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Botanic Cannabinoids and the Endocannabinoid System: A Mechanistic Model for Motion Sickness Intervention

David A. Dawson *

Department of Research, Publication, and Education, AMCANN, LLLP (Independent Research Organization), Murrieta, California, USA.

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Abstract

Motion sickness is a highly prevalent condition characterized by nausea, vomiting, and autonomic symptoms triggered by sensory conflict between the vestibular and visual systems. Current pharmacological treatments, including anticholinergics and antihistamines, often produce undesirable side effects such as sedation and dry mouth, and do not address the underlying neurophysiological dysregulation. The endocannabinoid system is a key neuromodulator of stress responses, emesis control, and homeostatic balance. Evidence from parabolic flight studies indicates that motion-susceptible individuals exhibit reduced circulating anandamide levels and downregulation of CB1 receptor expression, suggesting that hypoactivity of the endocannabinoid system contributes to symptom development. This theoretical paper proposes that targeted modulation of the ECS via botanic cannabinoids—such as Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD)—and selected terpenes may restore ECS tone, attenuate vestibular hyperactivation, normalize gastric rhythm, and reduce motion-induced nausea. We outline a mechanistic model for cannabinoid intervention, discuss key phytochemical candidates, and identify biomarker-driven endpoints for future clinical studies.

Keywords: Motion sickness; Endocannabinoid system; Cannabinoid pharmacology; Nausea and emesis; Vestibular-autonomic integration; Botanic cannabinoids

1. Introduction

Motion sickness arises when incongruent signals from vestibular, visual, and proprioceptive systems trigger a mismatch between predicted and actual motion, activating brainstem emetic networks and producing nausea, vomiting, and dysautonomia. Pharmacologic countermeasures such as scopolamine and antihistamines can be effective but frequently cause sedation, dry mouth, or cognitive slowing, and they do not directly resolve the underlying neurophysiology. [1]

The endocannabinoid system, comprising CB1 and CB2 receptors, endogenous ligands (anandamide, 2-arachidonoylglycerol), and metabolic enzymes, acts as a homeostatic buffer across stress and emesis circuits. In a landmark human parabolic-flight study, volunteers who became motion-sick exhibited significantly lower endocannabinoid concentrations during kinetic stress than non-sick controls (with divergent anandamide and 2-arachidonoylglycerol dynamics), consistent with impaired endocannabinoid system signaling during symptom onset. [2]

Preclinical and clinical evidence indicate that cannabinoids can modulate nausea and emesis via CB1-rich vestibular and brainstem nodes and by interacting with serotonergic mechanisms (notably 5-HT_3). Cannabinoid-focused reviews detail CB1-mediated suppression of emetic transmission and suggest that CBD's allosteric effects at 5-HT_3 and 5-HT_1A activity may further contribute to anti-nausea actions. [3] Furthermore, because circulating endocannabinoids are

* Corresponding author: David A. Dawson

stress-responsive and correlate with physiological load in humans (e.g., robust increases in anandamide after acute exercise), biomarker-anchored clinical designs that monitor anandamide and 2-arachidonoylglycerol, autonomic indices (HRV), and gastric rhythm may be particularly informative when testing endocannabinoid system-targeted interventions for motion sickness. [3, 4]

2. The Endocannabinoid System and Motion Sickness

The endocannabinoid system (ECS) is a neuromodulatory network comprising CB1 and CB2 receptors, the endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and metabolic enzymes including FAAH, MAGL, NAPE-PLD, and DAGL that modulate ligand synthesis and degradation. [4] CB1 receptors are widely expressed in the central nervous system and are particularly enriched in regions involved in motion processing and emetic control, including the medial and inferior vestibular nuclei, nucleus tractus solitarius (NTS), area postrema, and dorsal vagal complex. [3, 5] These regions integrate vestibular and visceral sensory input and project to the central pattern generator for vomiting, positioning the endocannabinoid system as a critical regulator of motion-induced autonomic output. [5]

