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Motion Sickness: Current Pharmacological Treatment Strategies and the Emerging Role of Tradipitant

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Abstract

Background. Motion sickness is a prevalent clinical syndrome triggered by sensory conflict, causing severe autonomic distress. While legacy treatments (anticholinergics and antihistamines) effectively manage symptoms, they cause a debilitating "pharmacological hangover" characterized by severe sedation and cognitive impairment.

Aim. This review evaluates tradipitant, a selective neurokinin-1 (NK1) receptor antagonist, investigating if targeting the Substance P pathway provides robust emetic protection without the functional decline of traditional therapies.

Material and methods. A narrative review of PubMed, Google Scholar, Embase, ClinicalTrials, and FDA databases was conducted to analyze tradipitant's pharmacology, efficacy, and safety, emphasizing Phase 2 (Motion Sifnos) and Phase 3 (Motion Syros, Serifos) trials.

Results. Tradipitant competitively inhibits Substance P in brainstem emetic centers without binding to histaminergic or cholinergic receptors. Sifnos data demonstrated a 78% relative risk reduction in vomiting during rough seas. Syros confirmed significant reductions in primary and repeated vomiting across varying sea intensities. Somnolence rates remained low (6–12%), successfully decoupling anti-emetic protection from cognitive impairment, though mild-to-moderate nausea sometimes persisted.

Conclusions. Representing the first major motion sickness advancement in 40 years, tradipitant’s targeted, non-sedating profile preserves physical comfort and cognitive clarity. It addresses a critical unmet need for travelers, though further multi-environment research is warranted.

Key words: Motion sickness, Tradipitant, Neurokinin-1 receptor antagonist, Substance P, Emesis

1. Introduction

Although motion sickness is often viewed as a modern inconvenience associated with cars and digital screens, it is a physiological challenge that has been documented in medical literature for over 2,000 years. Starting with the Greek physician Hippocrates, who observed that “sailing on the seas proves that motion disorders the body”, the condition has historically functioned as a strategic “plague at sea” capable of deciding naval conflicts and land-based

military campaigns alike (Huppert, Benson & Brandt, 2017; Golding, 2016). In contemporary medicine, motion sickness represents a prevalent and multifaceted clinical syndrome triggered by a discordance between actual and perceived movement. Its clinical profile is notably broad, encompassing a spectrum of gastrointestinal distress, central nervous system impairment, and autonomic dysfunction. Furthermore, human sensitivity to these triggers is highly unique; while some individuals experience profound incapacitation from even minor stimuli, others demonstrate a robust resilience, requiring extreme levels of provocation before symptoms manifest (Koch et al, 2018). This paper summarizes existing pharmacological treatments for motion sickness. Furthermore, it explores the potential of tradipitant, a selective NK1 receptor antagonist, as a new therapeutic option.

2. Research materials and methods

This narrative review investigates the clinical potential of tradipitant as a novel intervention for motion sickness. To identify relevant data, a structured search was performed across the PubMed, Google Scholar, Embase, Clinical Trials and FDA databases, prioritizing research on the pharmacology, efficacy, and safety of this neurokinin-1 (NK1) receptor antagonist. Special attention was given to the primary outcomes of the Phase 2 trial: Motion Sifnos (Polymeropoulos et al, 2020) and Phase 3 trials: Motion Syros, Motion Serifos (Polymeropoulos et al, 2025; Vanda Pharmaceuticals Inc, 2025). The gathered literature was evaluated based on study architecture, participant demographics, and key clinical endpoints, such as the reduction of emesis and nausea severity. By assessing these findings and their methodological constraints, this review synthesizes the existing evidence to determine the prospective role of tradipitant in the modern management of travel-related vestibular distress.

2.1 AI.

In this study, AI (Gemini - Google) was utilized for two primary purposes: analysing clinical reasoning narratives to identify linguistic patterns associated with logical fallacies, and refining the academic English of the manuscript to ensure grammatical accuracy, stylistic consistency, and clarity. It is important to emphasize that Gemini was employed strictly as an assistive instrument under direct human supervision. All final interpretations of the results, classification of errors, and overarching conclusions were determined solely by human experts in clinical medicine and formal logic. Gemini served primarily to enhance efficiency in data processing, pattern recognition, and linguistic presentation, and did not replace human judgment at any stage of the analytical process.

