Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Updates in the Treatment of Rosacea with γ-Aminobutyric Acid Derivatives

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Abstract: Neurogenic inflammation plays an important role in the pathogenesis of rosacea. Recently, several clinical studies have found that γ-aminobutyric acid (GABA) derivatives can effectively improve the erythema and burning symptoms of rosacea. The underlying mechanisms may relate to the ability of GABA derivatives to inhibit the transient receptor potential channel pathway, subsequently reducing abnormal neuronal activation, inhibiting neuropeptide release, and suppressing neurogenic inflammation. This paper aimed to comprehensively review the progress of fundamental and clinical research on the role of neurogenic inflammation in the pathogenesis of rosacea and the application of GABA derivatives in rosacea treatment. We believe this paper will provide new directions for the treatment of rosacea. PubMed, China National Knowledge Infrastructure, and Web of Science databases were searched for relevant literature. The literature review revealed that GABA derivatives, such as pregabalin and gabapentin, may be effective in relieving the redness and erythema symptoms of rosacea. The potential mechanisms and the effects of GABA derivatives in rosacea treatment were reviewed, providing a new basis for the treatment of rosacea.

Keywords: Rosacea, neurogenic inflammation, γ-aminobutyric acid derivatives, GABA derivatives

Introduction

Rosacea is a chronic, inflammatory skin disease that typically presents in the center of the face. It is mainly characterized by paroxysmal flushing, persistent erythema, papules, pustules, telangiectasia, phymatous changes, and ocular manifestations. Often, rosacea is accompanied by burning and tingling skin sensitivity.[1] As a disfiguring disease, rosacea affects the facial appearance of patients, often triggering anxiety and depression.[2] Rosacea is a prevalent condition affecting 5.1% of the world's population, highlighting the importance of establishing more effective treatment strategies.[3]

The pathogenesis of rosacea is complex. Multiple factors are believed to contribute to the development and progression of rosacea, including genetic predisposition; environmental triggers, such as ultraviolet radiation; dysregulation involving microorganisms, such as Demodex mites; and reactive oxygen species (ROS). These factors trigger a series of vascular alterations and inflammatory responses through neurovascular dysregulation and innate immunoregulatory disorders. Ultimately, these factors result in the clinical symptoms of rosacea.[4] Neurogenic inflammation is an important aspect of neurovascular regulation. Multiple neuropeptides and inflammatory factors play a role in the pathogenesis of rosacea.[5] Recently, clinical studies have shown that the oral administration of gamma-aminobutyric acid (GABA) derivatives, such as pregabalin and gabapentin, is effective in relieving the erythema, flushing, and burning symptoms of rosacea.[6] However, previous studies in this field primarily comprise case series or case reports, and a comprehensive synthesis of existing basic and clinical research findings is lacking. Due to the emerging evidence on the role of neurogenic inflammation in rosacea pathogenesis and the related therapeutic potential of GABA derivatives, a comprehensive systematization of current evidence would help fill this critical gap in research.

Received: 30 June 2025
Accepted: 2 September 2025
Published: 6 September 2025

Neurogenic Inflammation in Rosacea

Neurogenic inflammation is a localized inflammatory response initiated by nerve endings and the neuropeptides they secrete, independent of the direct involvement of the immune system. Various cells, including keratinocytes, Langerhans cells, endothelial cells, and mast cells, are involved in neurogenic inflammation,[7] and densely distributed nerve fibers in the skin communicate with these cells. These nerve fibers activate skin cells by releasing neuropeptides, such as substance P (SP) or calcitonin gene-related peptide (CGRP). The activated skin cells—especially mast cells—then release histamine or proinflammatory cytokines, thereby activating sensory nerve endings. By this means, a bidirectional positive feedback loop is created, which amplifies the cascade response and increases inflammation.[8]

