Ann Med Res

Current issue list available at Ann Med Res

Annals of Medical Research

journal page: annalsmedres.org

Safe analgesic alternatives in patients with NSAID-exacerbated respiratory disease: The role of tramadol and celecoxib

Saltuk Bugra Kaya ,*

İnönü University, Faculty of Medicine, Department of Chest Diseases, Division of Allergy and Clinical Immunology, Malatya, Türkiye

**Corresponding author: saltukbugrakaya@gmail.com (Saltuk Bugra Kaya)*

MAIN POINTS

- Celecoxib and tramadol were well tolerated by all patients with N-ERD.
- Both agents showed significantly lower adverse reaction rates compared with other analgesics.
- Negative skin tests alongside positive aspirin challenges indicate a non–IgE-mediated mechanism.
- Tramadol may be considered a safe alternative analgesic for patients with NSAID hypersensitivity.
- Individualized provocation testing remains essential prior to clinical use.

Cite this article as: Kaya SB. Safe analgesic alternatives in patients with NSAID-exacerbated respiratory disease: The role of tramadol and celecoxib. *Ann Med Res*. 2026;33(3):99–103. doi: 10.5455/annalsmedres.2025.10.332.

ABSTRACT

Aim: This study aimed to determine which analgesic agents can be safely administered to patients with nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD) and to evaluate the safety of tramadol as a potential alternative.

Materials and Methods: A total of 51 patients (34 females, 17 males; mean age 39.5 ± 14.2 years) with a history of NSAID hypersensitivity were retrospectively analyzed. All patients underwent oral drug provocation tests with celecoxib, paracetamol, nimesulide, meloxicam, and tramadol. In patients with a history of hypersensitivity to a single NSAID, negative skin test results were followed by an oral aspirin challenge to confirm N-ERD. Reaction rates among analgesics were compared using Cochran's Q test, followed by Dunn–Bonferroni pairwise analysis. A p-value <0.05 was considered statistically significant.

Results: Eleven patients (21.6%) had hypersensitivity to a single NSAID; all demonstrated negative skin test results but positive aspirin challenge outcomes, indicating a non–IgE-mediated mechanism. Celecoxib and tramadol showed significantly lower reaction rates compared with nimesulide, paracetamol, and meloxicam (p<0.001). More than half of the cohort (52.9%) required moderate- or high-dose inhaled corticosteroids, while 25.5% of patients with severe asthma were receiving biologic therapy.

Conclusion: Celecoxib and tramadol were well tolerated in all patients with N-ERD, suggesting that these agents are safe and effective analgesic alternatives. Individualized evaluation and supervised provocation testing remain essential to ensure safety before clinical use.

Keywords: Celecoxib, Nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, Safe alternative analgesic, Tramadol

Received: Nov 03, 2025 **Accepted:** Dec 03, 2025 **Available Online:** Mar 25, 2026

INTRODUCTION

In susceptible individuals with asthma, chronic rhinitis, or nasal polyposis, the administration of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger upper or lower airway symptoms. These reactions typically present with nasal obstruction, watery rhinorrhea, sneezing, cough, wheezing, dyspnea, or, in severe cases, bronchospasm; systemic manifestations such as urticaria, angioedema, gastrointestinal discomfort, or hypotension may also occur [1,2].

This condition has historically been described using various terms—such as Samter's triad, Widal syndrome, and aspirin-sensitive asthma—but the designation *NSAID-Exacerbated Respiratory Disease (N-ERD)* is now widely accepted in clinical and academic practice [3]. Current guidelines classify NSAID hypersensitivity into four major phenotypes: NSAID-induced cutaneous reactions, NSAID-exacerbated cutaneous disease, NSAID-exacerbated airway disease, and single-agent–induced cutaneous reactions [4,5].

The underlying pathophysiology of N-ERD primarily reflects dysregulated arachidonic acid metabolism rather than IgE-mediated allergy. In most patients, inhibition of cyclooxygenase-1 (COX-1) alters eicosanoid balance and promotes leukotriene-driven airway inflammation, resulting in characteristic respiratory symptoms [6]. In contrast, single-agent reactions may involve drug-specific IgE but are far less common.

Given the clinical burden associated with N-ERD and the high frequency of analgesic requirements in this population,

identifying safe and well-tolerated alternatives to traditional NSAIDs is essential. This study aimed to determine which analgesics can be safely used in patients with N-ERD and to evaluate the safety of tramadol as a potential alternative option.

