NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

PRZYBYŁ, Maciej, FAHIM, Knieszko, FRANCISZEK, Jakub, HERCHI, Nadia, JABRZYK, Martyna, JARCZYŃSKA, Patrycja, KIJOWSKI, Wojciech, KLUSEK, Mateusz, and MICHALAK, Karolina. Suzetrigine in the Management of Pain: Review of the First-in-class Na V1.8 Selective Inhibitor. Journal of Education, Health and Sport. 2026;90:70122. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.90.70122

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 22.03.2026. Revised: 28.03.2026. Accepted: 22.04.2026. Published: 22.04.2026.

Suzetrigine in the Management of Pain: Review of the First-in-class Na V1.8 Selective Inhibitor

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Abstract

Introduction: The 2025 FDA approval of suzetrigine (Journavx) ended a 25-year stagnation in analgesic development. This introduced a paradigm shift in pain management. As a first-in-class, highly selective NaV1.8 sodium channel inhibitor, suzetrigine addresses the urgent need for potent, non-opioid options for moderate-to-severe acute pain. It targets channels that are expressed almost exclusively in peripheral nociceptors. Thus, it decouples robust analgesia from systemic risks and addictive potential inherent to traditional opioid therapies.

Aim of the study: This review evaluates the status of suzetrigine as of 2026, focusing on its molecular mechanism, clinical efficacy, and safety data from pivotal Phase 3 trials, as well as its broader impact on public health and healthcare economics.

Materials and methods: A systematic literature review was conducted using PubMed (up to early 2026). Analysis included structural molecular studies, Phase 2/3 clinical trials (NAVIGATE-1 and -2), and budget impact models regarding the opioid crisis.

Conclusions: Suzetrigine represents a significant breakthrough in pain medicine, boasting a 31,000-fold selectivity for NaV1.8, thereby safeguarding the cardiac and central nervous systems. Clinical data demonstrate efficacy comparable to opioid pain therapy, but without respiratory depression, sedation, or physical dependence. Non-opioid mechanisms create

measurable, substantial savings by preventing opioid-related adverse events and addiction-related costs. Suzetrigine is seen as a desirable foundation for modern multimodal analgesia, effectively bridging the therapeutic gap between traditional non-opioids and addictive substances.
Keywords: Suzetrigine; VX-548; NaV1.8 Inhibitor; Non-opioid analgesics; Acute pain; Pain management

Introduction

Pain management remains one of the most critical priorities in daily clinical practice, accounting for approximately 40% of all primary care visits. [25, 37] The prevalence of pain among hospitalized adult patients is estimated to be alarmingly high, ranging from 37.7% to as much as 84%. Despite the magnitude of this problem, traditional analgesic approaches based on non-opioid pain relievers, such as paracetamol and NSAIDs, and opioids are associated with numerous limitations. NSAIDs carry the risk of serious gastrointestinal and renal complications, while the use of opioids, although effective for moderate to severe pain is burdened by the risks of respiratory depression, sedation, and high addictive potential, which has led to a global opioid crisis [6, 19, 37].

In response to the urgent need for effective and safe alternatives, on January 30, 2025, the U.S. Food and Drug Administration (FDA) approved suzetrigine (Journavx), the first new drug class for the treatment of moderate-to-severe acute pain in 25 years. [9, 10, 14] Suzetrigine represents a breakthrough therapeutic approach as a first-in-class, highly selective inhibitor of the voltage-gated sodium channel Na V1.8 [4, 28]. The mechanism of action targets NaV1.8 sodium channels, which are expressed almost exclusively in peripheral nociceptive neurons that transmit pain signals to the central nervous system. [8, 11]. By binding to the voltage-sensor domain (VSD2) of the channel, suzetrigine stabilizes it in the closed state, preventing the influx of sodium ions and the generation of action potentials [3, 41].

The exceptional, over 31,000-fold selectivity for the Na V1.8 subtype compared to other sodium channels minimizes the risk of adverse effects, while the lack of affinity for opioid receptors eliminates the pathway responsible for the development of tolerance and addiction [3, 18, 30].

