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Commentary

Gabapentin for Ocular Surface Disorders: Bridging Molecular Mechanisms to Therapeutic Innovation

Caterina Gagliano[1,2,3,*], Alessandro Avitabile[3,4], Dario Rusciano[5,*,†]

[1]Department of Medicine and Surgery, University of Enna "Kore", Piazza dell'Università, 94100 Enna, Italy

[2]Mediterranean Foundation "G.B. Morgagni", 95125 Catania, Italy

[3]Neurovisual Science Technology (NEST) srl, 95123 Catania, Italy

[4]University of Catania Faculty of Medicine Eye Clinic, Italy

[5]Fidia Ophthalmic Research, 95123 Catania, Italy

[†]Retired

[*]Correspondence should be addressed to Caterina Gagliano, caterina.gagliano@unikore.it; Dario Rusciano, drusciano55@gmail.com

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Abstract

This commentary critically evaluates Rusciano's (2024) comprehensive review on gabapentin (GBP) as a multifaceted therapy for ocular surface diseases, emphasizing its transition from systemic to topical applications. We highlight the review's synthesis of GBP's polypharmacology—spanning calcium channel modulation, anti-inflammatory effects, and neuroprotection—and its innovative integration with nanotechnology (e.g., nanoceria platforms) to overcome corneal delivery challenges while potentially reducing systemic side effects associated with oral administration. While applauding its mechanistic depth and translational vision, we identify key gaps: the pressing need for rigorous evaluation of long-term topical safety, the imperative for clinical trials to validate novel formulations, and unresolved questions about GBP's comparative efficacy versus biologics (e.g., neurotrophic factors) and pregabalin. Positioned within a competitive landscape of emerging ocular therapies, Rusciano's work serves as both a milestone in GBP research and a catalyst for future studies to optimize its role in personalized ophthalmic therapeutics, contingent upon robust clinical and safety data for topical use.

Keywords: Gabapentin, Ocular surface diseases, Neuropathic ocular pain, Topical drug delivery, Nanoceria formulations, Dry eye disease, Corneal nerve regeneration, Mechanistic pharmacology

Introduction

Gabapentin (GBP), a structural analog of gamma-aminobutyric acid (GABA), was first approved in the 1990s for epilepsy and postherpetic neuralgia. However, its pharmacological versatility—mediated through interactions with the α2δ subunit of voltage-gated calcium channels, modulation of glutamate release, and anti-inflammatory effects—has led to off-label applications in chronic pain, psychiatric disorders, and even wound healing [1]. This systemic profile has spurred interest in topical GBP formulations, which aim to retain therapeutic benefits while minimizing off-target adverse effects—a paradigm-shift central to this commentary's focus on ocular applications. Indeed, recent research has uncovered novel mechanisms, including GBP's ability to enhance tear secretion via aquaporin-5 upregulation [2], and its neuroprotective effects when delivered via advanced nanocarriers [3].

In ophthalmology, GBP's potential is particularly promising for neuropathic ocular pain (NOP) and dry eye disease (DED), conditions often refractory to conventional therapies. Traditional treatments, such as topical NSAIDs or corticosteroids, carry risks of corneal toxicity and delayed healing, while systemic GBP can cause drowsiness and dizziness [4]. Clinical evidence from Ongun *et al.* [5], supports GBP's efficacy in alleviating ocular discomfort in dry eye patients, reinforcing its translational relevance. The review object of this commentary

[6], arrives at a critical juncture, as emerging preclinical and clinical studies suggest that topical GBP formulations may bypass systemic side effects while maintaining efficacy. For instance, the thiolated gelatin nanoceria platform takes advantage of its mucoadhesive properties, thus increasing corneal contact time 4-fold compared to conventional drops [3]. Their work on DED models demonstrated that nanoceria-encapsulated GBP enhances tear secretion, reduces oxidative stress, and prolongs drug retention in DED models—a breakthrough for topical neuropathic pain management. Moreover, GBP-lactam, a cyclic derivative of gabapentin, demonstrates distinct neuroprotective properties in retinal ischemia, as evidenced by the pioneering work of Pielen *et al.* [7]. Such *in vitro* study revealed that GBP-lactam significantly enhanced retinal ganglion cell (RGC) survival under ischemic conditions—a finding attributed to the compound's activation of mitochondrial ATP-sensitive potassium (mitoKATP) channels, a critical pathway in cellular resilience against oxidative stress and apoptosis. This mechanistic insight aligns with broader evidence that mitoKATP channel openers (e.g., diazoxide) confer neuroprotection in central nervous system injuries, suggesting GBP-lactam's potential as a targeted therapeutic for ocular neurodegenerative diseases. Though Pielen's [7], *in vitro* original work logically remains agnostic to administration routes, the neutral charge of GBP-L (unlike GBP) suggests potential for better cellular penetration, which could theoretically favor topical applications. Therefore, the review's emphasis on GBP derivatives like GBP-L highlights unexplored opportunities for localized neuroprotection in ocular diseases.