In addition to the transient receptor potential vanilloid type 1 channel (TRPV1) and the transient receptor potential ankyrin type 1 channel (TRPA1), five important G protein-coupled receptors (GPCRs) have been identified as the primary contributors to neurogenic inflammation: protease-activated receptor (PAR)-2 and −4, and the C11, A3, and X isoforms of Mas-related GPCRs. Upon activation, these receptors induce skin sensations by increasing the cytoplasmic Ca^{2+} concentration. An elevated cytoplasmic Ca^{2+} concentration has been demonstrated to induce the release of sensory neuropeptides from the skin, thereby exacerbating the inflammatory response.[9,10]

Neurogenic inflammation is an important pathogenic mechanism of rosacea.[11] Further, triggers of rosacea, such as ultraviolet light, high and low temperatures, alcohol, spicy foods, and exercise, may activate peripheral sensory nerve endings.[12]

Abnormal Neuronal Activation: Overexpression of TRP

Multiple TRPV receptors are significantly overexpressed in different subtypes of rosacea.[13] In addition, TRPV1 and TRPV4 are increased in the skin tissues of patients with rosacea and in capsaicin-treated keratinocytes, along with increased levels of inflammatory factors, such as cathelicidin (LL37) and tumor necrosis factor-alpha (TNF-α).[14] Infestation with demodex mites can increase TRPV1, nerve growth factor (NGF), and tropomyosin receptor kinase A (TRKA) expression levels in rosacea, consequently exacerbating cutaneous neurogenic inflammation mediated by the activation of the TRPV1–NGF–TRKA pathway.[15] An LL37-induced rosacea-like mouse model confirmed that TRPV1 upregulation is associated with inflammation.[15] TRPV4 interacts with the transient receptor potential melastatin 8 channel (TRPM8) and is involved in rosacea pruritus.[16] Furthermore, TRPA1 and TRPV1 are often co-expressed in neurons, and together, they induce neurogenic inflammation.[17]

Increased Release of Neuropeptides

Increased SP expression in rosacea activates the endothelial cell neurokinin 1 receptor (NK-1), contributing to mast cell degranulation. This leads to vasodilation and an inflammatory response, exacerbating pruritus and swelling.[18,19] In individuals with rosacea, plasma CGRP levels are elevated,[20] which can significantly dilate skin capillaries and exacerbate persistent erythema. Based on this mechanism, Erenumab—an anti-CGRP-receptor monoclonal antibody—has demonstrated efficacy in relieving rosacea-associated erythema and flushing.[21] Mutations in the *LRRC4, SH3PXD2A*, and *SLC26A8* genes in rosacea can cause human neuronal cells to produce vasoactive intestinal peptide (VIP), which induces inflammation.[22] Neurokinin B, which is involved in vasodilatation and inflammatory modulation, also co-exists with rosacea.[18,23]

Activation of Immune Cells

Mast cells play a vital role in neurogenic inflammation in rosacea. When stimulated by temperature change, spicy foods, and other triggers, skin sensory nerve endings release various neuropeptides, including pituitary adenylate cyclase-activating polypeptide (PACAP), CGRP, SP, and VIP. These neuropeptides induce mast cell degranulation via MRGPRX2, subsequently causing the release of proinflammatory cytokines—such as histamine, tryptase-like protease (TPS), and TNF-α—and triggering downstream inflammatory responses.[24,25] On the other hand, the histamine and TPS produced following mast cell degranulation prompts nerve endings to release more neuropeptides, cyclically amplifying inflammation.[26]

Oxidative stress is an important cause of rosacea. It mediates vascular changes and inflammatory cascades by producing ROS.[27] In recent years, it has been found that the expression levels of TRPA1 and related inflammatory genes are upregulated in mast cells following elevated ROS production,[28] which promotes mast cell degranulation, increases TPS release, and exacerbates neurogenic inflammation. Mast cells are also involved in the pathogenesis of rosacea through LL-37. LL-37 increases TRPV4 expression by acting on the Mas-associated MRGPRX2 receptor on mast cell surfaces. This leads to an increase in the concentration of intracellular Ca^{2+} and mast cell degranulation.[29] In addition, mast cells play an important role in the immune response, vascular changes, and hyperplastic hypertrophy in rosacea.[30]

