

# Review of pathophysiology, epidemiology, diagnosis and treatment methods in motion sickness; a special issue

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## Abstract

Motion sickness (MS) is a syndrome characterized with nausea and vomiting, pallor, cold sweating, headache, dizziness, increased salivation, apathy, hyperventilation, and stomach awareness. Nausea is one of the most prominent symptoms of MS and very little known about the neural substrate of this sensation. There is no abrupt accepted explanation about why people get motion sickness. It has long been suspected that genetic and /or evolutionary factors govern motion sickness susceptibility. The prevalence is higher among the female gender. The main causes in adulthood are still unknown, but it has been suggested that this condition can be related to the hormonal cycle. Patients with migraine and Meniere's disease are prone to experience MS especially in female patients. MS is a common physiological response to real or virtual motion. Numerous studies have investigated the neurobiological mechanism and the control measures of MS. The sensory conflict hypothesis is the most widely accepted theory for MS. Questionnaires, heart rate variability and electrogastrogram are useful for diagnosis and evaluating MS. Habitual training and drugs are the treatment modalities. The drugs can be divided into the categories: antimuscarinics, H1 antihistamines, and sempathomimetics. The aim of this review is to remind the current knowledge about pathogenesis, epidemiology, diagnosis and treatment methods of the special issue: motion sickness.

**Keywords:** Motion Sickness; Nausea; Vomiting; Vestibular.

The term "nausea" derives from the Greek root word 'naus,' hence 'nautical', meaning a ship. The general term "motion sickness" is best applied across all of those stimulus specific terms such as car-sickness, space-sickness or sea-sickness. Spatial orientation, maintenance of balance, stabilising of vision through vestibular ocular reflexes are the primary functions of the vestibular system (1).

Motion sickness (MS) is a syndrome that occurs when a patient is exposed to certain types of motion. It is a common response to motion stimuli during travel. The symptoms usually resolve soon after its cessation (2).

MS is characterized by a combination of signs and symptoms that accompany movement or perceived movement in the environment. Many different circumstances can elicit motion sickness, including travel in automobiles, aircraft, spacecraft and boats and exposure to moving visual scenes. If a mismatch between the visceral "body position signal" and vestibular signals were present, then the resulting sensory conflict could theoretically induce MS during vertical motion. The hallmark indicators of

MS include nausea, vomiting, pallor, cold sweating. Money et. al. (3) reported that these responses should be categorized into two categories: those related to emptying the stomach and those related to "stress" that may be secondary to stomach emptying (4). Motion sickness includes a wide range of signs and symptoms and symptoms including cold sweating, pallor of varying degrees, increases in salivation, drowsiness, headache and even severe pain, as well as nausea and vomiting (5).

Little is known about the factors that control individual differences in susceptibility to motion sickness. It has long been thought that genetic and/or evolutionary factors govern motion sickness susceptibility (6). Motion sickness depends on the sensitivity of each individual and the ability of the vestibular system to adapt to continued exposure to the stimulus (7).

A common pattern of all the motions which induce motion sickness is a repetitive linear or angular acceleration of the head. The greatest incidence of MS was found at a heave frequency of about 0.2 Hz, increasing with the acceleration level from a threshold value of 0,1ms<sup>-2</sup>. It

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has been suggested that as the break frequency between tilt and oscillation perceptions of the otoliths is around 0.2 Hz, this frequency zone is prone to perceptual uncertainty, leading to the development of MS. A functional vestibular system is a pre-requisite for MS to occur (8).

The pathogenesis of MS is thought to be related to conflict between the vestibular, visual and other proprioceptive systems. Rotatory, vertical and low frequency motions produce more exaggerated symptoms than linear, horizontal and high frequency motions. Before treating symptoms it is important to prevent MS. Drugs are more effective when taken prophylactically, or as soon as possible after the onset of symptoms. Behavioral strategies should be combined with medications to maintain the best effectiveness. Scopolamine, is the first choice in MS. First-generation antihistamines have been used to treat MS since the 1940s. Cyclizine, dimenhydrinate, promethazine and meclizine are effective in preventing or treating MS. Benzodiazepines are administered for severe symptoms of MS. The serotonin agonist rizatriptan also reduce MS symptoms (2).