3. Research results

3.1. Pathophysiology and Etiology of Motion sickness.

Maintaining body orientation and tracking physical movement depends on a constant stream of data from three primary sources: vestibular (balance), somatosensory (touch and pressure), and visual inputs (de Haan & Dijkermann, 2020). Under normal conditions, these channels work in harmony to provide a clear picture of motion. The semicircular canals within the inner ear detect angular rotation, while the otolith organs (the saccule and utricle) measure linear acceleration and the pull of gravity. Simultaneously, proprioceptive afferents from the neck and joints report the body's exact posture and position (Koch et al, 2018; Bertolini & Straumann, 2016). The brainstem and cerebellum act as a central processing unit, merging these signals and weighing them based on their reliability to create an accurate estimate of movement (Purves, Augustine & Fitzpatrick, 2001).

The most widely accepted explanation for why this system fails is the "sensory conflict and neural mismatch" model, first proposed by Reason and Brand. This theory suggests that motion sickness symptoms emerge when incoming sensory data is incongruent or deviates from the brain's "internal model"—the expectations built from previous experience (Reason & Brand, 1975).

In many modern environments, this system faces a challenge it had not evolved to handle passive, artificial motion. When traveling by sea or road, the body is moved by an external force rather than its own muscles, producing stimuli that the brain cannot easily reconcile. For example, the vestibular system often cannot distinguish between the tilt of a ship and the force of gravity, while the visual system may struggle to separate the movement of the vehicle from the movement of the environment. When these sensory channels provide clashing information, the central nervous system cannot solve the conflict using its stored internal models. This "unnatural" mismatch triggers a stress response, leading to the autonomic distress and nausea characteristic of the syndrome (Gupta et al, 2021).

The model organizes these discrepancies into two distinct groups based on the specific sensory systems involved in the disagreement. Category A, defined as inter-sensory conflict, involves a visual-vestibular mismatch that arises when there is a lack of harmony between what the eyes see and what the vestibular system feels, such as during simulator sickness or while reading in a moving car. In contrast, Category B describes intra-vestibular conflict, which is an internal inner ear mismatch occurring when the semicircular canals responsible for detecting

rotation provide information that conflicts with the otolith organs that monitor linear movement and gravity (Bertolini & Straumann, 2016).

3.2. Epidemiology and Individual Susceptibility of Motion Sickness

While almost any individual with a functioning vestibular system can experience motion sickness, thresholds vary significantly (Golding, 2006). A functioning inner ear is a requirement, as patients with a total loss of labyrinthine function are entirely immune (Golding, 2016; Lackner, 2014). Beyond this baseline, several factors including age, sex, genetics, and physical fitness influence risk. Infants under 2 years of age are typically unaffected, but susceptibility rises and peaks between ages 7 and 12 before declining through adulthood, likely due to habituation. While elderly individuals are generally the least affected, a small minority may see increased sensitivity in old age.

Surveys show women are more susceptible than men, though this effect is smaller than that of age. This sensitivity correlates with hormonal fluctuations including pregnancy, the menstrual cycle, cortisol levels, and the use of oral contraceptives which complicates a simple association with biological sex. Genetics and medical history also play a role, as twin studies suggest that 55 to 70 percent of individual variation is hereditary and involves multiple genes. Furthermore, those with a history of migraines, vertigo, or vestibular disorders are significantly more prone to symptoms. Finally, high levels of aerobic fitness may surprisingly increase susceptibility, potentially due to a more reactive autonomic nervous system (Golding, 2025; Golding, 2006; Koch et al, 2012).

