European Journal of Clinical and Experimental Medicine

ONLINE FIRST

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Article type: Review

Received: 1 July 2025

Accepted: 9 November 2025

Published online: 12 January 2026

eISSN: 2544-1361

Eur J Clin Exp Med

doi:10.15584/ejcem.2026.1.19

Ocular and systemic adverse effects of topical non-steroidal anti-inflammatory drugs – a narrative review with quantitative synthesis

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ABSTRACT

Introduction and aim. The impacts of topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs) have been studied, with instances of an unprecedented quantitative assessment of adverse drug reaction prevalence among several NSAID classes. This study aimed to systematically observe and synthesize the relevant information on the pharmacodynamic mechanism of adverse drug reactions (ADR) corresponding to topical NSAID administration.

Material and methods. A preliminary search on PubMed Central, Google Scholar, and ScienceDirect databases yielded 83 articles.

Analysis of literature. Conditions such as corneal perforation, ulceration, infiltration, keratitis, melt, corneal issues involving epithelial defects, tissue loss, stromal thinning, and delayed wound healing accentuate a comprehensive range of consequences on corneal integrity and physiology. The topical NSAID group also conveys more diversified systemic adverse reactions involving dilated ventricle, tricuspid regurgitation, pulmonary insufficiency, closure of the ductus arteriosus, and prenatal ductal constriction, which constitute a concern for their impact on cardiac activity and developing embryos.

Conclusion. Burning sensation is reported to be the most commonly reported frequency after photophobia. Notably, preferential COX-2 inhibitors had a significantly greater prevalence of ADRs than both nonselective COX inhibitors (mean difference=1.05, p=0.023) and selective COX-2 inhibitors. Longitudinal studies with frequent follow-ups are essential to fully characterize the incidence, severity, and long-term effects of adverse consequences.

Keywords. adverse drug reactions, anti-inflammatory medications, ocular drug delivery, ocular pharmacokinetics, topical ophthalmic non-steroidal anti-inflammatory drugs

Introduction

One of the cornerstones of healthcare is the administration of drugs. Adverse drug reactions are a frequent cause of practitioner-related litigation in ophthalmology. Owing to potentially devastating triggers, drug oversight can be expensive to prosecute, compensate, and/or resolve.[1,2] Regularly recommended drugs may have detrimental impacts on the eyes, about distinct parts of the eyes. Monitoring toxicity, limiting dosage, attempting to alternate therapies, and divulging negative effects are all ways to lessen the risk.[3-5]

Adverse drug reactions (ADR) are deleterious, unintended, but preventable, as briefed by the WHO. Reporting ADR, with qualitative information, eventually improves medication safety across the globe and can impact prompt protocols that promote patients' safety.[6] The majority of the most prevalent sources of adverse medication effects associated with the sequel of ocular complications are NSAIDs (approximately 25% of all adverse drug events).[7-9] Considerable adverse effects relating to the eyes may result from their application, necessitating close observation in clinical contexts.[10] Eyelids, conjunctiva, and cornea are often impacted by exposure to drugs, which may culminate in inflammation and hypersensitivity responses.[11-14] Patients with crippled corneas as an aftermath of surgical procedure, diabetes, or autoimmune disorders are at increased risk for NSAID-induced corneal melt (NICM), which initially raised concerns but has now been validated. The precise repetition in the form of dose and duration of NSAIDs is yet uncertain, and possibly had a profound effect on the occurrence of adverse effects.[15] The current evidences does not provide a definitive, class-specific comparison of the occurrence of adverse medication reactions associated with NSAIDs. A comprehensive narrative evaluation is required to synthesize fragmented material and elucidate these risk disparities among principal NSAID classes.

Aim

The aim of this narrative review was to synthesize current evidence on ocular and systemic adverse reactions to topical ophthalmic NSAIDs and to provide a quantitative overview of the prevalence of these adverse effects, including comparative analysis across non-selective, selective, and preferential COX-2 inhibitors.