MATERIALS AND METHODS

Study design and participants

This retrospective study included 51 patients who were evaluated for suspected NSAID hypersensitivity between 2024 and 2025 at the Department of Allergy and Immunology. Eligible participants had a documented history of hypersensitivity to at least one NSAID, whereas individuals with incomplete medical records were excluded. Ethical approval was granted by the İnönü University Medical Ethics Committee (Decision No: 2025/8382, Date: 30 September 2025). All procedures adhered to the Declaration of Helsinki, and written informed consent was obtained from each participant.

Drug provocation protocol

All provocation tests were performed under continuous supervision by an allergist, with full emergency preparedness including access to resuscitation equipment and emergency medications. Baseline assessments—including physical examination, peak expiratory flow (PEF), blood pressure, and heart rate—were obtained prior to each dose. Testing was conducted between 09:00 and 12:00, and patients were monitored until 17:00 if no reaction occurred or until complete recovery in cases of a positive response. Incremental doses were administered at 30-minute intervals.

Patients with a history of hypersensitivity to a single NSAID first underwent skin testing to evaluate possible IgE-mediated mechanisms. If the skin test was negative, an oral aspirin challenge was performed to determine whether the reaction pattern represented true single-drug hypersensitivity or cross-intolerance consistent with N-ERD.

After determining the aspirin challenge outcome, oral provocation tests were conducted with alternative analgesic agents, including celecoxib (a selective COX-2 inhibitor), paracetamol, nimesulide, meloxicam (partial COX-2 inhibitors), and tramadol (a centrally acting opioid analgesic with low dependency potential).

A negative aspirin challenge indicated drug-specific hypersensitivity or limited cross-reactivity, permitting cautious substitution with alternative agents. Conversely, a positive reaction confirmed NSAID-exacerbated respiratory disease (N-ERD) or broad COX-1 cross-intolerance, necessitating strict avoidance of all COX-1 inhibitors. This structured, stepwise protocol enabled individualized risk assessment and evidence-based selection of safe analgesics. The diagnostic and management algorithm for evaluating NSAID hypersensitivity is presented in Figure 1.

Table 1. Demographic and clinical characteristics of the patients (n = 51).

Parameter	Value
Age (years), mean ± SD	39.5 ± 14.2
Female / Male	34 (66.7%) / 17 (33.3%)
Asthma	47 (92.2%)
Chronic rhinosinusitis with nasal polyps	38 (74.5%)
Moderate/high-dose inhaled corticosteroids	27 (52.9%)
Receiving biologic therapy	13 (25.5%)
Hypersensitivity to a single NSAID	11 (21.6%)
Positive aspirin provocation test	51 (100%)

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages, and continuous variables as mean ± standard deviation (SD).

Because each patient underwent multiple analgesic provocation tests, reaction rate comparisons were conducted using Cochran's Q test, which is appropriate for repeated categorical measurements within the same subjects. When Cochran's Q indicated statistical significance, pairwise comparisons were performed using Dunn's post-hoc test with Bonferroni correction.

A post-hoc power analysis was performed using G*Power version 3.1.9.7 based on the observed effect size (Cohen's w = 0.41). Using $\alpha = 0.05$, a confidence level of 0.95, and a sample size of 51, the achieved power ($1-\beta$) was 0.87, indicating sufficient statistical power to detect medium-to-large effect size differences. A p-value < 0.05 was considered statistically significant.

RESULTS

Among the 51 patients included in the study, 17 (33.3%) were male and 34 (66.7%) were female, with a mean age of 39.5 ± 14.2 years. Allergic rhinitis was present in 21 patients (41.1%), chronic urticaria in 17 patients (33.3%), and atopy in 24 patients (47%). Demographic and clinical characteristics are summarized in Table 1.

According to the Global Initiative for Asthma (GINA) classification [7], 27 patients (52.9%) were receiving step 4 or 5 treatment. Thirteen patients (25.5%) met the criteria for severe asthma, and among these, 4 were treated with omalizumab, 4 with mepolizumab, and 5 with benralizumab. Eleven patients (21.6%) reported a reaction to a single NSAID. All single-NSAID reactions showed negative skin test results but positive oral aspirin challenge outcomes, confirming a non–IgE-mediated cross-intolerance pattern. Eight patients required aspirin desensitization due to recurrent nasal polyps.