2.1. Evidence from Human Motion Studies

Human data demonstrate that the ECS is dynamically modulated during kinetic stress. In a parabolic-flight experiment, Choukèr et al. [2] reported that motion-susceptible participants experienced significant decreases in plasma anandamide and 2-arachidonoylglycerol concentrations and downregulation of leukocyte CB1 mRNA. In contrast, motion-resilient individuals exhibited increases in these endocannabinoids. These findings suggest that endocannabinoid system hypoactivity removes inhibitory control over excitatory vestibular–brainstem neurotransmission, leading to enhanced activation of emetic pathways and greater symptom severity. [6]

2.2. Circuit-Level Mechanisms

- *Vestibular Nuclei:* CB1 receptors presynaptically inhibit glutamate and acetylcholine release, dampening excitatory drive within vestibular circuits and reducing mismatch signaling during passive motion. [3]
- *Nucleus Tractus Solitarius (NTS):* CB1 activation in the NTS suppresses glutamatergic input to the dorsal motor nucleus of the vagus, attenuating vagal efferent activation and the emetic reflex. [5]
- *Area Postrema:* This chemosensory trigger zone is rich in *5-HT_3* receptors; CB1 receptor stimulation reduces serotonin-induced neuronal firing, moderating a key trigger for nausea and vomiting. [5,6]
- *Vagal Afferents:* Endocannabinoid system activation decreases vagal afferent excitability, helping to normalize gastric motility and reduce dysrhythmias that contribute to visceral distress. [5,6]

The proposed mechanistic model of ECS involvement in motion sickness is illustrated in Figure 1. Restoring endocannabinoid system tone during kinetic stress may reestablish inhibitory control of vestibular-brainstem pathways, normalize gastric rhythm, and improve motion tolerance.

2.3. Stress Buffering and Autonomic Modulation

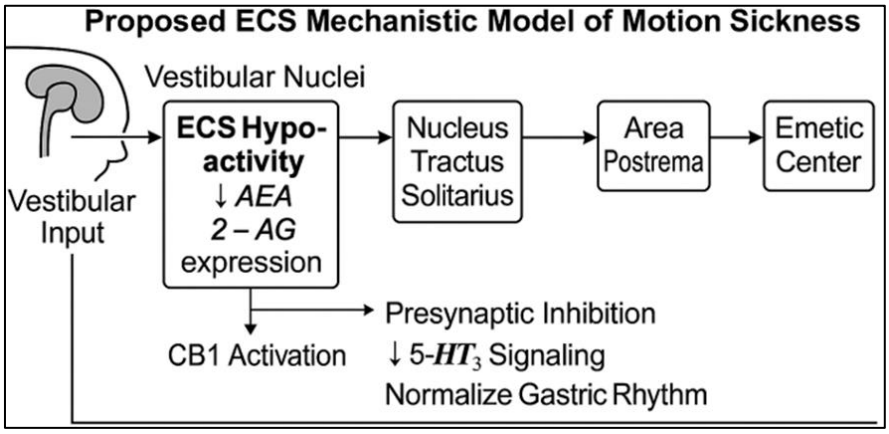

Figure 1 Proposed Endocannabinoid System mechanistic model of motion sickness. Vestibular input activates the vestibular nuclei, NTS, and area postrema, leading to emetic center activation. ECS hypoactivity (↓AEA, ↓2-AG, ↓CB1 expression) disinhibits excitatory signaling. CB1 activation reinstates presynaptic inhibition, reduces *5-HT_3* signaling, and normalizes gastric rhythm

The endocannabinoid system also exerts top-down control over the hypothalamic-pituitary-adrenal (HPA) axis and autonomic balance. Under stress, rising endocannabinoid levels act via CB1 receptors to constrain corticotropin-releasing hormone (CRH) release and limit cortisol secretion. [4] This mechanism promotes recovery of parasympathetic tone and restoration of homeostasis. In motion-susceptible individuals, a blunted endocannabinoid system response may permit excessive cortisol elevation, reduced heart-rate variability, and persistent sympathetic dominance, physiological states that correlate with more severe nausea and reduced motion tolerance. [2]