Material and methods

We focused our search exclusively on peer-reviewed publications, and employed a strategic construction to uncover information about the adverse effects of NSAIDs on the eyes, concentrated on keywords and Medical Subject Headings (MeSH) corresponding to "Administration, topical", "Anti-inflammatory agents, non-steroidal/adverse effects", "Anti-inflammatory agents, Non-steroidal/therapeutic use", "Cornea/drug effects", "Cyclooxygenase 2", "Cyclooxygenase 2 inhibitors", "Cyclooxygenase inhibitors/pharmacology", "Diclofenac/adverse effects", "Drug Hypersensitivity/diagnosis", "Drug

hypersensitivity/etiology", "Drug hypersensitivity/therapy", "Drug-related side effects and adverse reactions", "Eye", "Hypersensitivity/complications", "Ketorolac tromethamine", "Ophthalmic solutions", "Ophthalmic solutions/administration & dosage", "Ophthalmic solutions/therapeutic use". A preliminary search on PubMed Central, Google Scholar, and the ScienceDirect database yielded 347 text articles. Studies with clear outcome data, such as clinical trials, cohort, and case-control studies, that reported adverse reactions to topical NSAID use in human subjects met the inclusion criteria. Animal research, conference papers, and studies with insufficient or imprecise adverse event data were not included. In the initial phase, articles were initially eliminated due to retracted publications, unclear reporting of the specific treatment regimen, incorrect outcome measures, inappropriate interventions, and publications that were not retrieved (Fig. 1).[16] The reporting frequency with which each ADR is documented in the literature is the sole factor used to calculate Reporting frequency (%), whereas frequency of reporting in publications (%) shows the percentage of included studies that documented the particular adverse drug reaction. All interval estimates are now explicitly labeled as "95% CI" for clarity. The ADR ranking, utilizing reporting frequency and publication-based reporting frequency, serves as a preliminary measure for individualized drug-risk assessment and may yield clinically and financially significant insights.