Mechanism and Clinical Application of GABA Derivatives

GABA is the major inhibitory neurotransmitter in the central nervous system; it regulates neurotransmitter release and neuronal excitability by binding to GABA receptors. There are three main GABA receptor subtypes: GABAA, GABAB, and GABAC. GABAA receptors are composed of 5 protein subunits and at least 19 subunit subtypes (α1-6, β1-3, γ1-3, δ, ε, θ, π, and ρ1-3). GABAB receptors are GPCRs consisting of GABAB1 and GABAB2 subunits. They mediate GABA-induced responses by activating the G protein system.[31] GABA derivatives, such as pregabalin[32] and gabapentin,[33] are similar to GABA in structure; however, they generally remain inactive when bound to classical GABAA and GABAB receptors. Conversely, other GABA derivatives, such as pregabalin,[34] gabapentin,[35] and crisugabalin,[36] have a strong binding affinity for the α2δ subunit of neuronal voltage-gated calcium channels.

Voltage-gated calcium channels in neurons are composed of three main subunits: the α1 pore-forming subunit, the intracellular β subunit, and the α2δ subunit.[37] The α2δ subunit—with a total molecular weight of 170 kDa[38]—is a highly glycosylated protein complex consisting of α2 and δ subunits that are interconnected by disulfide bonds. There are four different subtypes of α2δ: α2δ1, α2δ2, α2δ3, and α2δ4.[39–41] α2δ increases the density and release probability of presynaptic membrane calcium channels, thereby increasing calcium inflow and neurotransmitter release.[42] Recent studies on neuropathic pain have revealed that α2δ1 activation directly increases TRPA1 expression[43] and TRPV1/TRPA1 phosphorylation, subsequently increasing the probability of channel opening, amplifying calcium signaling,[44] and exacerbating the inflammatory response. By this mechanism, it can be inferred that GABA derivatives inhibit abnormal neuronal activation and suppress neurogenic inflammation by inhibiting TRPA1 and TRPV1 (Figure 1).

GABA derivatives exert clinical effects by binding to different α2δ proteins of voltage-gated calcium channels. This binding inhibits Ca^{2+} release and inflow, thereby reducing the release of excitatory transmitters, such as glutamate and SP.[45] The currently approved drugs for clinical use include gabapentin, pregabalin,[35] mirogabalin, and crisugabalin.[46] Common indications of GABA derivatives include epilepsy,[47] neuropathic pain[48] (including adult diabetic peripheral neuropathic pain[49] and postherpetic neuralgia[50]), and chronic pruritus.[51]

GABA Derivatives in the Treatment of Rosacea

A limited number of studies exist on the treatment efficacy of GABA derivatives in rosacea. Six articles reporting on GABA derivatives for the treatment of rosacea (Table 1) were identified in PubMed and Web of Science databases using the following search terms: "(Pregabalin) AND (rosacea)", "(gabapentin) AND (rosacea)", and "Neurogenic Rosacea".[52,53]

In 2011, Scharschmidt et al used GABA derivatives for the first time in the treatment of rosacea and introduced the concept of neurogenic rosacea.[57] They found that GABA derivatives were effective in relieving burning or stinging sensations among patients with rosacea. Later, in 2015, Parkins et al reported the successful treatment of a patient with refractory rosacea and psychiatric symptoms using pregabalin (300 mg once every morning and 225 mg every night). Pregabalin successfully relieved the patient's symptoms of facial burning, redness, and swelling. Moreover, these authors have reported the successful treatment of three other patients with neurogenic rosacea using pregabalin over the past decade.[58] In 2020, Kim et al conducted a review of 17 Korean patients with neurogenic rosacea. Among these patients, 14 (82.3%) exhibited clinical improvements in severe persistent erythema, burning sensations, and stinging following treatment with anticonvulsants (eg gabapentin, pregabalin) combined with antidepressants (eg tianeptine, diazepam, duloxetine).[12] In 2024, Hurtado et al reported a case of neurogenic rosacea treated with pregabalin (150 mg, once daily) combined with duloxetine (90 mg, once daily) for 6 months. The patient's pain and burning symptoms were significantly reduced. However, erythema persisted; therefore, intense pulsed light (IPL) therapy (Harmony-Alma Laser®, wavelength 550–650 nm, energy density 10 J/cm², pulse width 12 ms) was added. The patient received IPL therapy