Purpose of Commentary: Bridging Evidence and Innovation

The comprehensive review object of this commentary represents a significant synthesis of gabapentin research spanning decades, from its foundational mechanisms—such as its modulation of calcium channels, first elucidated by Taylor [8], to its emerging applications in ophthalmology. For this work, literature was systematically identified through PubMed, Scopus, and Web of Science databases, finally focusing on peer-reviewed articles published between 2000–2024 to capture both foundational and cutting-edge advancements. This commentary seeks to critically engage with previous work by evaluating how it consolidates the diverse pharmacological effects of GBP, including its anti-inflammatory, secretagogue, and analgesic properties, into a cohesive framework for ocular therapeutics. Importantly, the comprehensive synthesis of GBP's ocular benefits [6], gains multidimensional support from recent mechanistic and translational studies. The foundational work of Martins *et al.* [9]. established GBP's engagement with spinal adenosine A1 receptors - a critical pathway for its anti-hyperalgesic effects in neuropathic pain models that likely extends to ocular pain pathways. This adenosine-ergic mechanism finds new relevance in Wu *et al.* [10]. demonstration of GBP's efficacy in a rodent model of neuropathic corneal pain induced by ciliary nerve ligation, which specifically implicates peripheral nociceptive modulation in ocular tissues. Simultaneously, Li Z *et al.* [11]. reveals an additional, potentially complementary anti-inflammatory axis through PPAR-γ-dependent suppression of macrophage polarization in myocardial injury. While these three studies illuminate distinct mechanisms—adenosine receptor modulation [9], peripheral nerve targeting [10], and macrophage-mediated inflammation control [11] —together they underscore GBP's pleiotropic potential for ocular therapeutics. However, the translation of these systemic and neural mechanisms to topical ophthalmic applications, particularly for inflammatory conditions like uveitis or dry eye disease, remains an open question requiring targeted investigation, as well as its divergent impacts on wound healing in diabetic versus non-diabetic models [12]. These contemporary findings not only enrich the context of Rusciano's review but also invite a reassessment of some of its central claims.

The commentary will further explore lingering controversies and unresolved questions in the field. For instance, while the previous review [6], compellingly outlines GBP's potential in managing dry eye disease and corneal ulcers, the broader literature presents conflicting evidence regarding its influence on wound repair, with some studies suggesting delayed healing [13], and others demonstrating accelerated recovery in diabetic wounds when GBP is combined with novel delivery systems [12]. Similarly, the review's emphasis on topical GBP as a superior alternative to systemic administration raises important questions about its comparative efficacy relative to pregabalin, a closely related gabapentinoid. Clinical data addressing this question remain sparse [14], leaving a gap that future research must urgently address.

Looking ahead, the advocacy for topical GBP formulations [6] resonates with contemporary innovations in drug delivery, such as the aforementioned nanoceria platforms that enhance corneal retention and bioavailability [3]. Yet, the translation of these preclinical advances into clinical practice remains hampered by a scarcity of rigorous trials. Critical questions persist: Can topical GBP truly supplant systemic administration in conditions like neuropathic ocular pain? Do its anti-inflammatory mechanisms, so promising in animal models, extend to human ocular pathologies such as uveitis or glaucoma? By situating GBP review [6], within this broader landscape—bridging classical mechanistic studies with cutting-edge applications—this commentary aims to highlight its dual role as both a retrospective summation of GBP's journey and a catalyst for future research. In doing so, it underscores the imperative for interdisciplinary collaboration to unlock GBP's full potential in ophthalmology and beyond.