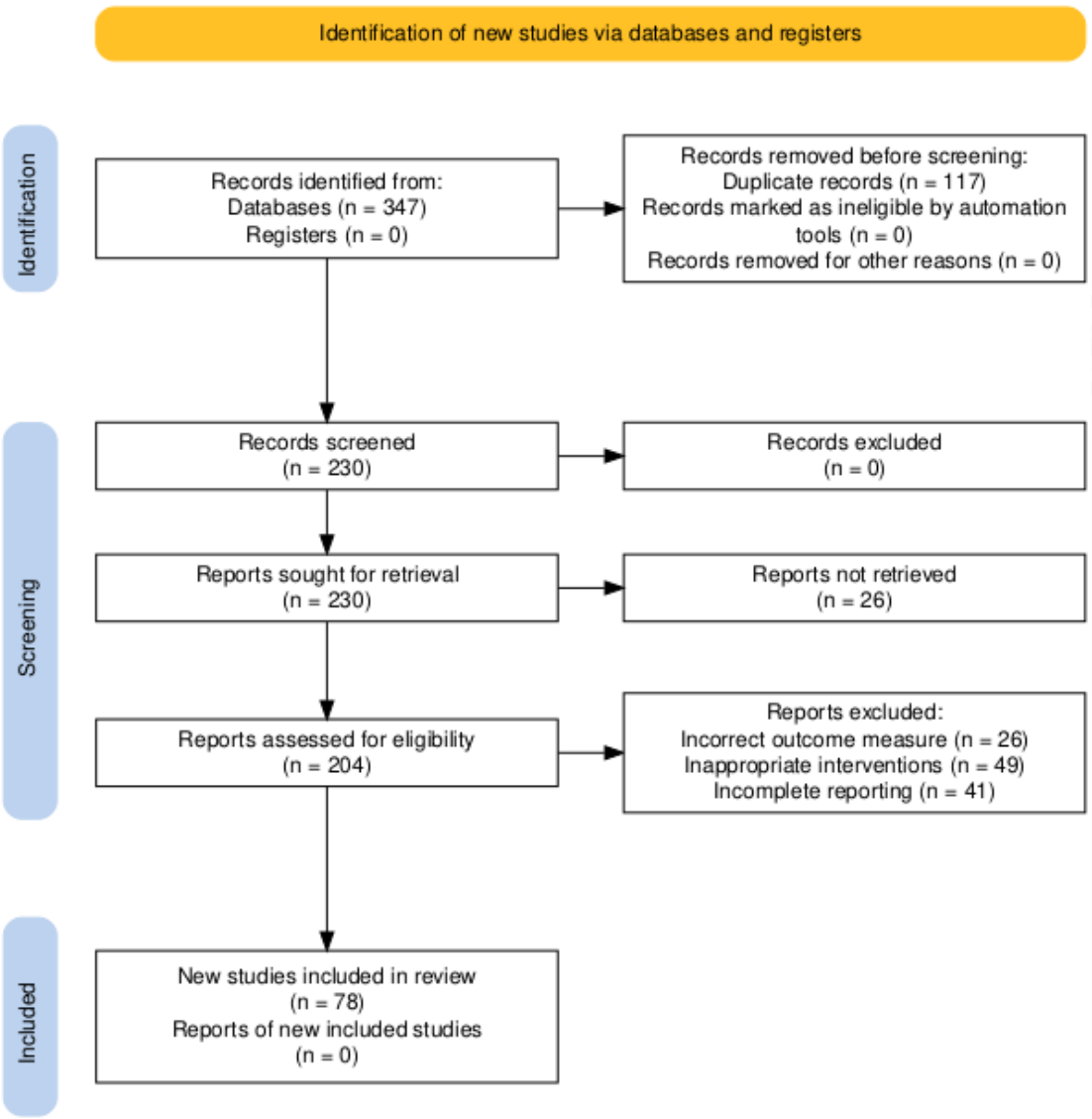

Fig 1. The literature selection processing[16]

All literature that has been identified has been reviewed by two authors who worked separately on data abstraction. Since publications conducted between 2000 and 2025 had precedence in the review, a few convincing fundamental studies before 2000 were solicited to establish the suitability of each identified literature for our analysis.

Analysis of the literature

Comprehensive description of adverse effects

Reported adverse effects

Multiple studies have established an elevated prevalence of various adverse effects corresponding to the use of topical NSAIDs (Table 1).

Table 1. The tabulation of reported adverse effects[17-50]

Adverse effects/sign	Reporting frequency (%)	Frequency of reporting in publications (%)
Corneal perforation	16.81	28.12
Corneal ulcer	5.31	6.25
Corneal infiltration	4.42	9.37
Declined corneal sensation	12.39	31.25
Keratitis	4.42	6.25
Tissue loss	4.42	6.25
Epithelial defect	6.19	12.50
Corneal melt	7.08	12.50
Descemetocele	6.19	9.37
Epithelial wound	0.88	3.12
Superficial punctate	0.88	3.12
Delayed corneal wound healing	0.88	3.12
Stromal thinning	0.88	3.12
Reduced corneal responsiveness	2.65	3.12
Lower Schirmer value	1.77	3.12
Scleral melt	1.77	3.12
Hyperemia	3.54	9.37
Conjunctival injection	0.88	3.12
Edematous swelling of the eyelids	0.88	3.12
Periorbital dermatitis	0.88	3.12
Iritis	0.88	3.12
Eye pruritus	1.77	6.25
Posterior capsule opacification	0.88	3.12
Iris prolapse	0.88	3.12
Neurotrophic keratopathy	0.88	3.12
Shrunken eye	0.88	3.12
Low concentration of breast milk	2.65	3.12
Dilated ventricle	0.88	3.12
Tricuspid regurgitation	0.88	3.12

Pulmonary insufficiency	16.81	28.12
Closure of the ductus arteriosus	5.31	6.25
Prenatal ductal constriction	4.42	9.37
Asthma	12.39	31.25

The cornea seems highly exposed, demonstrating conditions such as corneal perforation, ulceration, infiltration, keratitis, and melt, all indicative of severe damage to the transparent outermost layer of the eye. In addition to the comprehensive adverse ocular effects, Cardiovascular issues are significant, involving dilated ventricle, tricuspid regurgitation, pulmonary insufficiency, closure of the ductus arteriosus, and prenatal ductal constriction, which constitute a concern for their impact on cardiac activity and developing embryos.

Spearman correlation between frequency of reporting in publications and reporting frequency of adverse effects in included studies

Table 2. Correlations between frequency of reporting in publications and reporting frequency of adverse effects[a]

			Frequency of reporting in publications (%)	**Reporting frequency (%)**
Spearman's rho	Frequency of reporting in publications (%)	Correlation coefficient	1.00	0.89**
		Sig. (2-tailed)	.	<0.001
		n	33	33
	Reporting frequency (%)	Correlation coefficient	0.89**	1.00
		Sig. (2-tailed)	<0.001	.
		n	33	33

[a] ** – correlation is significant at the 0.01 level (2-tailed)

The Spearman's correlation analysis demonstrated a strong positive association between study frequency and prevalence, with a correlation value (ρ) of 0.891, as the data were non-normally distributed and ordinal in nature, and that standard tie-handling procedures inherent to the Spearman method. This indicates that the prevalence is likely to increase in accordance with study frequency. At the value of 0.01, the association is statistically significant ($p<0.001$, two-tailed), signifying that this association would not have emerged by default (Table 2).