The most frequently implicated culprit NSAIDs were dexketoprofen (n = 36), diclofenac (n = 22), and ibuprofen (n = 14).

https://doi.org/10.5455/annalsmedres.2025.10.332

Table 2. Drug challenge test results

Drug Tested	Type of Inhibitor	Positive n (%)	Observed Reactions
Celecoxib	Selective COX-2 inhibitor	0 (0%)	None
Tramadol	Non-NSAID analgesic	0 (0%)	None
Nimesulide	Partial COX-2 inhibitor	6 (11.7%)	Dyspnea, urticaria, nasal congestion
Meloxicam	Partial COX-2 inhibitor	4 (7.8%)	Wheezing, urticaria, rhinitis
Paracetamol	Weak COX-1 inhibitor	3 (5.8%)	Dyspnea, rhinitis, urticaria

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug.

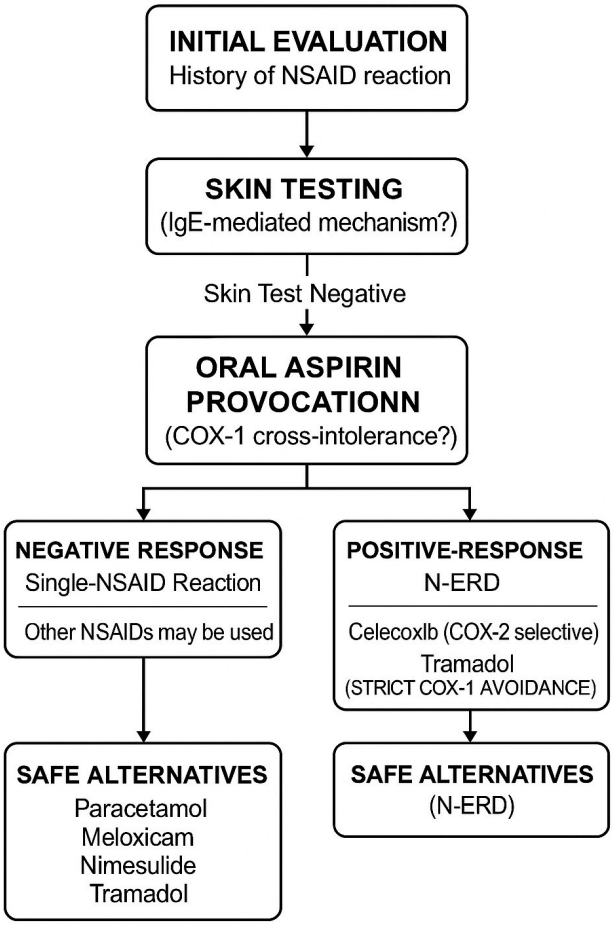

Figure 1. The diagnostic and management algorithm for evaluating NSAID hypersensitivity.

Drug Provocation Outcomes

Celecoxib and tramadol were tolerated by all patients undergoing provocation testing. In contrast, partial COX-2 inhibitors such as nimesulide, meloxicam, and paracetamol elicited significantly higher reaction rates.

Overall comparison of reaction frequencies among tested analgesics using Cochran's Q test demonstrated a significant difference ($p<0.001$). Post-hoc pairwise analyses using the Dunn–Bonferroni method showed that celecoxib and tramadol had significantly lower reaction rates than nimesulide, paracetamol, and meloxicam ($p<0.001$ for all comparisons). The detailed provocation outcomes are presented in Table 2.

DISCUSSION

In this study, all 11 patients who initially reported hypersensitivity to a single NSAID demonstrated negative skin test results but positive aspirin challenge outcomes. This finding suggests that these reactions were not IgE-mediated but instead reflected COX-1–related cross-intolerance [8]. Clinically, this is an important observation: even patients who appear to react to only one NSAID may have underlying NERD, and objective aspirin provocation remains essential for accurate classification [8].

The universal positivity of the aspirin challenge in this subgroup also highlights a major diagnostic pitfall. Without provocation testing, these individuals could be misclassified as "single-drug reactors," potentially leading clinicians to assume a drug-specific IgE mechanism. Our results emphasize that single-NSAID histories should not be equated with true selective allergy and that broad cross-reactivity remains likely unless proven otherwise [8–10]. This has significant implications for analgesic selection and long-term management.

Consistent with current evidence, none of the patients reacted to celecoxib. Selective COX-2 inhibitors are well known for their high tolerability in NERD, and our findings support celecoxib as a reliable and safe analgesic when COX-1 inhibitors must be avoided. The complete absence of reactions in our cohort aligns with previously reported tolerability rates [11–16], reinforcing celecoxib as the preferred first-line alternative.