The Competitive Landscape of Topical Ocular Therapies

The emergence of gabapentin as a potential treatment for ocular surface diseases arrives amid a rapidly evolving therapeutic landscape, where novel biological agents and regenerative approaches are challenging traditional paradigms. Neurotrophic factors, such as nerve growth factor (NGF) [15,16] and recombinant human insulin-like growth factor-1 (rhIGF-1) [17], have garnered attention for their ability to promote corneal nerve regeneration in neurotrophic keratitis—a condition often refractory to conventional therapies. Nishida and colleagues specifically demonstrated that rhIGF-1, when combined with neuropeptides, can restore persistent epithelial defects in this patient population. These biologics, while promising, face limitations in cost, stability, and the need for invasive administration, creating an opportunity for small molecules like GBP to offer a more practical alternative. Similarly, lubricin—a glycoprotein with potent anti-adhesive and anti-inflammatory properties—has demonstrated efficacy in restoring ocular surface homeostasis in dry eye disease, as evidenced by its boundary-lubricating and anti-inflammatory actions in recombinant formulations [18]. However, variability in glycosylation and stability across production methods [18], underscores the advantages of GBP's synthetic consistency and compatibility with advanced delivery systems.

Lacritin, another endogenous tear protein, has demonstrated potential in stimulating basal tear secretion and maintaining epithelial health [19], but its clinical translation remains in early stages, leaving room for GBP's well-characterized safety profile and off-label adaptability. Autologous serum [20], and colostrum-derived eye drops [21], rich in growth factors and immunomodulators, have long been used for severe ocular surface disorders, yet their variability in composition, logistical challenges in preparation, and risk of contamination underscore the appeal of standardized pharmaceutical options like GBP. What distinguishes GBP in this competitive field is its unique combination of mechanisms—simultaneously addressing neuropathic pain, inflammation, and tear deficiency [6]—while offering formulation flexibility, from nanoceria conjugates to mucoadhesive gels. However, the absence of head-to-head comparative studies between GBP and these emerging biologics leaves a critical gap in understanding their relative niches. As the field moves toward personalized ocular therapeutics, the integration of GBP's pharmacological strengths with the regenerative potential of biologics may ultimately define the next generation of treatment strategies, rather than a zero-sum competition between modalities.

Against this backdrop of biological and logistical challenges, Rusciano's review refocuses attention on GBP—a small molecule with pleiotropic actions that could circumvent many of these limitations—while critically examining its untapped potential.

Table 1. Competitive landscape of gabapentin vs. biologics for ocular surface diseases.

Feature	**Gabapentin**	**NGF (e.g. cenegermin)**	**rhIGF-1**	**Lubricin (rhPRG4)**	**Lacritin**
Class	Small molecule (gabapentinoid)	Neurotrophic factor	Growth factor	Glycoprotein	Tear glycoprotein
Primary mechanism	α2δ subunit modulation (reduces pathological Ca^{2+} influx & glutamate release), glutamate inhibition); AQP5 upregulation (tear secretion); PPAR-γ (anti-inflammatory)	TrkA receptor activation (nerve growth/survival and regeneration); BDNF upregulation (neuroplasticity)	IGF-1 receptor signaling (epithelial repair); AKT/mTOR activation (cell survival)	Boundary lubrication (friction reduction); CD44 interaction (anti-inflammatory)	Syndecan-1 binding (basal tear stimulation); EGFR activation (epithelial health)
Key indications	Neuropathic ocular pain, DED, post-surgical pain	Neurotrophic keratitis (NK)	Persistent epithelial defects	Severe DED, friction-related disorders	Aqueous-deficient DED, neurotrophic keratitis
Administration	Topical (nanocarriers), oral	Topical (eye drops)	Topical (drops/gel)	Topical (recombinant)	Topical drops
Advantages	- Multimodal (pain + tear secretion) - Lower cost - Formulation flexibility (nanocarriers)	- Direct nerve regeneration - FDA-approved for NK	- Synergistic with neuropeptides - Promotes healing	- Natural tear component - Anti-adhesive properties	Tear secretion boost, homeostatic
Limitations	- Long-term topical safety data lacking - Potential wound-healing modulation	- High cost ($48K/course) - Stability challenges	- Limited clinical data - Requires combination therapy	- Glycosylation variability - Early-stage clinical validation	Early-stage trials, production challenges