Ranking

Table 3. Ranks assigned to each data point based on the frequency of reporting in publications and reporting frequency of adverse effects

Adverse effects/sign	Rank of reporting frequency	Rank of the frequency of reporting in publications
Corneal perforation	33.00	32.00
Corneal ulcer	28.00	23.50
Corneal infiltration	26.00	27.00
Declined corneal sensation	32.00	33.00
Keratitis	26.00	23.50
Tissue loss	26.00	23.50
Epithelial defect	29.50	30.00
Corneal melt	31.00	30.00
Descemetocele	29.50	27.00
Epithelial wound	9.00	11.00
Superficial punctate	9.00	11.00
Delayed corneal wound healing	9.000	11.00
Stromal thinning	9.00	11.00
Reduced corneal responsiveness	21.50	11.00
Lower Schirmer value	19.00	11.00
Scleral melt	19.00	11.00
Hyperemia	23.50	27.00
Conjunctival injection	9.00	11.00
Edematous swelling of the eyelids	9.00	11.00
Periorbital dermatitis	9.00	11.00
Iritis	9.00	11.00
Eye pruritus	19.00	23.50
Posterior capsule opacification	9.00	11.00
Iris prolapse	9.00	11.00
Neurotrophic keratopathy	9.00	11.00
Shrunken eye	9.00	11.00
Low concentration of breast milk	21.50	11.00

Dilated ventricle	9.00	11.00
Tricuspid regurgitation	9.00	11.00
Pulmonary insufficiency	9.00	11.00
Closure of the ductus arteriosus	9.00	11.00
Prenatal ductal constriction	9.00	11.00
Asthma	23.50	30.00

In Spearman's correlation, raw numbers are modified into ranks to appraise the magnitude and direction of an exponential equation between two variables. Substantially higher rank (e.g., 33.00, 32.00, 30.00) indicate studies with relatively greater frequencies, while lower rank values (e.g., 11.00) correspond to studies with smaller frequencies. Recurring ranks like 11.00 and 23.50 suggest identical ranks, implying that several studies shared equal frequency (Table 3).

Reported symptoms

Multiple investigations have established an elevated incidence of symptoms corresponding to the use of topical NSAIDs.

Table 4. The tabulation of symptoms reported in publications[17,18,20,22,25,40,41]

Symptoms	**Reporting frequency (%)**	**Frequency of reporting in publications (%)**	**Rank of reporting frequency**	**Rank of frequency of reporting in publications**
Pain	13.04	9.37	3.50	3.50
Photophobia	21.73	15.60	5.00	5.50
Burning sensation	34.78	15.60	6.00	5.50
Stinging	13.04	9.37	3.50	3.50
Eye irritation	8.69	6.25	1.50	1.50
Partial vision loss	8.69	6.25	1.50	1.50

In reported adverse eye symptoms, burning sensation is implied to be the most prevalent, impacting 34.78% of individuals. Subsequently, photophobia remains a profound concern for 21.73% of those affected. Both pain and stinging are specified by 13.04% of individuals, exhibiting a considerable amount of difficulty (Table 4). Burning sensation and photophobia arise as the most frequent symptoms (ranked 6.0 and 5.0, respectively) and also scored strongly concerning frequency (5.5 for both), indicating that these are the

frequently occurring and described symptoms within participants, feasibly expressive of underlying ocular surface disorder or digital eye strain (Table 4).

Correlations

Table 5. Correlations between the frequency of reporting in publications and reporting frequency of reported symptoms[a]

			Frequency of reporting in publications	**Reporting frequency**
Spearman's rho	Frequency of reporting in publications	Correlation Coefficient	1.00	0.98**
		Sig. (2-tailed)	.	<0.001
		N	6	6
	Reporting frequency	Correlation Coefficient	0.98**	1.00
		Sig. (2-tailed)	<0.001	.
		N	6	6

[a] ** – correlation is significant at the 0.01 level (2-tailed)

A Spearman's rank correlation analysis portrayed a statistically significant (ρ=0.985, $p<0.001$) observation, proposing a compatible trend in the literature where reported symptoms also emerge to be more extensive amidst the population exposed to the drug (Table 5).