### **Vestibular Anatomy and Physiology**

The vestibular system is phylogenetically the oldest part of the inner ear. The sensory organs comprise two types of sensors: the three semicircular canals, which sense angular acceleration in all three dimensions, and the two otolith organs (the saccule and utricle) which sense linear acceleration (i.e. gravity and translational movements) in all three dimensions. The afferent fibers of the vestibular component of the VIII nerve carry signals from the receptor cells of these sensory organs to the vestibular nuclei project to the neural structures that control eye movements, posture and balance, as well as to upstream structures involved in the computation of self-motion. The vestibular system encodes self-motion information by detecting the motion of the head-in-space. It provides us with our subjective sense a self-motion and orientation thereby playing a vital role in the stabilization of gaze, central of balance and posture.

The vestibular system's role in ensuring the accuracy of three specific classes of behaviours:

1. The control of gaze to ensure clear vision during everyday activities.
2. The production of the compensatory neck and limb movements required to ensure postural equilibrium during both self generated and externally applied movements.
3. More complex voluntary motion tasks such as navigation and reaching (9).

The sensory receptors within the semicircular canals respond to angular acceleration, which occurs when the head is rotated or when the entire head and body is turned. Angular head movements produce a change in the discharge pattern of afferents innervating at least two of the six semicircular canals on the two sides of the head: the degree to which different canal afferents are affected

depends on the direction otolith organs, the utricle and the saccule, provide information about linear accelerations placed on the head. The two otolith organs are located perpendicular to each other. This position allows them to detect linear accelerations and head tilts in many different planes. The central nervous systems can decipher the position of the head in space by analyzing the pattern of otolith organ afferent discharges (4).

### **Etiology and Pathogenesis**

The precise etiology of MS is unknown (10). Vestibular system acts as a toxin-detector. The toxin detector, hypothesis proposes that the brain has evolved to recognise any derangement of expected patterns of vestibular, visual and kinaesthetic information as evidence of central nervous system malfunction and to initiate vomiting as a defence against a possible ingested neurotoxin. People who are more susceptible to MS are more susceptible to toxins, chemotherapy and postoperative nausea and vomiting. The generally accepted explanation of the "how" of MS is based on same form of sensory conflict or sensory mismatch. The sensory conflict or sensory mismatch is between actual versus expected invariant patterns of vestibular, visual and kinaesthetic inputs. These include intra-vestibular conflicts between rotational accelerations sensed by the semi-circular canals and linear-translational accelerations sensed by the otoliths (1).

The sensory conflict and neural mismatch, theory was originally proposed by Reason and Brand (11-12). MS will develop when mismatches happened between the integrated pattern of sensory information under real motion (e.g. in boats, cars and airplanes) or visual environment (e.g. watching 3D videofilms) and the anticipated internal mode, formed under normal or experienced conditions. Activating sensory conflict neurons may trigger autonomic reaction through vestibulo-autonomic pathways that connect the vestibular nucleus complex with central autonomic regions. MS accompanies stress hormones release and endocrine responses habituated over repeated motion exposure (13).

Von Baumgarten et. al (14) have suggested that asymmetries in otolith function between the two labyrinths, which result from different masses of the otoconia, cause MS subjects with large asymmetries between their ocular counter-rolling responses for leftward and rightward body tilts were found to be significantly more susceptible to MS when passively exposed to variations in gravito-inertial force load. Riccio and Staffagen (15) hypothesized that MS is caused by instability of body postural control. This theory predicts increased incidence of sickness when external motion at the frequency range of 0.1-0.3 Hz is imposed because of wave interference with the naturally occurring spontaneous sway activity. Ebenholtz et al. (16) suggest that MS is secondary to eye movements mediated by the vestibular nuclei. The motion-induced nystagmic responses result in significant traction of the extraocular muscles with activation of the extraocular

muscles with activation of the oculocardiac reflex and vagus nerve stimulation. Bles et al. (17) support the subjective vertical conflict theory. According to this theory, all situations that provoke MS are characterized by a condition in which the sensed vertical, as determined on the basis of integrated information from the eyes, the vestibular system, and the non-vestibular proprioceptors, is at variance with the subjective vertical as expected from previous experience (8).

The prevalence is higher among the female gender. Chang et al. (18) reported that MS incidence was greater among girls than boys on a sample of 25 children. The literature also reports a greater incidence of MS in women (19,21). MS is rare in children below 2 years of age, but after this period is a frequent and relevant problem, reaching a peak between the ages of 4 and 10-12 years (22,24).

Takakashi et al (25) have found in their study in 90 children aged 4 to 15 years a gradual increased of frequency and severity of sickness during growth, but the severity of disorder become milder as age increased. The coordination of postural responses and the functional efficiency of the vestibular system develop between 10 and 15 years of age.