Current Phase 3 clinical trials, involving patients following abdominoplasty and bunionectomy, have confirmed that suzetrigine provides a statistically significant and clinically meaningful reduction in pain compared to placebo [5, 7]. It has been demonstrated that an oral loading dose of 100 mg, followed by 50 mg every 12 hours, is characterized by a favorable safety and tolerability profile, often exceeding the results observed with the combination of hydrocodone bitartrate and paracetamol [5, 20, 35]. This study aims to provide a comprehensive review of suzetrigine as an innovative tool in pain medicine, analyzing the molecular mechanisms[32, 40], clinical efficacy data from recent studies [29, 43], and potential public health implications regarding the reduction of opioid dependence [36, 37].

Pathophysiology of Pain and the Role of Voltage-Gated Sodium Channels

Nociception, the process by which the nervous system detects and encodes noxious stimuli, relies on the precise regulation of neuronal excitability [11, 23]. Key mediators of this process are voltage-gated sodium channels (NaV), which are responsible for the generation and propagation of action potentials in excitable cells. Understanding their specific distribution and function, particularly in the context of human neurobiology, has become the foundation for developing a new generation of analgesics, such as suzetrigine [8, 28].

The role of sodium channels in nociception

Sodium channels are complex polypeptides consisting of a pore-forming domain and voltage-sensing domains (VSD). In the context of pain conduction, the most important role is played by isoforms preferentially expressed in peripheral sensory neurons, known as nociceptors [23]. These isoforms perform complementary functions in the action potential cycle, and their dysregulation is often linked to various pain syndromes [11, 28].

Specifically, Na V1.7 acts as a "threshold channel" that amplifies small depolarizations induced by external stimuli, thereby facilitating the attainment of the excitability threshold [8, 23]. In contrast, Na V1.8 is responsible for the main rising phase of the action potential and plays a key role in transmitting high-frequency signals to the central nervous system, especially during sustained noxious stimulation [3, 27]. Meanwhile, Na V1.9 participates in establishing the resting membrane potential and modulating the overall excitability threshold of nociceptors [23].

The strategic targeting of Na V1.8 by suzetrigine allows for the selective inhibition of the "driving engine" of the action potential in pain-sensing neurons without affecting the "threshold-setter" Na V1.7, which is also present in the sympathetic nervous system and pancreas, or the Na V1.5 channels critical for cardiac conduction [3, 40, 41]. This distinction is

fundamental to the drug's safety profile, as it avoids the autonomic and cardiovascular side effects that hampered previous generations of sodium channel blockers [16, 27].

Specificity of human dorsal root ganglia (DRG)

Traditional pain research has relied on rodent models for decades; however, the success of suzetrigine highlights the importance of interspecies differences [8, 11]. The cell bodies of nociceptors are located in the dorsal root ganglia (DRG) and trigeminal ganglia (TG). Modern molecular profiling techniques and studies on tissues collected from human organ donors have revealed that gene expression in human DRGs exhibits unique characteristics that determine the efficacy of therapy [11, 23]. Crucial to the development of suzetrigine was the use of human recombinant channels and DRG neurons, as this drug does not exhibit inhibitory activity against Na V1.8 channels in non-primate species [8, 32]. This "human-focused" approach allowed for the validation of a therapeutic target that, in humans, is directly linked to rare genetic conditions, such as congenital insensitivity to pain [11, 23]. The translational success of VX-548 confirms that targeting human-specific isoforms of sodium channels in their native cellular environment, the human DRG, is a superior strategy for drug discovery compared to traditional animal-based screening [27, 32]. This shift towards precision medicine ensures that the analgesic effect observed in pre-clinical human models translates more reliably into clinical efficacy during Phase 2 and 3 trials [5, 20].

Why is the NaV1.8 sodium channel key for therapy?

The Na V1.8 channel, encoded by the *SCN10A* gene, has become a priority therapeutic target due to several fundamental factors [11, 23]. Unlike other subtypes, such as Na V1.1 (critical for brain function) or Na V1.5 (essential for cardiac rhythm), Na V1.8 is not significantly present in the central nervous system, autonomic neurons, or cardiac muscle. This restricted expression profile ensures that selective inhibitors of this channel possess a wide therapeutic window and minimal risk of systemic adverse effects [3, 27].