Pharmacodynamic basis of adverse effects

Post hoc tests

Table 6. Multiple comparisons (Tukey HSD) with the specific NSAID group differences[a]

Dependent variable: prevalence						
Tukey HSD						
		Mean difference			**95% Confidence interval**	
(I) Drug group	**(J) Drug group**	**(I-J)**	**Std. Error**	**Sig.**	**Lower bound**	**Upper bound**
Nonselective COX inhibitors	Preferential COX-2 inhibitors	-1.046*	.39	.023	-1.97	-0.12

	Selective COX-2 inhibitors	0.35	0.39	0.64	-0.58	1.28
Preferential COX-2 inhibitors	Nonselective COX inhibitors	1.04*	0.39	0.02	0.12	1.97
	Selective COX-2 inhibitors	1.39*	0.39	0.002	.47	2.32
Selective COX-2 inhibitors	Nonselective COX inhibitors	-0.35	0.39	0.64	-1.28	0.58
	Preferential COX-2 inhibitors	-1.39*	0.39	0.002	-2.32	-0.47

[a] based on observed means, the error term is mean square (error)=2.510, * – the mean difference is significant at the 0.05 level

Preferential COX-2 inhibitors exhibit a considerably greater frequency than Non-selective COX inhibitors and selective COX-2 inhibitors. Notably, preferential COX-2 inhibitors expressed a significantly greater prevalence of ADRs compared to both nonselective COX inhibitors (mean difference=1.05, p=0.023) and selective COX-2 inhibitors (mean difference=1.39, p=0.002) (Table 6).

Discussion

The reporting frequency of adverse effects identified encompasses a multitude of ocular and systemic consequences, with variable ranges observed through various studies. A greater quantity of research corresponds to a higher predominance of corneal complications such as corneal perforation (rank 33), decreased corneal sensation (rank 32), epithelial defects, and corneal melt (both rank 30). Inflammatory conditions like corneal infiltration (rank 27), keratitis, tissue loss, and eye pruritus (all rank 23.5) additionally display with significant frequency. Conversely, an assortment of less frequently reported adverse effects (all rank 11) consists epithelial wound, superficial punctate keratitis, delayed corneal wound healing, stromal thinning, reduced corneal responsiveness, lower Schirmer values, scleral melt, conjunctival injection, edematous swelling of the eyelids, periorbital dermatitis, iritis, posterior capsule opacification, iris prolapse, neurotrophic keratopathy, and shrunken eye. Remarkably, systemic observations were also incorporated in the assessment, like low concentration of breast milk, dilated ventricle, tricuspid regurgitation, pulmonary insufficiency, closure of the ductus arteriosus, prenatal ductal constriction (all rank 11), and asthma (rank 30), reflecting an expanded spectrum of feasible adverse outcomes taken into consideration in the study. The substantial positive association indicates that a greater frequency of findings is related to a higher probability of identifying and documenting these adverse consequences, particularly the more significant ocular issues. Preferential COX-2 inhibitors, particularly for topical applications, may

be a "gift and a burden" in clinical administration, considering the realization that they are often conceived of as exhibiting significantly severe adverse effects as opposed to non-selective NSAIDs.