3.3. Clinical Manifestations and Symptoms of Motion Sickness

The transition from sensory conflict to physical illness is managed by a complex neural network where the vestibular nuclei serve as the primary integration centre. These nuclei are modulated by a diverse array of neurotransmitters, including histamine, acetylcholine, dopamine, serotonin, and substance P, which act as chemical messengers to signal distress (Takeda et al, 2001). From this central hub, signals are transmitted through several key projections that determine the clinical presentation of the syndrome. Ascending projections reach the thalamus and cortex to process the conscious sensations of dizziness and spatial disorientation, while signals sent to the hypothalamus and autonomic centres trigger involuntary "fight or flight" responses such as cold sweats, pallor, and fluctuations in heart rate. Simultaneously, a specialized network in the brainstem, centred around the nucleus tractus

solitarii, serves as a central switchboard for the body's physical reactions. This area integrates inputs from the vestibular system and the gastrointestinal tract alongside data from the area postrema, which acts as the brain's chemical detector for potential toxins. Once the underlying sensory conflict crosses a critical physiological threshold, this integrated system initiates the physical reflex of vomiting. (Golding, 2016; Dieterich & Brandt, 2008; Yates et al, 2014). Consequently, motion sickness manifests as a multifaceted clinical syndrome that extends far beyond simple nausea, typically following an inciting movement and varying in its physiological impact. The resulting autonomic and gastrointestinal symptoms often include retching, increased salivation, and a total loss of appetite, which are frequently accompanied by vasomotor responses such as facial pallor and feelings of excessive warmth. Furthermore, neurological distress including dizziness, vertigo, headaches, and hyperventilation completes the clinical profile, reflecting the widespread and systemic nature of the body's response to perceived motion discordance (Leung & Hon, 2019; Lackner, 2014).

A distinct clinical subset of motion sickness is the Sopite Syndrome, which focuses on profound drowsiness and fatigue. This syndrome can occur even in the absence of nausea and is often the only remaining symptom once an individual has "adapted" to a moving environment. Key indicators include frequent yawning and persistent sleepiness, physical and mental disinclination for work apathy, irritability and social withdrawal (Matsangas & McCauley, 2014; Graybiel & Knepton, 1976; Foster et al, 2020).

4. Current Pharmacological Management of Motion Sickness

Pharmacological intervention is primarily indicated for individuals for whom natural habituation is unfeasible, such as during infrequent or short-term travel. For maximum efficacy, medications must be administered prophylactically; once the clinical symptoms of motion sickness are established, the resulting gastric stasis often impairs the absorption of oral drugs, rendering them significantly less effective. A defining characteristic of all successful anti-motion sickness agents is their ability to cross the blood-brain barrier to exert a central effect on the vestibular nuclei and the vomiting centre. There are at least 9 different groups of drugs used with various effect, although most commonly used drugs against MS are included within two groups: anticholinergic, antihistamine. Beyond the primary drug classes, various other approaches have been explored. The list includes dopamine antagonists (metoclopramide), 5-HT1B/1D receptor agonist (Rizatriptan), sympathomimetics (D-amphetamine), neuroleptics, (phenytoin, baclofen), calcium channel blocker (flunarizine), μ-Opiate receptor agonist

(loperamide), hormones (dexamethasone) and many combinations of those presented above. While these options exist, they lack the reproducible data required for broad use and present specific limitations of their own. (Zhang et al, 2016; Golding, 2025)

4.1 Anticholinergics

Scopolamine (hyoscine) remains the most effective prophylactic agent for motion sickness. It functions as a non-selective muscarinic antagonist, primarily inhibiting sensory inputs to the vestibular nuclei. While it binds to all five muscarinic receptor subtypes (M1-M5), research using selective antagonists like zamifenacin suggests that its therapeutic effects are largely driven by M3 and M5 antagonism. (Zhang et al, 2016; Golding & Stott, 1997; Schmäl, 2013).

Its utility depends heavily on the route of administration. Transdermal (TTS) - the most common form, these patches provide 72 hours of protection. However, they require application to the mastoid area 4–8 hours before travel to ensure therapeutic plasma levels. Intranasal (IN) - developed for high-performance environments (e.g., by NASA), nasal gels and aerosols offer faster absorption and higher peak concentrations than oral or transdermal routes. Crucially, this method provides predictable efficacy without significant cognitive or sedative impairments (Simmons et al, 2010). Oral - while effective, oral bioavailability is variable and can be increased by grapefruit juice, which inhibits the enzymes responsible for its metabolism (Schmäl, 2013).

Scopolamine's non-selective nature frequently causes dry mouth, blurred vision, and drowsiness. More severe risks include acute angle-closure glaucoma, urinary retention, and confusion. Consequently, it is contraindicated for children under 12 and must be used with extreme caution in elderly populations. (Ghossein, Kang & Lakhkar, 2023; Takov & Tadi, 2023).