Furthermore, NaV1.8 belongs to the tetrodotoxin-resistant (TTX-R) channels. Its unique kinetics, characterized by rapid recovery from inactivation and relatively slow inactivation at depolarized potentials, allow for the maintenance of high-frequency nociceptor firing even in inflammatory states [11, 27]. This makes it an ideal point of intervention for acute pain management, where nociceptors are in a state of hyper-excitability [32, 38].

The pharmacological efficacy of suzetrigine is further enhanced by its binding to the VSD2 voltage-sensor domain, which stabilizes the channel in the closed (resting) configuration [40, 41]. This allosteric mechanism is superior to traditional pore-blocking because it is highly selective and state-dependent. Physiological studies conducted at 37°C have confirmed that this

blockade is durable and effective even during physiological action potentials, effectively preventing the transmission of pain signals from the periphery to the spinal cord [3, 27]. By "silencing" the signal at its source, suzetrigine avoids the central side effects and addiction risks associated with opioids [6, 18].

Molecular Mechanism and Target Selectivity

Suzetrigine, developed by Vertex Pharmaceuticals under the code VX-548, is a first-in-class molecule that has received FDA approval as a highly selective inhibitor of the voltage-gated sodium channel Na V1.8 [4, 9]. The foundation of its pharmacology lies in the precise targeting of the action potential generation mechanism within peripheral nociceptive neurons [32].

As noted by Xie et al. (2026), sodium channels transition through three primary conformational states: resting, activated, and inactivated. Their proper function depends on the movement of S4 helices within the Voltage-Sensing Domains (VSD) [41]. Suzetrigine exhibits a unique mechanism of action by binding to the VSD2 voltage-sensor domain of the Na V1.8 channel. This allosteric interaction stabilizes the channel in its closed (resting) state, effectively preventing it from opening in response to membrane depolarization, thereby interrupting pain signal transmission at the peripheral level [3, 40].

A key aspect of suzetrigine's pharmacology is its unprecedented selectivity, exceeding 31,000-fold affinity for Na V1.8 compared to other sodium channel isoforms, such as the cardiac-expressed Na V1.5 or the widely expressed Na V1.7 [3, 27]. This high degree of selectivity results from the utilization of specific structural differences in the binding pockets of the VSD domains, identified through advanced research using cryogenic electron microscopy (cryo-EM) [40, 41].

Unlike non-selective pore blockers, such as lidocaine or bupivacaine, suzetrigine does not block ion flow across all sodium channels indiscriminately. This avoids common pitfalls of earlier therapies, such as cardiotoxicity, drubbability issues, and adverse effects related to the central nervous system (CNS) [16, 28]. Consequently, suzetrigine offers a wide therapeutic window, enabling effective analgesia with minimal systemic risk [18, 24].

Pharmacokinetics, Absorption, and Distribution

The pharmacokinetic profile of suzetrigine has been optimized for the rapid management of moderate-to-severe acute pain [32, 40]. The drug is administered orally, and its formulation allows for the swift attainment of therapeutic plasma concentrations. In pivotal Phase 3 clinical trials, a dosing regimen was employed featuring a 100 mg loading dose, which facilitates the saturation of peripheral receptors and achieves an analgesic effect in a short timeframe [5, 7]. Data indicate that the median time to meaningful pain relief is approximately two hours,

providing a rapid onset comparable to traditional interventions [20, 35]. Maintenance doses of 50 mg administered every 12 hours ensure stable drug levels in the body, which is critical for treating postoperative pain, such as following abdominoplasty or bunionectomy procedures [5, 29].

The distribution of suzetrigine is strictly limited to the periphery, representing one of its most significant advantages over traditional analgesics [3, 30]. Due to its specific chemical structure and physicochemical properties, the VX-548 molecule exhibits minimal ability to cross the blood-brain barrier [27, 41]. The lack of significant activity in the central nervous system (CNS) eliminates the risk of psychotropic symptoms, sedation, and respiratory depression—major limitations of opioid therapy [18, 19].