NSAIDs are progressively being formulated for topical ophthalmic administration, driven by compelling scientific evidence recommending their therapeutic potential in ophthalmic pathologies like diabetic retinopathy, age-related macular degeneration, and other ocular tumors.[51-55] Their mechanism of action essentially is based on the dominant inhibition of cyclooxygenase (COX) enzymes, crucial catalysts in the biosynthesis of eicosanoids, including prostaglandins (PGs) and thromboxanes, obtained from arachidonic acid.[52,56-58] Encased in the ocular province, PGs devote substantially to inflammatory activities by stimulating vasodilation, yielding the blood-ocular barrier, and promoting leukocyte migration.[59-63] NSAIDs' efficacy stems from their capability to conquer these pernicious PG-mediated consequences.[64] The pharmacokinetic portrait of NSAIDs, regardless of their division (salicylates, indole acetic acid derivatives, aryl acetic acid derivatives, aryl propionic acid derivatives, enolic acid derivatives, and fenamates), effectively implies admirable gastrointestinal absorption, triggering peak serum concentration within 1 to 3 hours.[64-65] An important property is their extensive plasma protein binding, ordinarily immense 95%, particularly to albumin, which restricts their capacity for distribution to plasma. This systemic absorption, even considering topically administered NSAIDs via mucosal surfaces of the nasolacrimal outflow network, enhances the significance of conceiving systemic resonances.[66-71] Nevertheless, innovative topical approaches like 0.1% nepafenac and 0.09% bromfenac illustrate ameliorated retinal probing and efficacy in impeding retinal prostaglandin formation.[65] This reinforces the continuing expansion of preparation with intensified pharmacokinetics to optimize therapeutic advantages in posterior segment pathologies. Pharmacodynamically, NSAIDs comprehensively restrain COX enzymes, hence alleviating the overactive secretion of endogenous PGs (e.g., PGE2, PGD2, PGF2a, PGI2), which are involved in miosis, vasodilation, blood-ocular barrier breakdown, leukocyte movement, and pain sensitivity within the eye. This article also demonstrates the way topical NSAIDs permeate the vitreous, particularly their increasing application for the therapy of retinal diseases.[65,72-75] The findings of this study readily demonstrate that, in contrast to simultaneous application of non-selective and selective COX-2 inhibitors, they are associated with a higher occurrence of adverse treatment outcomes. The following intricate pharmacological pattern may be a possible explanation for the observed hypersensitivity and higher frequency of complications, despite topical therapy.[64,76] Despite preferential COX-2 inhibitors concentrating on the stimulated COX-2 enzyme in inflammatory regions, a certain level of COX-1 inhibition is assumed, considering their "preferential" instead of "selective" trait.[64,78] The sensitive physiological equilibrium that COX-1 sustains may still be disrupted by this partial inhibition of intrinsically obtained COX-1, through systemic absorption employing topical application. More specifically, a disruption in the delicate balance within the production of pro-thrombotic thromboxane

(primarily COX-1 facilitated) and anti-thrombotic prostacyclin (primarily COX-2 transmitted) may trigger the identified higher ADR frequency.

Study limitations

Although the topic has been extensively reviewed, the nonexistence of subgroup analyses reveals an important research space, particularly when it comes to different age groups or population-focused data that can advance clinical application with potentially different reactions and adverse consequences, and also, the majority of the included studies did not disclose comprehensive information on NSAID dosage. To have a more thorough grasp of the effects of NSAIDs, future studies should investigate dose-dependent and population-specific effects.

Conclusion

The diversified behavior and different intensity of the documented adverse effects underline the critical importance of proactive approaches to lessen ADRs in clinical activities. A comprehensive outlook to risk evaluation, attentively monitoring individual patient factors such as age, comorbidities, polypharmacy, and genetic predispositions, may increase their susceptibility to ADRs. Continuous medication reconciliation, comprising over-the-counter drugs and supplements, is appropriate to evaluate probable drug interactions. Administering the lowest effective concentration and dose for the shortest span of time is a promising option to mitigate the complications. Constant observation and follow-up for early signs and symptoms of ADRs, coupled with patient education on potential adverse events, are important. As an instance, whenever reduced corneal responsiveness or lower Schirmer values are stated, close monitoring for corneal health is justified. Equivalently, comprehending the potential for systemic effects like pulmonary insufficiency or changes in neonatal circulation necessitates prudent consideration when prescribing medications to pregnant women or breastfeeding mothers. The evidence revealed indicates that in order to effectively reduce ADRs, subsequent studies must concentrate on prolonged safety profiles and tailored individualized therapy. Longitudinal studies with frequent follow-ups are essential to completely constitute the incidence, severity, and long-term effects of the reported adverse effects, particularly the less frequent but potentially harmful ones, such as neurotrophic keratopathy or the impact on the health of the infant, even though the current analysis shows associations.

Acknowledgments

We express our heartfelt gratitude to all our supporters and well-wishers for their invaluable counsel and encouragement throughout the preparation of this evaluation.

Declarations

Funding

This study did not receive any grant and/or funding.

Author contributions

Conceptualization, S.S and M.D.; Methodology, S.S.; Software, S.S.; Validation, S.S., and M.D.; Formal Analysis, M.D.; Investigation, S.S.; Resources, M.D.; Data Curation, M.D.; Writing – Original Draft Preparation, S.S.; Writing – Review & Editing, M.D.; Visualization, M.D.; Supervision, M.D.; Project Administration, S.S.; Funding Acquisition, M.D.

Conflicts of interest

The authors declare no competing interests.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This article reviews existing research and does not include any investigations involving human volunteers or animals done by the authors. Consequently, ethical approval and informed consent were not required for this study.

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