Tramadol also demonstrated excellent tolerability. Although opioids rarely provoke respiratory reactions in NERD, pseudoallergic responses can occur, particularly with morphine or codeine. A prior study reported codeine reactions in 7.3% of NERD patients [13], underscoring the need for caution when selecting opioid analgesics. The absence of tramadol reactions in our population supports its role as a practical and safe option, especially when non-opioid analgesics are contraindicated or poorly tolerated.

The clinical characteristics of our cohort are consistent with the established NERD phenotype. More than half of the patients required moderate-to-high-dose inhaled corticosteroids, and nearly one-third were receiving biologic therapy, underscoring the heavy disease burden associated with NERD [17–20]. As in previous studies, chronic rhinosinusitis with nasal polyps—a hallmark of NERD—was common and severe, suggesting that patients frequently require inter-

https://doi.org/10.5455/annalsmedres.2025.10.332

ventions that may increase the likelihood of analgesic exposure [21,22].

These findings collectively highlight the real-world challenge of pain management in patients with NERD. Because many analgesics carry a substantial risk of cross-reactivity, safe alternatives must be identified through structured, supervised testing. Our results show that celecoxib and tramadol can reliably serve this purpose.

Limitations

This study has some limitations, including its retrospective design and relatively small sample size. However, the uniform tolerability findings observed for both celecoxib and tramadol provide clinically meaningful guidance for everyday practice. Larger prospective studies incorporating molecular phenotyping could help clarify patient subgroups and further refine individualized analgesic strategies. Overall, our findings add to the growing evidence supporting the safety and practicality of celecoxib and tramadol for patients with NERD confirmed by provocation testing.

CONCLUSION

Celecoxib and tramadol were well tolerated by all patients with NSAID-exacerbated respiratory disease in this cohort, indicating that these agents may serve as safe and practical analgesic options when NSAID avoidance is required. The universal positivity of aspirin challenge among single-NSAID reactors underscores the importance of objective testing to accurately classify hypersensitivity patterns and guide individualized treatment. Although our findings support the use of celecoxib and tramadol in routine clinical practice, supervised drug provocation testing remains essential to confirm tolerability on a patient-specific basis. Larger prospective studies are needed to further validate these observations and refine evidence-based analgesic strategies for this challenging population. These findings support incorporating celecoxib and tramadol into standardized analgesic algorithms for patients with N-ERD.

Ethics Committee Approval: Ethical approval was obtained from the İnönü University Health Sciences Scientific Researchs Ethics Committee (Decision No: 2025/8382, Date: 30 September 2025).

Informed Consent: Written informed consent was obtained from each participant.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The author declares no conflicts of interest.

Financial Disclosure: This research received no external funding.

Artificial Intelligence Disclosure: I would like to clarify that I used ChatGPT (OpenAI, GPT-4 version) only to help improve the English language of the manuscript. It was used for grammar correction and to make some sentences clearer and more fluent. It was not used for designing the study, analyzing data, interpreting results, selecting references, or developing any scientific conclusions. All scientific ideas, clinical interpretations, and the overall content of the manuscript were prepared entirely by me. I carefully reviewed and edited all suggested language changes myself before submission. I take full responsibility for the accuracy, originality, and integrity of the manuscript. I confirm that the use of AI was limited to language editing and is in line with the journal's ethical policies.