4.2 Antihistamines

The therapeutic use of antihistamines for motion sickness began in 1949 with the discovery that dimenhydrinate could effectively prevent seasickness. (Gay & Carliner, 1949). First-generation H1-antihistamines represent a primary therapeutic choice for the management of motion-induced vertigo, nausea, and vomiting, with clinical preference generally given to agents that offer the lowest possible sedative potential. Unlike the newer, "non-sedating" second-generation antihistamines, such as cetirizine or fexofenadine, which are excluded from the central nervous system, first-generation H1 antagonists readily penetrate the blood-brain barrier (Cheung, Heskin & Hofer, 2003; Seibel et al, 2002; Buckey, Alvarenga & MacKenzie, 2007). To be effective, these medications must act directly within the central nervous system. They function by dampening the nerve signals sent from the inner ear's semicircular canals and suppressing the histaminergic activity in the hypothalamus (Zhang XY, et al, 2013).

Evidence suggests that drugs such as dimenhydrinate, meclizine, and cinnarizine focus their action on the medial vestibular nucleus (MVN). Because this area serves as the brain's primary "switchboard" for balance and contains a high concentration of H1 and H2 receptors, it is particularly responsive to these antihistaminergic effects (Zhou L et al, 2013).

The clinical selection of an antihistaminic drug often depends on the dosage form, the desired duration of action, and the acceptable level of sedation for the user. Dimenhydrinate and diphenhydramine represent the most common over-the-counter options, with dimenhydrinate frequently utilized in sublingual or chewing gum formulations to accelerate absorption and bypass gastrointestinal distress (Murdin, Golding & Bronstein, 2011; Seibel et al, 2002). For those requiring day-long protection, meclizine is often favoured due to its longer half-life; while it remains sedating, recent suspension formulations have been developed to provide a more rapid onset compared to traditional tablets (Wibble et al, 2020; Wang Z et al, 2012). Cinnarizine is notable for its high efficacy and relatively low sedative profile, functioning as both an antihistamine and a calcium channel blocker. This dual action allows it to suppress the vestibular system more comprehensively than many other agents, and it is frequently combined with dimenhydrinate to achieve a synergistic effect that dampens sensory conflict signals more effectively than either medication used alone (Kirtane et al, 2019). Finally, recognized as one of the most potent H1 antagonists, promethazine provides a global suppression of the vestibular system. It is a mainstay in space medicine, where it is often administered intramuscularly to astronauts, though its profound sedative effects frequently

require pairing it with stimulants like caffeine or d-amphetamine to maintain operational performance (Cowings et al, 2000; Huang M, 2012).

Recent research has expanded beyond the H1 receptor, identifying H3 and H4 receptors as potential therapeutic targets. Betahistine, a weak H1 agonist and H3 antagonist, has shown promise in increasing tolerability to motion by reducing histamine release in the medial vestibular nucleus (Wang et al, 1995; Matsnev & Sigaleva, 2007). Additionally, H4 receptor antagonists have demonstrated an inhibitory effect on primary vestibular neurons in animal models, offering a path for future drug development (Desmadryl et al, 2012). From a clinical standpoint, a recent systematic review involving 658 participants confirmed that first-generation antihistamines are significantly more effective than placebos, preventing symptoms in roughly 40% of susceptible individuals compared to 25% for the placebo group. While their efficacy is comparable to scopolamine, the trade-off remains the high incidence of side effects. Sedation is the primary complication, affecting approximately 66% of users, followed by dry mouth and, less frequently, blurred vision. (Karrim et al, 2022).

As with anticholinergics, these medications are most effective when taken 30 to 60 minutes before exposure, as they are less successful at resolving symptoms once nausea and gastric stasis have already commenced.

4.3 Other Drugs

Sympathomimetics such as d-amphetamine and ephedrine have long been recognized for their synergistic effects when paired with scopolamine or promethazine. By stimulating dopaminergic and noradrenergic pathways, these drugs can counteract the profound sedation and cognitive impairment caused by primary treatments. Historically, the combination of scopolamine and d-amphetamine has been regarded as one of the most effective anti-motion sickness regimens available. However, due to the high risk of drug dependence and legal restrictions, their use is largely confined to specialized environments, such as space flight and military operations (Wood et al, 1966; Zhang LL et al, 2016).