Summary of Key Contributions from the Review

The review under analysis [6] represents a seminal effort to consolidate three decades of gabapentin (GBP) research into a cohesive framework for ophthalmic applications. The work's most significant contribution lies in its exhaustive delineation of GBP's poly-pharmacology, which extends far beyond its initial classification as a GABA analogue. The review's mechanistic foundation is strengthened by recent breakthroughs in structural biology, particularly Page *et al.* [22], cryo-EM work defining the 'cache domains' within α2δ subunits that confer gabapentinoid selectivity. Their study reveals how GBP's cyclohexyl moiety docks into a hydrophobic pocket of the α2δ-1 cache domain, sterically hindering pathological calcium channel trafficking to neuronal membranes while leaving basal calcium homeostasis intact. This structural precision explains GBP's unique ability to target maladaptive synaptic plasticity—a hallmark of neuropathic ocular pain—without disrupting essential neurotransmission, addressing a key limitation of broader calcium channel blockers. This structural insight, not covered in previous reviews, provides a molecular rationale for GBP's favorable safety profile in ocular applications.

The review's analysis of GBP's glutamate-modulating effects is particularly timely given emerging understanding of corneal neuropathic pain mechanisms. The review builds on seminal work by Chen *et al.* [23], which first identified the physical coupling between α2δ-1 subunits and NMDA receptors in spinal pain pathways. Their finding that GBP disrupts this complex—reducing synaptic NMDA receptor trafficking and subsequent central sensitization—has since been validated in ocular pain models [9], suggesting a conserved mechanism across neural tissues. This is further strengthened by discussion of GBP's discovered inhibition of microglial activation. The complex interplay between gabapentin (GBP) and neuro-immune signaling is illuminated by two pivotal studies that bookend a decade of research. Yang JL *et al.* [24], first established GBP's capacity to suppress pathological microglial activation in monoarthritic rats, demonstrating its reduction of spinal CX3CL1 (fractalkine) signaling—a key neuron-to-microglia communication pathway. Their work revealed that GBP decreases microglial IL-1β release and subsequent pain hypersensitivity by interrupting this CX3CR1-dependent crosstalk, providing the foundational evidence for GBP's immunomodulatory potential in centralized pain states. A decade later, Lee *et al.* [25], added crucial nuance by showing that GBP's microglial effects are context-dependent. In their peripheral nerve injury model, GBP unexpectedly inhibited the beneficial aspects of microglial activation - specifically, the hepatocyte growth factor (HGF)-mediated nerve regeneration process. By disrupting microglial c-Met receptor signaling, GBP attenuated HGF-induced axonal growth and functional recovery, suggesting its immunomodulatory actions may impair reparative neuro-immune functions while still suppressing maladaptive signaling.

This apparent paradox can be reconciled through several mechanistic insights. 1) Target Specificity: Yang *et al.* focused on CX3CL1/CX3CR1 axis inhibition (pro-nociceptive), while Lee *et al.* examined c-Met pathway disruption (pro-repair). 2) Temporal Factors: Acute vs. chronic pain states may differentially engage these microglial subpopulations. 3) Spatial Considerations: Spinal [24], vs. peripheral [25], microenvironments exhibit distinct neuro-immune interactions.

For ocular applications, these findings carry important implications. The cornea and trigeminal system rely on both CX3CL1-mediated microglial activation in neuropathic pain (similar to Yang's spinal model); HGF-dependent nerve regeneration in conditions like neurotrophic keratitis (paralleling Lee's findings). Thus, while GBP's suppression of CX3CL1 signaling [24] may benefit inflammatory ocular pain, its inhibition of HGF-mediated repair [24] could potentially delay corneal nerve regeneration—a trade-off that merits careful consideration in clinical use. Recent advances in targeted delivery systems, such as nanoparticle-encapsulated GBP for corneal pain [3], may help navigate this balance by localizing therapeutic effects while minimizing systemic impact on regenerative processes.

Regarding topical formulations, the review [6], provides the most comprehensive analysis to date of GBP's secretagogue effects. The review builds on foundational work by Cammalleri *et al.* [2], who first demonstrated GBP's ability to upregulate AQP5 in lacrimal and corneal tissues—a mechanism explaining its secretagogue effects. The review contextualizes these preclinical findings with clinical observations from Ongun *et al.* [5], whose study of dry eye patients revealed that systemic GBP administration increased tear production and reduced pain scores, though AQP5 expression was not directly measured in humans. This translational gap highlights the need for future studies correlating topical GBP exposure with ocular AQP5 levels in clinical settings. The discussion of corneal healing benefits is enhanced by inclusion of the first randomized trial data [26] comparing GBP with standard therapies for post-surgical corneal wound repair.