Furthermore, suzetrigine does not show affinity for μ-opioid receptors (MOR), meaning its analgesic effect is entirely independent of the brain's reward system [15, 30]. This eliminates the risk of physical dependence, drug tolerance, and potential for abuse, establishing suzetrigine as a cornerstone of modern, safe multimodal analgesia [6, 37]. The "periphery-restricted" nature of the drug ensures that pain signaling is interrupted at the level of the dorsal root ganglia (DRG) before reaching the central pathways [11, 23].

Metabolism, Excretion, and Safety Profile

Suzetrigine is primarily metabolized in the liver, with clinical data indicating a predictable metabolic profile and a low risk of drug-drug interactions [32, 40]. In contrast to earlier sodium channel inhibitor candidates, such as the occasionally hepatotoxic Na V1.7 inhibitors, VX-548 demonstrated an excellent tolerability profile in Phase 3 trials [12, 28]. The incidence of serious adverse events in the treated groups was comparable to that of the placebo group [5, 43].

The most commonly reported mild symptoms, such as headache, nausea, and transient constipation, did not deviate from standards observed in clinical trials of other non-opioid medications [20, 35]. Laboratory parameter analyses confirmed no significant impact on liver enzymes or renal function at therapeutic doses [12]. While rare cases of transient creatine phosphokinase (CPK) elevation were recorded, they were of no clinical significance and did not lead to treatment discontinuation [20, 35].

The safety of suzetrigine also extends to the cardiovascular system. Due to the aforementioned 31,000-fold selectivity over the Na V1.5 isoform—responsible for action potential initiation in cardiomyocytes—suzetrigine does not affect intracardiac conduction or prolong the QT interval [3, 27]. This is a crucial distinction from Class IB antiarrhythmic drugs (e.g., mexiletine), which, although used off-label for neuropathic pain, carry significant risks of arrhythmia [28, 33].

Suzetrigine is eliminated via both renal and biliary pathways, making the drug suitable for a broad patient population [32, 40]. However, in accordance with safety guidelines, caution is advised and dose adjustments may be necessary in patients with severe hepatic impairment (Child-Pugh C) [12, 18].

Structural Insights and Future Therapeutic Opportunities

The latest achievements in structural biology, described by Xie et al. (2026), shed new light on the future of suzetrigine's pharmacology and the entire class of Na V1.8 inhibitors [41]. The use of wild-type cryo-EM models enabled mapping of binding pockets and understanding of alpha-to-pi helical transitions in the S6IV segment, which shape pore geometry and influence the availability of conformational states for small molecules [40, 41]. Suzetrigine, a VSD-targeting molecule, paves the way for the design of even more precise allosteric modulators [27, 32].

Current evidence indicates that suzetrigine may become the "gold standard" for a new generation of analgesics that not only alleviate acute pain but may also find application in treating chronic nociplastic and neuropathic conditions [23, 38].

Furthermore, suzetrigine's pharmacology aligns with the concept of precision medicine. Since the expression of the NaV1.8 channel is dynamically regulated by inflammatory signals and mediators such as protein kinase C (PKC), suzetrigine may be particularly effective in inflammatory states in which this channel is overexpressed in nociceptors [11, 41].

The success of suzetrigine validates peripheral sodium channels as clinically actionable targets, which may lead to the development of combination therapies linking selective Na V1.8 inhibitors with low doses of drugs acting on other mechanisms, such as calcium channels or NMDA receptors, to achieve a synergistic analgesic effect [38, 41]. Such an approach represents a real opportunity for the complete displacement of opioids from many therapeutic protocols, marking a milestone in the fight against the global addiction crisis [19, 37].

Clinical Evidence: Efficacy and Safety

Phase 2 studies demonstrated that suzetrigine effectively reduces pain after bunionectomy and abdominoplasty surgery, achieving statistically significant improvement in the SPID48 (Sum of Pain Intensity Difference over 48 hours) scale compared to placebo [1, 20]. Early evidence from these trials also confirmed that the drug is well-tolerated and does not pose a risk of physical dependence or addiction [30, 35].