It is a common clinical misconception that any potent anti-nausea medication will treat motion sickness. However, agents such as 5-HT3 antagonists (e.g., ondansetron) and dopamine D2 antagonists (e.g., metoclopramide) are generally ineffective. While these drugs are highly successful in treating chemotherapy-induced or postoperative nausea, they target the gastrointestinal tract and the area postrema rather than the central vestibular nuclei (Wang & Dutia, 1995; Zhang LL et al, 2016; Carlisle & Stevenson, 2017; Hershkovitz et al, 2009).

For patients seeking alternative or non-synthetic options, ginger (Zingiber officinale) has shown potential as a local antiemetic (Chrubasik et al, 2005; Palatty et al, 2013). Additionally, high-dose Vitamin C has been studied for its potential antihistaminergic properties, which may reduce symptoms in some travellers (Jarisch et al, 2014). While cannabis and its constituent delta-9-THC have shown anti-motion sickness properties in animal models, a lack of controlled human trials means no firm clinical recommendation can yet be made (Cluny et al, 2008; Bolognini et al, 2013).

5. Tradipitant: A Novel Approach Targeting the Neurokinin-1 (NK1) Receptor in the Management of Motion Sickness

5.1 Mechanism of action

Representing the first significant advancement in motion sickness pharmacology in more than 40 years, tradipitant offers a highly specialized therapeutic profile that addresses the limitations of conventional treatments. As a selective, high-affinity antagonist of the human neurokinin-1 (NK1) receptor, the drug precisely targets the Substance P signalling pathway at its neurochemical origin (Polymeropoulos et al, 2020).

A defining clinical advantage of tradipitant is its exceptional molecular selectivity; unlike traditional multi-receptor therapies, it demonstrates no significant affinity for serotonin (5-HT3), dopamine (D2), cholinergic, or histamine (H1) receptors. This specificity allows for the robust prevention of emesis while bypassing the heavy sedation and anticholinergic toxicity frequently described as a "hangover effect" associated with older, less targeted medications (Polymeropoulos et al, 2025).

The drug effectively neutralizes the emetic reflex by intervening at the site of sensory integration within the central nervous system. In response to provocative motion, the neuropeptide Substance P is released within the brainstem to signal distress. Tradipitant successfully crosses the blood-brain barrier to act as a competitive inhibitor, physically occupying NK1 receptors in critical regulatory areas such as the nucleus tractus solitarii (NTS) and the area postrema. By preventing Substance P from binding to these receptors, tradipitant silences the primary neurological signal required to initiate the vomiting cascade, thereby preserving both physical comfort and cognitive clarity for the traveller (Carlin et al, 2024).

The therapeutic versatility of this mechanism is further supported by clinical investigations into other emetic conditions, such as chemotherapy-induced emesis and gastroparesis. In studies involving patients with idiopathic and diabetic gastroparesis,

tradipitant has demonstrated the potential to significantly improve nausea severity. Pharmacokinetic exposure-response analyses from these trials indicate that the drug's efficacy is closely tied to achieving adequate blood levels; when therapeutic exposure is maintained and confounding factors are controlled, the blockade of the NK1 pathway consistently alleviates distress. These findings reinforce that tradipitant serves as a robust, broad-spectrum anti-emetic that effectively modulates nauseogenic pathways across diverse clinical presentations (Saito et al, 2003; Carlin et al, 2024).

5.2 Clinical efficacy

The clinical efficacy of tradipitant has been rigorously evaluated through the studies including two key Phase 3 trials – Motion Syros and Motion Serifos. These trials were designed to address the significant limitations of current therapies, which often provide inadequate relief or cause dangerous side effects like severe sedation and cognitive impairment.