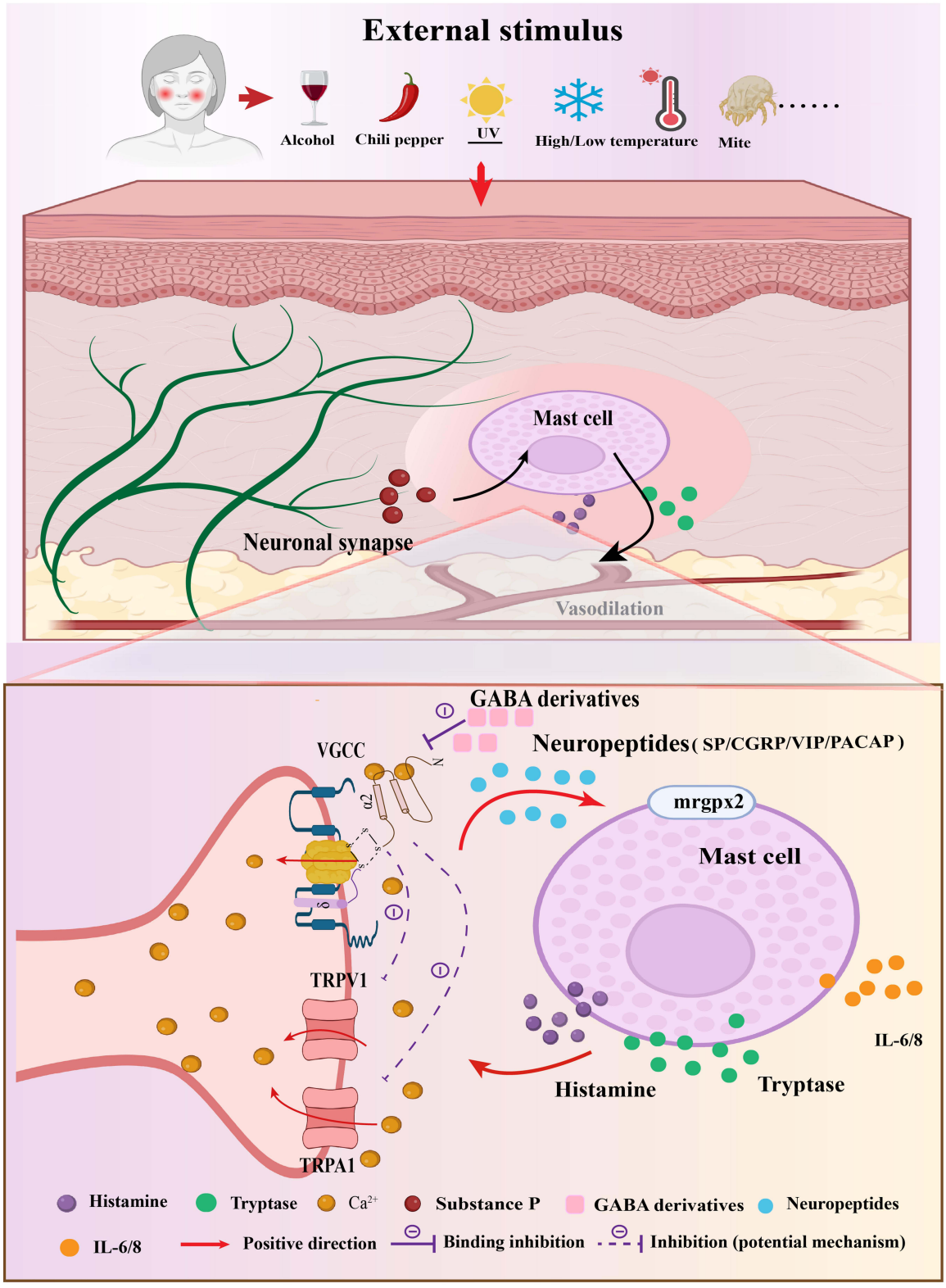

Figure 1 The potential mechanisms of γ-aminobutyric acid derivatives for rosacea treatment. Triggers for rosacea (eg alcohol, chili peppers, ultraviolet radiation, temperature extremes, Demodex mites) activate cutaneous sensory nerve endings, releasing neuropeptides (eg SP, CGRP, VIP, PACAP). These act on mast cells, inducing histamine and tryptase, and pro-inflammatory factors, including interleukin (IL)-6 and IL-8, leading to vasodilation and inflammation. Histamine and tryptase further stimulate nerve endings to release neuropeptides, creating a feed-forward loop that augments inflammation. The mechanism of γ-aminobutyric acid (GABA) derivatives in rosacea treatment may involve binding to the α2δ subunit of voltage-gated Ca^{2+} channels (VGCCs), further inhibiting TRPV1/TRPA1 expression, blocking calcium influx, and decreasing the release of neuropeptides related to the pathogenesis of rosacea.

Table 1 Studies on GABA Derivatives for Treating Rosacea

Year	Author	Study Type	Participants	Treatment Protocol	Therapeutic Effect	Limitation
2011	Scharschmidt et al[54]	Case series study	12 patients with rosacea and prominent neurological symptoms	Pregabalin or gabapentin or both, no specific dose mentioned	Gabapentin effective in 5/11 cases; pregabalin effective in 1/4 cases	Observational study without a control group
2015	Parkins et al[55]	Case report	1 female patient with neurogenic rosacea (61 years old)	Maintenance dose: pregabalin (300 mg morning + 225 mg night)	Pregabalin showed remarkable efficacy with significantly improved symptoms (burning, redness, swelling). Another 3 similar patients were successfully treated in this clinic during the past 10 years.	Single case report with limited generalizability of results
