do not clearly explain how a preferential recommendation emerged despite these methodological limitations. We suggest reconsideration of the certainty assessment and revision of the recommendation to a conditional, no-preference statement between AF and OM for adult patients with allergic rhinitis.

Conflict of Interest

The authors declare no conflict of interest in relation to this editorial.

Author's Contribution

All authors contributed to the drafting and writing of this editorial.

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