Chang et al. (18) reported that MS tended to increase with age, and by age 10. Children did not differ from adults. The MS should be considered as an additional criteria for the diagnosis of migraine in childhood (7).

The main causes in adulthood are still unknown, but it has been suggested that this condition can be related to the hormonal cycle. The cause of greater motion sickness susceptibility in women has been suggested to involve the female hormonal cycle. However, although susceptibility probably varies over the menstrual cycle, it is unlikely that this can fully account for the greater susceptibility in females because the magnitude of fluctuation in susceptibility across the cycle is only around one third of the overall difference between male and female susceptibility (26). The elevated susceptibility of females to motion sickness or indeed to post-operative nausea and vomiting or chemotherapy induced nausea and vomiting (27), may serve an evolutionary function. Thus, more sensitive sickness thresholds in females may serve to prevent exposure of the foetus to harmful toxins during pregnancy, or subsequently through milk. This elevated susceptibility in females may be 'hardwired' but capable of up-regulation albeit variably by hormonal influences during the menstrual cycle and even further during pregnancy (1).

Evidence from twin studies has shown that a large proportion of individual variation in susceptibility is due to genetic factors, with heritability estimates in the range 55-70%. Some groups of patients are particularly susceptible. Self reported motion sickness is higher in people who have migraines than in those who have other types of headache. migraineurs characteristically

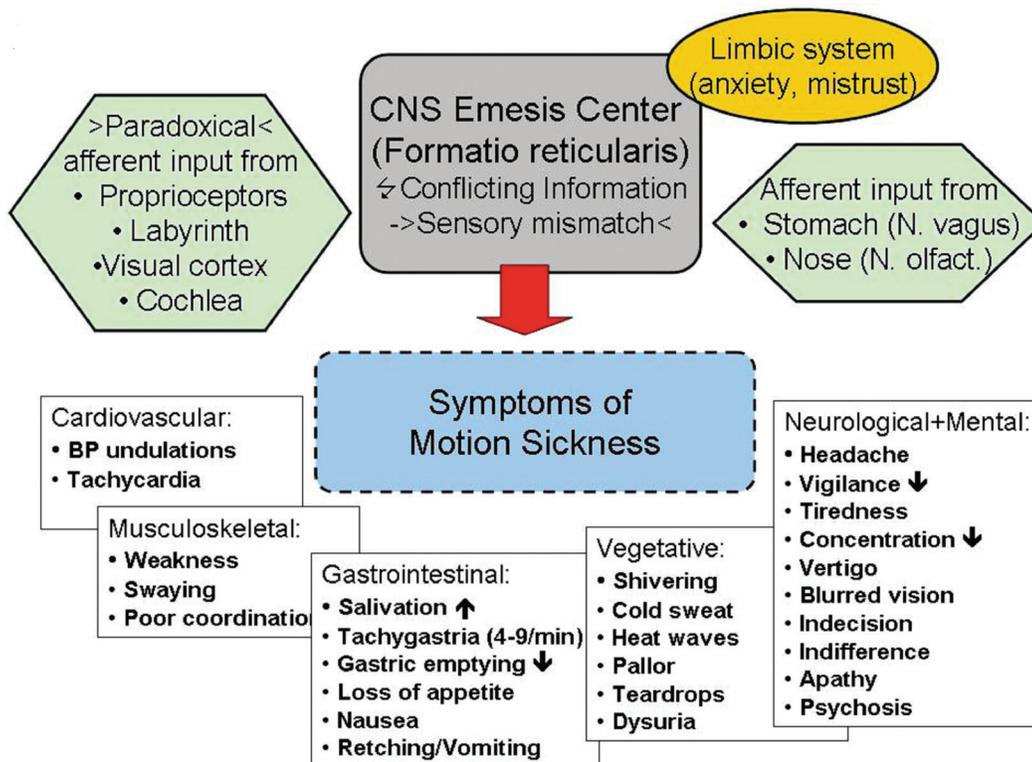
report heightened sensitivity of all senses for example, phonophobia and photophobia including vestibular and visual-vestibular inputs. Many symptoms of motion sickness are reminiscent of a migraine attack (28).

MS is a conserved and a cross-species phenotype (from fishes, amphibia to mammals) with a heritability around 57-70% in humans (29). Race disparity is also significant. Chinese are more sensitive to MS than Caucasian (1). Finley et al (30) for the first time reported that a single-nucleotide polymorphism (SNP) in the  $\alpha_2$ -adrenergic receptor gene correlated with individual differences in autonomic responsiveness to provocative motion and other stressors. Patients with migraine and Meniere's disease are prone to experience MS especially in female patients (31-32). Mutations in genes related to vasculopathy and cortical spreading depression are responsible for vestibular symptoms and MS hypersusceptibility in migraine patients (33). Previous studies have found sporadic Meniere's disease might be associated with mutations in genes of aquaporins and voltage-gated potassium channel expressed in the inner ear (34). These genes play important roles in endolymphatic homeostasis, their mutations ought to contribute to subnormal or asymmetrical otolith function associated with MS hypersusceptibility in Meniere patients (13).