Perhaps the review's most forward-looking section examines next-generation delivery systems. Beside the thiolated gelatin nanoceria platform [3], the review's forward-looking discussion of advanced delivery systems aligns with growing interest in extracellular vesicle (EV)-based therapies for neurotrophic keratitis. For instance, recent work by Massoumi *et al.* [27]. underscores the broader potential of EVs to deliver neuroprotective cargo (e.g., growth factors, miRNAs) to injured corneal nerves. Although GBP-loaded EVs remain hypothetical, Massoumi's demonstration that MSC-derived

EVs promote corneal nerve regeneration provides a proof-of-concept for targeted delivery—a strategy that could theoretically be adapted for gabapentinoids. This represents a logical extension of the review's emphasis on precision medicine for ocular neuropathic pain. However, these advanced systems have yet to enter clinical trials, according to regulatory challenges outlined in the FDA guidance on ophthalmic nanotherapeutics [28].

The review's translational framework is strengthened by its parallel discussion of lessons from non-ocular GBP use. For instance, it draws important comparisons with recent findings in diabetic neuropathy [29], where topical GBP showed superior nerve regeneration compared to oral administration—suggesting similar benefits might be achievable for corneal nerves. This systems-level perspective differentiates Rusciano's work from previous narrowly focused reviews.

Significance in Light of Older Literature

The evolution of gabapentin (GBP) from a systemic anticonvulsant to a multifaceted therapeutic agent for ocular surface diseases reflects a remarkable expansion in pharmacological understanding. The recent review by Rusciano [6], represents a critical synthesis of this trajectory, bridging historical insights with contemporary innovations. To fully appreciate its contributions, it is essential to contextualize the review within the broader landscape of earlier research, which laid the mechanistic groundwork but left key translational gaps unfilled.

Early investigations into GBP's pharmacology, such as those by Taylor [30], established its binding to the α2δ subunit of voltage-gated calcium channels as a cornerstone of its action. This discovery clarified GBP's role in modulating presynaptic calcium influx and attenuating glutamate release—a mechanism later validated in models of neuropathic pain by Coderre *et al.* [31]. While these studies provided a robust foundation for understanding GBP's systemic effects, they remained narrowly focused on central and peripheral neural pathways, with little consideration of its potential in ocular tissues. Similarly, comparative analyses like Tzellos *et al.* [32]. underscored the relative efficacy of GBP and pregabalin in spinal cord injury and other systemic neuropathic conditions, yet their scope was confined to oral administration, overlooking the possibilities of localized delivery.

Rusciano's review [6] breaks new ground by integrating these foundational mechanisms into a cohesive framework for ocular therapeutics. Where older literature remained silent on GBP's applicability to the eye, this review draws critical connections between systemic actions and ocular pathophysiology. For instance, while Chen *et al.* [23]. elucidated the role of α2δ-1–NMDA receptor complexes in spinal neuropathic pain, Rusciano extends this paradigm to the cornea, highlighting analogous pathways in neuropathic ocular pain. This translational leap is further reinforced by recent work, such as Wu *et al.* [10], which demonstrates GBP's efficacy in modulating ciliary nerve-mediated hyperalgesia—a finding that aligns with but expands upon earlier systemic models.

Another significant advancement is the review's exploration of GBP's anti-inflammatory and neuroprotective properties in ocular contexts. Earlier studies, such as Park *et al.* [33], identified GBP's suppression of NF-κB in neural cells, but their implications for ocular inflammation were left unexplored. Rusciano addresses this gap by incorporating evidence like Anfuso *et al.* [34], which demonstrates topical GBP's ability to mitigate endotoxin-induced uveitis, reducing key inflammatory markers in corneal tissues. Equally noteworthy is the discussion of GBP-lactam, as already reported above [6], though absent from prior systemic reviews. This inclusion not only broadens the therapeutic scope of GBP but also underscores the review's role in connecting disparate lines of research.

Rusciano's review advances beyond earlier systemic comparisons by addressing a critical gap in ocular formulation science. Where traditional approaches focused solely on oral pharmacokinetics, the review highlights innovative delivery systems like nanoceria-encapsulated GBP [3], that overcome corneal penetration barriers—a transformative approach absent from prior literature. This formulation-centric perspective provides new clarity to previously contradictory wound-healing findings.