The foundational evidence for tradipitant's efficacy was established in the Motion Sifnos study (2020), a randomized, double-blind, placebo-controlled trial involving 126 adults with a history of motion sickness. This trial served as a critical proof-of-concept, conducted during seven boat trips on the Pacific Ocean. Participants were randomized 1:1 to receive a single 170 mg dose of tradipitant or a placebo. The environmental stimulus was specifically chosen to reflect the most provocative vertical sinusoidal oscillations (heave), with wave frequencies ranging from 0.09 to 0.20 Hz. The incidence of vomiting across all trips was significantly lower in the tradipitant group (17.5%) compared to the placebo group (39.7%, p=0.0039). In trips exposed to rough sea conditions (peak wave heights ≥1 meter), the therapeutic effect was most pronounced. The incidence of vomiting in the placebo group reached 72.22%, while the tradipitant group remained remarkably stable at 15.79% (p=0.0009). Tradipitant demonstrated a 78% relative risk reduction (RRR) in vomiting during high-provocation scenarios (Polymeropoulos et al, 2020).

Building upon the Sifnos trial, the Motion Syros (2025) study represented a pivotal expansion of clinical evidence. This larger trial involved 365 participants across 34 boat trips in diverse U.S. coastal waters, reinforcing the drug's efficacy across broader geographical locations and variable sea conditions. Motion Syros evaluated both the 85 mg and 170 mg doses of tradipitant, confirming that both strengths were superior to placebo in high provocation environments. A critical finding from this expansion was the drug's ability to prevent multiple episodes of vomiting. Repeated emesis poses a severe clinical risk, including dehydration and

electrolyte imbalance. Placebo: 31.1% experienced multiple vomiting episodes. Tradipitant 170 mg: 10.8% experienced multiple episodes (p=0.0001). Tradipitant 85 mg: 13.8% experienced multiple episodes (p=0.0011). This reduction in repeated emesis highlights the drug's utility in maintaining the physiological stability of travelers during long-duration journeys (Polymeropoulos et al, 2025).

Collectively, these trials demonstrate that tradipitant provides a robust and predictable protective effect. Unlike traditional antihistamines or anticholinergics, which often fail as environmental stressors (like wave height) increase, tradipitant's efficacy remains consistent. Across both studies, the incidence of vomiting in tradipitant participants remained consistently low (roughly 15–20%) regardless of whether sea conditions were calm or rough. Furthermore, tradipitant was well-tolerated; somnolence was reported by fewer than 10% of participants, a stark contrast to the heavy sedation associated with legacy medications. By effectively decoupling anti-emetic efficacy from cognitive impairment, tradipitant addresses the "unmet need" for a motion sickness therapy that preserves both physical comfort and operational performance (Polymeropoulos et al, 2025; Polymeropoulos et al, 2020).

5.3 Safety and Tolerability

The safety and tolerability of tradipitant have been extensively evaluated through cllinical trials, including Phase 3 trials: Motion Syros and Motion Serifos.

Data from these trials indicate that tradipitant is generally well-tolerated. In the motion sickness trials, the most common adverse reactions reported in at least 5% of subjects and at a higher frequency than placebo, included somnolence, headache, and fatigue. Specifically, somnolence occurred in 6% of the 85 mg group and 12% of the 170 mg group, compared to 4% and 6% in the respective placebo arms. Fatigue was noted in 6% of the 85 mg group and 8% of the 170 mg group. These findings highlight a favourable profile, particularly as the drug lacks the profound cognitive impairment and significant anticholinergic side effects found in legacy treatments like scopolamine or dimenhydrinate (Vanda Pharmaceuticals Inc, 2025).

The safety profile remained consistent when evaluated in chronic conditions such as gastroparesis. In a multicentre trial of patients with idiopathic or diabetic gastroparesis, 48.3% of the tradipitant group experienced treatment-emergent adverse events (TEAEs) compared to 45.1% in the placebo group. Discontinuation rates due to adverse events were low, occurring in approximately 5% of all subjects. The most frequent events in this population were diarrhoea, nausea, abdominal pain, dizziness, and headache, though these were rare and occurred at rates

similar to placebo. No deaths or serious safety concerns were identified in the evaluation phase, reinforcing the drug's utility for patients who may require treatment across varying clinical presentations. (Carlin et al, 2024).

From a clinical pharmacology perspective, tradipitant does not require dosage adjustments for patients with mild to moderate renal impairment, defined as an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m2. However, its impact on patients with severe renal impairment or any degree of hepatic impairment remains unknown and use in these populations should be avoided. Regarding drug interactions, tradipitant is a CYP3A4 substrate. While co-administration with midazolam or ethanol did not result in clinically significant changes to pharmacokinetics, clinicians should remain cautious when using tradipitant alongside strong CYP3A4 inhibitors (Vanda Pharmaceuticals Inc, 2025).