3. Environmental Effects on the Endocannabinoid System

The endocannabinoid system is not static; it adapts to environmental demands by modulating neuronal excitability, endocrine tone, and autonomic balance via CB1/CB2 receptors and activity-dependent changes in AEA and 2-AG metabolism. [4] In practical terms, the endocannabinoid system functions as a stress-buffering network that constrains HPA-axis output and dampens excessive excitatory transmission. When this buffering is blunted, vulnerability to dysautonomia and nausea rises. [4] Evidence from motion-related kinetic stress already supports this principle: motion-susceptible individuals show reduced circulating endocannabinoids and altered CB1 signaling during parabolic flight. [2] Converging lines of environmental stress research indicate similar ECS perturbations:

- **PTSD (human):** Multiple studies report lower circulating AEA and altered brain CB1 receptor availability on PET imaging, alongside signals consistent with upregulated AEA catabolism (FAAH activity), a constellation interpreted as endocannabinoid system hypoactivity under chronic stress load. [7–9].
- **Chronic stress (preclinical):** Repeated/unpredictable stressors decrease AEA (often in amygdala/hippocampus), can suppress 2-AG under sustained load, elevate CRH, and prolong glucocorticoid responses; FAAH or MAGL manipulations that preserve endocannabinoid tone restore stress resilience and normalize autonomic readouts [6,10].
- **Early-life and social stress models:** Early-life adversity and social defeat paradigms produce durable ECS changes (e.g., reduced AEA/2-AG in key limbic circuits, receptor/adaptor remodeling), linking environmental history to baseline ECS tone and later stress responsivity. [10]

3.1. Implication for the Current Model

If environmental stressors can depress ECS tone, then vestibular motion, a potent physiological stressor, may precipitate the same pattern of endocannabinoid system hypoactivity, removing presynaptic CB1 "brakes" within vestibular–brainstem circuits and facilitating emetic pathway activation. This provides a mechanistic bridge from environment → endocannabinoid system dysregulation → clinical motion sickness, and it motivates biomarker-anchored interventions that restore ECS tone (as outlined in our model and Figure 1). [2,4]

3.2. Phytocannabinoids and Terpenes: Mechanistic Rationale

A growing body of evidence indicates that phytocannabinoids and select terpenes can modulate the endocannabinoid system (ECS) and related neurotransmitter networks, potentially mitigating motion-induced nausea and dysautonomia. Δ^9-tetrahydrocannabinol (THC), the principal psychoactive cannabinoid, acts as a partial agonist at CB_1 receptors, producing presynaptic inhibition of glutamate release in vestibular nuclei and thereby dampening excitatory drive to brainstem emetic centers [11]. This mechanism may also reduce anticipatory anxiety via CB_1-mediated modulation of amygdalar circuits [12].

Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with a distinct pharmacological profile, functioning as a weak inhibitor of fatty acid amide hydrolase (FAAH), thereby prolonging anandamide (AEA) signaling and supporting ECS tone [13]. CBD also acts as a 5-HT_1A receptor agonist, which is implicated in anti-emetic and anxiolytic effects, and may exert prokinetic effects by normalizing gastric myoelectrical activity [14]. Other phytocannabinoids such as cannabigerol (CBG) have been reported to influence dopaminergic and serotonergic transmission, potentially contributing to improved nausea thresholds and regulation of gastric tone [15]. This botanic cannabinoid may offer adjunctive benefit when combined with THC and CBD, supporting a multimodal approach.