In light of these contributions, Rusciano's review [6] not only consolidates historical knowledge but also redefines its relevance for ocular therapeutics. By addressing gaps left by older studies and integrating emerging evidence, it positions GBP as a versatile agent for treating ocular surface diseases, from neuropathic pain to inflammatory and degenerative conditions. The review's forward-looking perspective, particularly its emphasis on targeted delivery systems and mechanistic synergies, invites further research into unanswered questions, such as the role of adenosine A1 receptors in corneal nociception or the potential of GBP-lactam in anterior segment diseases. In doing so, it serves as both a culmination of past discoveries and a catalyst for future innovation.

Integration with Recent Advances (2020–2024)

The period from 2020 to 2024 has yielded critical insights that both reinforce and expand upon the framework presented in Rusciano's review, particularly in translating GBP's mechanisms into clinical and technological innovations for ocular therapeutics. Recent studies have not only validated the review's central theses but also illuminated unresolved challenges, creating a dynamic interplay between confirmation and refinement.

Clinical investigations have significantly strengthened the case for GBP's role in managing neuropathic ocular pain, a cornerstone of Rusciano's argument. Yoon *et al.* [35]. and Ongun [5] provided compelling evidence that systemic GBP alleviates ocular discomfort in patients with refractory dry eye, particularly those exhibiting features of neuropathic pain. These findings resonate with the review's emphasis on GBP's dual capacity to modulate peripheral nociception and enhance tear secretion—a synergy that conventional therapies often fail to achieve. Importantly, these studies identified patient subgroups most likely to benefit from GBP, such as those with comorbid systemic conditions or reduced corneal sensitivity, thereby refining the precision of its clinical application.

Equally transformative has been the progress in drug delivery systems, which Rusciano's review anticipated as a pivotal frontier. Yang *et al.* [3]. epitomized this advance by engineering a nanoceria-encapsulated GBP formulation that merges mucoadhesion, antioxidant properties, and sustained release into a single platform. This innovation directly addresses the longstanding bioavailability challenges of topical GBP, while aligning with the review's call for nanotechnology-driven solutions. The nanoceria system's ability to preserve corneal nerve density and enhance tear production in dry eye models offers a tangible realization of the review's speculative vision, bridging molecular mechanisms with therapeutic practicality.

Yet, this progress unfolds against a backdrop of lingering controversies that underscore the specificity of GBP's efficacy. The divergent outcomes in psychiatric applications, as highlighted by Hong *et al.* [36], serve as a cautionary counterpoint to the robust ophthalmic data. Where GBP exhibits inconsistent performance in bipolar disorder and anxiety—partly due to systemic side effects and variable blood-brain barrier penetration—its ophthalmic successes underscore the importance of targeted delivery and tissue-specific mechanisms. This contrast reinforces Rusciano's thesis that GBP's therapeutic potential is maximized when its pharmacokinetic limitations are circumvented through formulation science, a principle less salient in systemic psychiatric use.

Together, these advances and contradictions refine the roadmap laid out in the review. They affirm GBP's niche in ocular surface diseases while highlighting the irreplaceable role of innovation in administration routes—a narrative that positions Rusciano's synthesis not merely as a summary of past work, but as a catalyst for future breakthroughs.

Critical Evaluation and Unanswered Questions

Rusciano's review represents a significant milestone in consolidating gabapentin's multifaceted mechanisms with its emerging ophthalmic applications, yet several crucial considerations emerge when examining its contributions and limitations. The review's principal strength lies in its unprecedented synthesis of molecular pathways with clinical potential, particularly in connecting GBP's calcium channel modulation to both neuropathic pain relief and enhanced tear secretion—an integrative perspective absent from prior literature. By emphasizing topical delivery systems, the work importantly shifts the therapeutic paradigm from systemic management of symptoms to targeted ocular intervention, offering new possibilities for chronic conditions requiring sustained treatment.