Nonclinical toxicology assessments further support the drug's safety. Tradipitant was found to be non-genotoxic across a battery of in vitro and in vivo assays, and no effects on fertility or reproductive performance were observed in animal models even at exposures exceeding the maximum recommended human dose. While long-term rat studies showed an increase in thyroid follicular cell tumours, these findings are considered rodent-specific due to hepatic enzyme induction and are not deemed relevant to human clinical use. Overall, tradipitant represents a significant therapeutic advancement, combining high molecular selectivity for the NK1 receptor with a safety profile that preserves the patient's physical and cognitive functional status. (Vanda Pharmaceuticals Inc, 2025).

6. Results

The clinical management of motion sickness has remained largely stagnant for over 40 years, relying on non-selective pharmacological agents that prioritize global vestibular suppression over molecular precision. As this review has demonstrated, the standard of care, primarily muscarinic antagonists and first-generation H1 antihistamines, effectively dampens sensory conflict but at a high functional cost. The high incidence of sedation, blurred vision, and cognitive impairment associated with these legacy therapies often mirrors the very incapacitation the drugs are intended to prevent. (Carlin et al, 2024). In this context, the development of tradipitant represents a paradigm shift, moving away from broad-spectrum receptor blockade toward the targeted inhibition of the neurokinin-1 (NK1) receptor.

The clinical efficacy data from the Motion Sifnos, Motion Syros, and Motion Serifos trials underscore the potency of NK1 receptor antagonism, particularly in high-provocation

environments. The ability of tradipitant to maintain a stable anti-emetic effect regardless of sea conditions, reducing vomiting risk by up to 78% compared to placebo in rough seas suggests that Substance P is a primary mediator of the emetic reflex when physiological thresholds are crossed. While traditional antihistamines often fail as the intensity of the stimulus increases, tradipitant's performance indicates that the "final common pathway" of the vomiting reflex in the brainstem can be effectively silenced through selective NK1 blockade (Polymeropoulos et al, 2025; Polymeropoulos et al, 2020; Vanda Pharmaceuticals Inc, 2025).

A notable nuance in the clinical data is the "nausea paradox". While tradipitant proved superior in preventing vomiting and severe nausea, it did not reach statistical significance in resolving mild-to-moderate nausea alone. This finding highlights the physiological complexity of the nausea-vomiting continuum; by preventing the physical act of emesis, which often naturally abates nausea, tradipitant may leave the underlying sensation intact for a longer duration, albeit at a non-severe level.

Furthermore, the decoupling of efficacy from sedation is the tradipitant's most significant achievement. With somnolence rates significantly lower than those of legacy treatments, tradipitant offers a clear advantage for "operational" travellers such as naval personnel and astronauts—who must maintain high levels of psychomotor performance. However, because this represents a novel therapeutic class with recent regulatory approval, additional research is required. Expanding the clinical dataset through longitudinal studies in aviation, commercial spaceflight, and virtual reality will be essential to fully characterize its utility. Dedicated investigations into pediatric populations and the impact of varying stimulus intensities will also be necessary to refine personalized dosing strategies.

7. Conclusion

Motion sickness remains a complex physiological challenge, yet therapeutic innovation has lagged modern travel demands. For decades, the trade-off for preventing vomiting was the acceptance of a "pharmacological hangover". Tradipitant effectively breaks this cycle. As a selective NK1 receptor antagonist, it provides a predictable, high-affinity blockade of the emetic signalling pathway, preserving both physical comfort and mental clarity. The robust results of the Sifnos and Syros trials confirm that tradipitant is superior to placebo across variable sea conditions and diverse adult populations. While its non-sedating safety profile positions it as the most significant advancement in vestibular pharmacology in the 21st century,

the novelty of this finding necessitates continued data collection. Future trials will be vital to validate these results in broader clinical contexts and to establish a more extensive safety record over time. As travel continues to evolve toward higher-speed and multi-modal environments, tradipitant offers a refined, targeted solution, provided that ongoing research continues to support its integration into standard medical practice.

Disclossure

The authors declares no competing interests

Supplementary Materials

Not Applicable

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