Terpenes, the aromatic constituents of Cannabis sativa and other botanicals, also possess relevant bioactivity. Limonene, linalool, menthol, and β-caryophyllene have been shown to exert calming, anti-nausea, and vagotonic effects via serotonergic modulation, transient receptor potential (TRP) channel activation, and, in the case of β-caryophyllene, CB_2 receptor agonism [16]. Preclinical and early clinical evidence suggests that certain terpenes (e.g., limonene, linalool, β-caryophyllene) may enhance cannabinoid-mediated effects through complementary actions at CB_2 receptors,

serotonergic targets, and TRP channels, a phenomenon often described as the 'entourage effect,' which may translate into synergistic anxiolytic and potentially anti-emetic benefits.[17].

4. Proposed Mechanistic Model

4.1. Therapeutic Targets and Intervention Points

Figure 2 presents a schematic representation of the proposed Endocannabinoid System-Targeted Intervention Model. Motion-induced sensory conflict leads to vestibular hyperactivation, decreased circulating AEA/2-AG, and disinhibition of brainstem emetic circuits, culminating in nausea and vomiting.

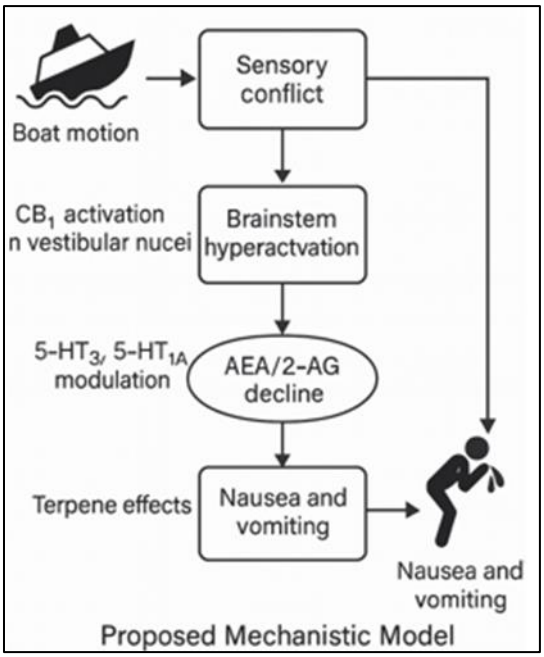

Figure 2 This model illustrates the hypothesized pathway by which motion stimuli provoke nausea and vomiting and how targeted cannabinoid interventions may restore homeostasis. Motion-induced sensory conflict activates vestibular pathways, resulting in brainstem hyperactivation and a subsequent decline in circulating endocannabinoids (AEA and 2-AG). This loss of ECS tone disinhibits the brainstem emetic circuits, culminating in nausea and vomiting

5. Clinical Implications

Globally, motion sickness affects up to 70% of travelers on sea voyages, with a significant economic burden in naval and maritime operations. Addressing this condition with ECS-targeted interventions could reduce operational losses and improve quality of life [18]

Motion sickness in humans is associated with impaired endocannabinoid activity, including reduced post-maneuver levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG) and decreased CB_1 receptor expression—suggesting that enhancing ECS signaling might be a viable therapeutic approach [19]. In animal models, Δ^9-THC significantly suppresses motion-induced emesis via CB_1 receptor activation, whereas CBD does not [20]. Moreover, the terpene d-limonene has been shown in healthy volunteers to selectively attenuate THC-induced anxiety, without altering cognitive, physiological, or subjective effects—indicating a potential strategy for improving tolerability [17]. Finally, conventional anti-motion sickness agents, such as scopolamine and first-generation antihistamines, are effective but frequently limited by anticholinergic and sedative side effects [21]. Together, this evidence supports the hypothesis that cannabinoid–terpene interventions could restore ECS homeostasis, reduce the severity of motion-sickness symptoms, and offer an improved side-effect profile relative to traditional anticholinergic and antihistaminic agents.