However, this otherwise wide-ranging evaluation leaves certain critical questions insufficiently explored. Despite its comprehensive mechanistic synthesis, the review's limited critical engagement with emerging safety data represents a notable gap in the otherwise thorough analysis. Growing pharmacovigilance evidence from Ahmad and Mehta [37], and Hu *et al.* [38]. highlights potential corneal epithelial toxicity associated with systemic long-term GBP use—a particularly crucial consideration for chronic ocular surface diseases like neurotrophic keratitis that may require sustained therapy. This is further supported by preclinical data showing GBP's dose-dependent inhibition of corneal epithelial migration [12], raising important questions about its long-term topical safety profile. This concern is compounded by dose-dependent effects observed in wound healing studies, where higher GBP concentrations have been shown to paradoxically inhibit corneal epithelial migration [12]. The absence of robust discussion regarding these safety considerations becomes increasingly significant as GBP transitions from systemic to topical administration, where local tissue exposure is more concentrated. Additionally, while the review comprehensively addresses GBP's mechanisms, direct comparisons with pregabalin - a related gabapentinoid with potentially superior bioavailability—remain unexplored in the ocular context, despite their established comparative analyses in systemic neuropathic pain [32]. This underscores an urgent need for randomized controlled trials (RCTs) specifically evaluating long-term topical GBP safety, a prerequisite for clinical adoption that remains unmet despite promising mechanistic data. Furthermore, while preclinical studies of advanced formulations (e.g., nanoceria-encapsulated GBP [3]) demonstrate promising results in animal models, the critical translational gap to human trials remains unaddressed—a limitation that must be resolved to fully evaluate both efficacy and safety in clinical populations. These omissions underscore the need for more rigorous safety profiling alongside the development of novel delivery systems to ensure therapeutic optimization.

The path forward for GBP in ophthalmic therapeutics presents several compelling opportunities. One particularly promising avenue involves exploring synergistic combinations with other neuroprotective agents, such as GBP-lactam derivatives [7], which could potentially address both anterior and posterior segment diseases through their distinct mechanisms of action. Additionally, as highlighted by

Albrecht's [39], recent work on pain biomarkers, there exists a critical need to better understand and predict variability in patient response. Developing phenotypic or molecular markers to identify optimal candidates for GBP therapy could significantly enhance treatment precision, moving beyond the current trial-and-error approach. These future directions, while challenging, could substantially build upon the foundation laid by Rusciano's review, transforming GBP from a promising option to a mainstay of ocular therapeutics.

Conclusions

Rusciano's 2024 review emerges as a seminal work that successfully bridges decades of gabapentin research with its emerging ophthalmic applications, offering both a comprehensive mechanistic synthesis and a visionary roadmap for therapeutic innovation. By systematically connecting GBP's polypharmacology—from calcium channel modulation to anti-inflammatory and neuroprotective effects—to ocular surface diseases, the review fills critical gaps left by earlier systemic-focused literature while establishing a new paradigm for targeted therapy.

The most transformative contribution lies in the review's emphasis on topical formulations, which addresses longstanding challenges of systemic administration while capitalizing on GBP's pleiotropic mechanisms. This shift is exemplified by breakthroughs like nanoceria-encapsulated delivery systems that enhance corneal retention and bioavailability—advances that were merely theoretical in prior reviews. However, as the commentary has highlighted, several crucial frontiers remain. The promising preclinical data on novel formulations must now be translated through rigorous clinical trials, with standardized evaluation of 1) long-term corneal epithelial safety (e.g., via serial *in vivo* confocal microscopy), 2) quantitative changes in tear secretion (Schirmer's test/tear osmolarity), and 3) validated neuropathic pain metrics (ocular analog scales, corneal sensitivity mapping). Additionally, the potential synergy between GBP derivatives like GBP-lactam and existing neuroprotective agents warrants exploration, as does the development of biomarkers to guide personalized therapy.

As the field stands at this inflection point, Rusciano's work serves both as a definitive summation of GBP's journey from systemic anticonvulsant to ophthalmic therapeutic, and as a catalyst for the next phase of research. Future studies should prioritize: 1) comparative efficacy assessments against pregabalin in ocular models, 2) standardized safety monitoring for topical applications, and 3) mechanistic investigations into patient-specific response variability. By addressing these priorities while building on the review's foundational insights, the scientific community can realize GBP's full potential as a mainstay in ocular therapeutics—one that combines mechanistic precision with clinical practicality for conditions ranging from neuropathic pain to degenerative diseases.

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Conflicts of Interest

There are no conflicts of interest to declare.

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DR was responsible for manuscript drafting and editing. CG and AA were responsible for bibliographic research and manuscript editing.

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