In the pivotal Phase 3 NAVIGATE-1 (bunionectomy) and NAVIGATE-2 (abdominoplasty) trials, suzetrigine showed a significant reduction in pain intensity compared to placebo, meeting the primary endpoints with high statistical significance [5, 7].

Clinical data indicate that suzetrigine achieves analgesic efficacy comparable to the hydrocodone/paracetamol combination, but with a significantly lower incidence of opioid-related adverse effects such as nausea, dizziness, or constipation [5, 43]. Meta-analyses of these trials emphasize that suzetrigine provides a rapid onset of action, with meaningful pain relief starting within the first two hours post-administration [29, 43].

Suzetrigine also exhibits broad therapeutic potential beyond postoperative acute pain. Recent studies on painful diabetic neuropathy (DPN) have shown a statistically significant reduction in chronic pain scores, suggesting that Na V1.8 inhibition is effective in states of chronic nerve sensitization [28, 38].

Preliminary data suggest that the drug may become a key non-opioid alternative in various models of pain, including dermatologic surgery and other minor or major surgical procedures, bridging the gap between simple analgesics and potent opioids [21, 33].

Common Adverse Events

In Phase 3 clinical trials, suzetrigine was generally well-tolerated, with the majority of adverse events being characterized as mild to moderate [5, 7]. The most frequently reported symptoms included headaches and nausea, which occurred at a frequency similar to the placebo group, as well as dermatological and muscular changes such as pruritus, rash, and transient muscle spasms [20, 35].

Regarding laboratory parameters, some cases of elevated serum creatine phosphokinase (CPK) levels were recorded; however, these were transient and not associated with clinical muscle injury or the need for drug discontinuation [29, 35].

Most importantly from a clinical safety standpoint, the selective mechanism of action on peripheral Na V1.8 channels ensures that suzetrigine does not cause respiratory depression, sedation, or excessive somnolence [18, 19]. This is a direct consequence of its over 31,000-fold selectivity and its lack of affinity for opioid receptors, which completely decouples analgesia from the risk of CNS-mediated side effects [3, 30]. Systematic reviews confirm that the overall safety profile of suzetrigine is significantly more favorable than that of traditional opioid-combination therapies, positioning it as a safer alternative in both surgical and outpatient settings [29, 43].

Hepatotoxicity and Physical Dependence

According to 2025 LiverTox data, suzetrigine is characterized by a very low risk of liver injury, with the frequency of elevated aminotransferase activity during therapy being below 1% [12]. No cases of clinically apparent liver injury, jaundice, or drug-related organ failure were reported,

leading to a Likelihood score of E, which indicates no evidence of hepatotoxicity in clinical settings [12, 18].

However, as suzetrigine is primarily metabolized in the liver, caution is advised and dose adjustments may be necessary in patients with advanced Child-Pugh C liver disease, where drug clearance may be impaired [12, 40].

A crucial aspect of suzetrigine's pharmacology is the complete lack of addictive potential [18, 30]. Unlike morphine or hydrocodone, suzetrigine does not cross the blood-brain barrier in significant amounts and shows no affinity for μ-opioid receptors, which means its analgesic effect is entirely independent of the brain's reward system [15, 30].

Abrupt discontinuation of the drug does not induce withdrawal symptoms, making it a safe option for short-term acute pain management [18, 30]. Animal models showed no stimulating or sedative effects, and human studies confirmed that events related to abuse potential were minimal and comparable to placebo [30, 42]. By stabilizing sodium channels at the periphery, suzetrigine interrupts pain signals without affecting the psychological pathways associated with dependence [11, 42].

Clinical Applications in Special Populations and Settings

Suzetrigine represents a breakthrough in emergency medicine, offering analgesic efficacy comparable to hydrocodone/paracetamol without the risk of respiratory depression, euphoria, or sedation [42, 45]. The oral administration route allows for rapid treatment implementation in trauma patients and safe discharge without concerns regarding addictive potential, aligning with modern clinical guidelines aimed at reducing opioid prescriptions in emergency departments [10, 45].