2021	Kim et al[12]	Multicenter, retrospective case–control study	17 patients with neurogenic rosacea	Anticonvulsants (gabapentin or pregabalin) or antidepressants, no specific dose mentioned	14/17 patients improved after treatment with anticonvulsants (gabapentin or pregabalin) or antidepressants (diazepam or paroxetine).	Small sample size in neurogenic group; retrospective design (inadequate control for confounders); non-standardized treatment (reliance on chart notes)
2023	Wei et al[52]	Randomized controlled trial	192 patients with ETR	Gabapentin (200 mg/400 mg thrice daily) vs carvedilol (5 mg twice daily)	Gabapentin group showed superior improvement in flushing, sleep, and migraines (especially the 400 mg group), with better efficacy in patients over 40 years old.	Unbalanced sample size between groups (carvedilol group n=58, other groups n>60)
2024	Hurtado et al[53]	Case report	1 female patient with neurogenic rosacea	Pregabalin (150 mg once daily) + duloxetine (90 mg once daily) + IPL (Harmony-Alma Laser®, wavelength 550–650 nm, energy density 10 J/cm², pulse width 12 ms; once daily)	The pain and burning symptoms were significantly reduced after 6 months of pregabalin and duloxetine; however, erythema persisted. Once daily IPL was added for the next 3 months; all symptoms disappeared.	Single case report with limited generalizability of results
2024	Wei et al[56]	Randomized non-inferiority trial	315 patients with ETR	Gabapentin (300 mg thrice daily) vs carvedilol (5 mg twice daily)	Gabapentin showed non-inferior CEA improvement by week 12, faster onset (week 4), better migraine/sleep outcomes, but poorer anxiety/depression effects. Safety profiles were similar.	Discontinuation follow-up period was only 4 weeks; long-term relapse rate was not assessed
2024	Ma et al[57]	Multicenter, randomized, double-blind, placebo-controlled trial	87 patients with rosacea (73 completed)	Gabapentin (200 mg/300 mg thrice daily) vs placebo.	High-dose gabapentin (300 mg) better improved flushing and redness, whereas CEA scores showed no significant difference. Good tolerability (dizziness/drowsiness common).	Small sample size; long-term efficacy not assessed