Targeted cannabinoid interventions act at multiple nodes in this cascade:

- **CB_1 receptor activation** in vestibular nuclei and the nucleus tractus solitarius reinstates inhibitory control, reducing excitatory neurotransmission. Activation of presynaptic CB_1 receptors reduces neurotransmitter release, including glutamate (excitatory) and GABA (inhibitory), across multiple CNS regions. Within the nucleus tractus solitarius, CB_1-mediated modulation of GABA release has been shown to influence synaptic control. These findings indicate that CB_1 activation can restore inhibitory regulation by dampening excitatory signaling in brainstem nuclei [22].
- **CBD-mediated 5-HT_3 and 5-HT_1A modulation** attenuates serotonin-driven emetic signaling and reduces anxiety. Cannabidiol (CBD) exerts antiemetic effects by indirect activation of somatodendritic 5-HT_1A autoreceptors in the dorsal raphe nucleus, reducing serotonergic firing and nausea-like behavior, and also acts as a negative allosteric modulator of 5-HT_3 receptors, which are key mediators of serotonin-induced emesis. These actions together attenuate serotonin-driven emetic signaling and contribute to anxiolytic effects [23].
- **Terpene contributions** (e.g., limonene, linalool) enhance vagal tone and provide mild sedative effects that may improve motion tolerance. Terpenes such as

linalool and limonene exhibit anxiolytic and sedative effects in humans—linalool inhalation reduces heart rate and stress biomarkers (e.g., cortisol, blood pressure), while limonene demonstrates sedative-like modulation of stress physiology—suggesting they may enhance autonomic (vagal) tone and improve motion tolerance by reducing excitatory arousal [24, 25]

This integrated model suggests that restoring ECS tone during kinetic stress may normalize gastric rhythm, reduce sympathetic overdrive, and improve symptom control Cannabinoid–terpene interventions have the potential to restore homeostatic endocannabinoid system function and reduce motion-sickness symptom severity, with an improved side-effect profile relative to conventional anticholinergic (scopolamine) and antihistaminic agents [26,21]. Unlike these agents, which are often limited by sedation and cognitive impairment, cannabinoid-based approaches act on the underlying pathophysiology of sensory mismatch and autonomic imbalance.

As with any pharmaceutical or nutraceutical intervention, proper dosing is essential. THC produces biphasic effects, with low-to-moderate doses offering anxiolysis and anti-nausea benefits, but higher doses potentially causing dysphoria, tachycardia, or paradoxical emesis (cannabinoid hyperemesis syndrome) [27,28]. CBD and terpenes are generally well tolerated, but dose standardization and pharmacokinetic considerations are essential for reproducible clinical outcomes.

Future Directions

Future work should include randomized, controlled clinical trials evaluating standardized formulations of THC, CBD, minor botanic cannabinoids, and select terpenes. Outcome measures should include both subjective symptom ratings and objective biomarkers such as plasma AEA/2-AG, heart rate variability (HRV), gastric myoelectrical activity, and cortisol as indices of stress buffering [29].

A particularly promising avenue is prophylactic Endocannabinoid System Modulation, wherein individuals with a known susceptibility to motion sickness could receive preemptive treatment before exposure to kinetic stress (e.g., prior to sea voyages or spaceflight). This approach could help maintain endocannabinoid system tone and prevent the cascade of emetic activation.

Given the safety and accessibility of standardized phytocannabinoid preparations, ECS-targeted motion sickness interventions represent a feasible, near-term translational research opportunity. We encourage clinical researchers to prioritize biomarker-anchored trials that test multimodal cannabinoid-terpene formulations against conventional anticholinergics, to provide practical, mechanism-based solutions for motion-susceptible populations.

The endocannabinoid system represents a compelling therapeutic target for motion sickness, bridging the gap between environmental stressors and autonomic dysregulation [19]. Botanical cannabinoids and terpenes offer a multimodal strategy for restoring ECS tone, dampening vestibular hyperactivation, and reducing emetic drive [30,31]. Collectively, these findings warrant rigorous biomarker-anchored clinical investigation and dose-optimized protocols to establish efficacy and safety in motion-susceptible populations [19].

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflict of interest.

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