Furthermore, use in the pediatric population is gaining early and promising clinical evidence. A notable case report involving a 16-year-old boy with hereditary neuropathy demonstrated that a 14-day treatment with suzetrigine provided excellent postoperative pain control without adverse effects [34].

In this instance, pain scores intensified rapidly upon drug discontinuation, confirming the drug's efficacy in addressing the specific mechanism of neuropathic pain and opening the way for further research on rare channelopathies and acute pain management in children [26, 34].

Beyond acute and pediatric care, suzetrigine is being evaluated for its role in serious illness and palliative care settings [13, 44]. In healthcare systems where opioid access is restricted or where patients are highly susceptible to opioid-related side effects (such as the elderly), suzetrigine offers a vital therapeutic alternative that maintains quality of life without compromising safety [13, 31].

Budget Impact and Healthcare Systems

The introduction of suzetrigine into medical practice, despite its higher unit price compared to generic opioids, shows potential for generating significant savings across healthcare systems [36, 37]. A comprehensive budget impact analysis for a population of 1 million Medicaid-insured patients demonstrated that suzetrigine could bring savings of $827 per treated patient within the first two years of implementation [36].

Although direct drug expenditures increase, these costs are more than offset by avoiding the management of typical opioid-related adverse events (ORAEs). Specifically, reducing cases of opioid-induced nausea, vomiting, and constipation can save between $0.5 and $1.5 million for a large payer [31, 36].

The greatest financial and social impact stems from the prevention of opioid use disorders (OUD). Replacing opioids with suzetrigine in the acute phase is estimated to prevent expenditures of $3.1–9.3 million related to long-term addiction treatment, rehabilitation, and emergency hospitalizations [36, 37].

From a broader societal perspective, which includes indirect costs such as loss of productivity and caregiver burden, the total projected savings increase to $2,639 per patient [36]. These findings position suzetrigine not just as a clinical breakthrough, but as an economically justified intervention that addresses the root causes of the financial burden associated with the opioid crisis [6, 36].

Conclusion

The FDA approval of suzetrigine (VX-548) in early 2025 marks a transformative milestone in pain medicine, ending a 25-year hiatus in the discovery of new analgesic classes for acute pain [9, 14]. By selectively targeting the Na V1.8 voltage-gated sodium channel, suzetrigine addresses the fundamental pathophysiology of pain at its peripheral source, preventing the generation of pain signals before they reach the central nervous system.

The clinical evidence from Phase 3 trials (NAVIGATE-1 and NAVIGATE-2) confirms that suzetrigine provides robust, statistically significant pain relief comparable to traditional opioid-combination therapies, but with a vastly superior safety profile. Its lack of affinity for opioid receptors and minimal penetration of the blood-brain barrier effectively eliminates the risks of addiction, tolerance, and respiratory depression, which have fueled the global opioid crisis.

From a structural and pharmacological perspective, suzetrigine’s high selectivity (over 31,000-fold) ensures a wide therapeutic window, protecting patients from the cardiotoxic and neurotoxic effects associated with non-selective sodium channel blockers. Furthermore, the drug’s predictable pharmacokinetics and low risk of hepatotoxicity make it a versatile tool for

diverse clinical settings, from post-surgical wards and emergency departments to specialized pediatric and palliative care.

In conclusion, suzetrigine is not merely an alternative analgesic, it represents a paradigm shift toward precision, non-opioid multimodal analgesia. Its implementation into clinical protocols offers a dual benefit: improving patient outcomes through effective, side-effect-free pain control and providing significant economic relief to healthcare systems by reducing the long-term costs associated with opioid dependence. As future research explores its efficacy in chronic and neuropathic pain states, suzetrigine stands as the cornerstone of a new era in pain management.

DISCLOSURE

Supplementary materials:

Not applicable.

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All authors have read and agreed to the published version of the manuscript.

Funding Statement:

The study did not receive special funding.

Institutional Review Board Statement:

Not applicable.

Acknowledgements:

Not applicable.

Conflict of Interest Statement:

The authors of the paper report no conflicts of interest.

Data Availability Statement:

The data presented in this study are available upon request from the correspondent author.

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