Abbreviation: CEA, Clinical Erythema Assessment.

https://doi.org/10.2147/CCID.S550614

once a month for the next 3 months while continuing medication, and eventually all symptoms disappeared.[59] In recent years, several randomized controlled trials (RCTs) have further demonstrated that gabapentin—a GABA derivative—is effective in improving flushing, erythema, and related symptoms in erythematotelangiectatic rosacea. A 2023 RCT (n = 192) conducted by Wei et al showed that gabapentin (200/400 mg, thrice daily) was superior to carvedilol (5 mg, twice daily) in relieving flushing symptoms and improving sleep and migraines. Gabapentin was also more effective in patients aged over 40 years, particularly at the 400 mg dose, than in younger patients.[60] A non-inferiority trial (n = 315) conducted by Wei et al in 2024 showed that gabapentin (300 mg, thrice daily) was comparable to carvedilol in efficacy. Specifically, patients reported a rapid reduction in Clinical Erythema Assessment (CEA) scores in the early stages (4 weeks), as well as significant improvements in migraines and sleep quality. However, gabapentin had weaker anxiolytic and antidepressant effects compared with carvedilol.[61] In the same year, Ma et al's multicenter RCT (n = 87) found that high-dose gabapentin (300 mg, thrice daily) did not significantly reduce CEA scores; however, it produced superior improvement in overall flushing symptoms and had a favorable safety profile compared with low-dose gabapentin (200 mg, thrice daily), with common side effects including dizziness and somnolence.[62] These studies indicate that gabapentin is an effective, fast-acting, and well-tolerated treatment for rosacea, especially for patients over 40 years of age who experience flushing, migraines, and sleep disorders.

Discussion

Neurogenic inflammation plays an important role in the pathogenesis of rosacea, evidenced by the elevated TRP pathway expression, abnormal neuronal activation, and release of numerous neuropeptides. These factors activate immune cells and trigger the release of histamine and other inflammatory mediators that cause vasodilation, inflammation, and itchiness. GABA derivatives, such as pregabalin and gabapentin, have been used to treat rosacea in many cases. Several clinical trials have verified that these derivatives can improve symptoms, such as redness and erythema, and are more effective in treating refractory rosacea accompanied by neuropsychiatric symptoms. GABA derivatives may be considered in clinical practice, especially for the treatment of patients with rosacea accompanied by neuropsychiatric symptoms, such as migraine, or prominent facial pain and burning symptoms. It should be noted that the use of GABA derivatives is currently considered off-label worldwide, and patients must provide voluntary, informed consent before treatment. The mechanism by which GABA derivatives effectively treat rosacea may be related to the inhibition of neurogenic inflammation. A likely mechanism involves the inhibition of TRPV1/TRPA1 expression in combination with the α2δ1 subunit of voltage-gated calcium channels, subsequently reducing neuronal activation. Another possible mechanism involves the direct inhibition of calcium inflow, reducing the release of excitatory transmitters, such as glutamate and SP.

Nonetheless, more basic research is necessary to clarify these mechanisms, and large-scale, randomized, controlled, clinical studies are needed to standardize the therapeutic regimen.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study received no funding.

Disclosure

The authors report no conflicts of interest relating to this work.

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