REFERENCES

1. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy.* 2013;68(10):1219–32. doi: 10.1111/all.12260.
2. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)—classification, diagnosis and management: review of the EAACI/ENDA and GA2LEN/HANNA. *Allergy.* 2011;66(7):818–29. doi: 10.1111/j.1398-9995.2011.02557.x.
3. Turner JH, Kato A. Understanding inflammatory heterogeneity in NSAID-exacerbated respiratory disease. *J Allergy Clin Immunol Pract.* 2024;12(11):2914–6. doi: 10.1016/j.jaip.2024.07.035.
4. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: a 2022 practice parameter update. *J Allergy Clin Immunol.* 2022;150(6):1333–93. doi: 10.1016/j.jaci.2022.08.028.
5. Aihara M. An update on diagnosis and management of drug allergy. *Arerugi.* 2018;67(10):1399–404. doi: 10.15036/arerugi.67.1399.
6. Jurado-Escobar R, Doña I, Perkins JR, Laguna JJ, Muñoz-Cano R, García-Sánchez A, et al. Polymorphisms in eicosanoid-related biosynthesis enzymes associated with acute urticaria/angioedema induced by nonsteroidal anti-inflammatory drug hypersensitivity. *Br J Dermatol.* 2021;185(4):815–24. doi: 10.1111/bjd.20440.
7. Venkatesan P. 2025 GINA report for asthma. *Lancet Respir Med.* 2025;S2213-2600(25)00242-5. doi: 10.1016/S2213-2600(25)00242-5.
8. Koh YI, Yu JE, Sim DW. Cross-reactive NSAID hypersensitivity: clinical findings from aspirin provocation and alternative drug challenge testing. *Clin Transl Sci.* 2025;18(9):e70335. doi: 10.1111/cts.70335.
9. Doña I, Jurado-Escobar R, Perkins JR, et al. Eicosanoid mediator profiles in different phenotypes of nonsteroidal anti-inflammatory drug-induced urticaria. *Allergy.* 2019;74(6):1135–44. doi: 10.1111/all.13725.
10. Saff RR, Banerji A. Management of patients with non-aspirin-exacerbated respiratory disease aspirin hypersensitivity reactions. *Allergy Asthma Proc.* 2015;36(1):34–9. doi: 10.2500/aap.2015.36.3800.
11. Cakmak ME. The safety of celecoxib in cutaneous hypersensitivity reactions with nonsteroidal anti-inflammatory drugs: a single-center care experience. *Alergol Pol.* 2022;9(4):250–5. doi: 10.5114/pja.2022.122005.
12. Cakmak ME. Which non-steroidal anti-inflammatory drug (NSAID) is safer in patients with non-steroid-exacerbated respiratory disease (N-ERD)? A single-center retrospective study. *Tuberk Toraks.* 2022;70(4):365–74. doi: 10.5578/tt.20229608.
13. Palmer GM. A teenager with severe asthma exacerbation following ibuprofen. *Anaesth Intensive Care.* 2005;33(2):261–5. doi: 10.1177/0310057X0503300218.
14. Celebioglu E, Karakaya G, Kalyoncu AF. The safety of codeine in patients with non-steroidal anti-inflammatory drug hypersensitivity: a preliminary study. *Allergol Immunopathol (Madr).* 2013;41(3):163–8. doi: 10.1016/j.aller.2012.04.010.

https://doi.org/10.5455/annalsmedres.2025.10.332

15. Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase-2 selective analgesic drug celecoxib. *J Allergy Clin Immunol.* 2003;111(5):1116–21. doi: 10.1067/mai.2003.1450.
16. Celik GE, Erkekol FO, Aydın O, Demirel YS, Misirligil Z. Are drug provocation tests still necessary to test the safety of COX-2 inhibitors in patients with cross-reactive NSAID hypersensitivity? *Allergol Immunopathol (Madr).* 2013;41(3):181–8. doi: 10.1016/j.aller.2012.03.006.
17. Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, et al. Near-fatal asthma phenotype in the ENFUMOSA cohort. *Clin Exp Allergy.* 2007;37(4):552–7. doi: 10.1111/j.1365-2222.2007.02683.x.
18. Bourdin A, Molinari N, Vachier I, Varrin M, Marin G, Gamez AS, et al. Prognostic value of cluster analysis of severe asthma phenotypes. *J Allergy Clin Immunol.* 2014;134(5):1043–50. doi: 10.1016/j.jaci.2014.04.038.
19. Makowska JS, Burney P, Jarvis D, Keil T, Tomassen P, Bislimovska J, et al. Respiratory hypersensitivity reactions to NSAIDs in Europe: the Global Allergy and Asthma Network (GA2LEN) survey. *Allergy.* 2016;71(11):1603–11. doi: 10.1111/all.12941.
20. Lee HY, Ye YM, Kim SH, Ban GY, Kim SC, Kim JH, Shin YS, Park HS. Identification of phenotypic clusters of nonsteroidal anti-inflammatory drug-exacerbated respiratory disease. *Allergy.* 2017;72(4):616–26. doi: 10.1111/all.13075.
21. Castillo JA, Plaza V, Rodrigo G, et al. Chronic rhinosinusitis with nasal polyps and allergic rhinitis as different multimorbid treatable traits in asthma. *J Allergy Clin Immunol Glob.* 2023;2(4):100134. doi: 10.1016/j.jacig.2023.100134.
22. Stevens WW, Peters AT, Hirsch AG, et al. Clinical characteristics of patients with chronic rhinosinusitis with nasal polyps, asthma, and aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol Pract.* 2017;5(4):1061–70.e3. doi: 10.1016/j.jaip.2016.12.027.

https://doi.org/10.5455/annalsmedres.2025.10.332