### Diagnosis and Clinical Evaluations

Nausea is one of the most prominent symptoms of MS and very little known about the neural substrate of this sensation. Vasopressin is likely to induce changes in blood flow during MS. Money et al. (3) categorized a number of signs and symptoms associated with MS, such as anxiety, release of stress hormones into the blood stream, facial pallor and cold sweating, headache, sopite (drowsiness), increased salivation, sensations of bodily warmth, dizziness, loss of appetite, increased sensitivity to odors. The headache provoked can be migrainous and disabling. Gastric dysrhythmias may provide a marker of nausea in motion sickness and drop in stomach fundus and sphincter pressure correlates with nausea (4-35). The MS is caused by inappropriate activation vestibular-cardiovascular reflexes (increased blood pressure and cardiac output) and the vestibular and visual systems influence autonomic control for the purpose of maintaining homeostasis during movement and changes in posture (1). Pathophysiology and symptomatology of motion sickness is summarized in Figure 1.

MS can be diagnosed according to the manifestations during motion exposure after excluding other pathological disorders. Heart rate variability (HRV) and electrogastrogram (EGG) are useful for assessing cardiac sympathovagal interactions and gastric motility during MS. HRV indices might be influenced by motion patterns intersubject variations, subjects, self-adjustments, vomiting process, and stress response (37).



**Figure 1.** Pathophysiology and symptomatology of motion sickness. (Adapted from: Wolffgram T. Motion- and seasickness (Kinetosis) – Update on pathophysiology, prophylaxis and therapy. *Medizinische Welt* 2000;132: 21–27 (36)

Stoffregen et al (37) proposed the postural instability as a precursor of MS susceptibility. Previous studies have demonstrated that computerized dynamic posturography data can be used as indicator of seasickness susceptibility and habituation. Baseline protein concentration and amylase activity in saliva as well as odor and tester sensitivity were also used as indicators for predicting MS susceptibility in human subjects (13).

It is important to quantificate the severity of MS and identify the objective physiological parameters of the MS, for follow-up the habituation process and examination of the efficacy of therapeutic measures. A wide variety of MS questionnaires have been used to assess MS susceptibility. The Coriolis Sickness Susceptibility Index MS test requires subjects to move their heads in pitch and roll while seated up-right on a chair rotating around an Earth-vertical axis. The visual vestibular interaction test is based on the observation that visual fixation during low frequency motion provokes sickness. The seated subject is reading lines of letters from an illuminated matrix attached to the chair while rotating in the dark in a low-frequency sinusoidal pattern. The percent of mistakes in the identification of the letters are highly correlated with air-sickness susceptibility. These tests are all highly provocative and this condition is an disadvantage of these tests. Increased salivation is one of the early signs commonly reported in MS. Contrary to the

reported increased salivation, in laboratory and open sea trials, it has been found a decreased salivary rate associated with motion and sea sickness severity. Increased protein and sodium concentration are correlated with MS severity. Electrodermal activity has also been found to be sensitive for diagnosis prediction of individual MS susceptibility (8).

#### Habituation Training

Repeated exposure may produce more sufficient habituation than single prolonged stimulation, but desensitization to one-provocative motion could not be transformed to a more severe motion stimulus. Horizontal suspension, parabolic flight, and neutral buoyancy stimulation have been used as microgravity simulation methods for astronaut training. Anti-MS drugs are not recommended during MS habituation training process. Using revolving chair, winding stair, idler wheel, and swing, combined visual vestibular habituation training is more effective and can produce long term effect against travel induced MS for up to 18 weeks in susceptible subjects. Smoking deprivation, pleasant music, and odors as well as head vibration and mental distraction have been found to be effective in reducing MS symptoms. Vit C was found to be effective in reducing sea sickness symptoms (13).

#### Medical Treatment

Occurrence of MS depends on factors such as individual susceptibility, and the type, magnitude and duration of stimulus. For these; it is important to decide the

drug for an individual. The most effective anti-MS drugs are central anticholinergic agents. MS is a CNS response to unfamiliar motion stimuli transmitted to the vestibular nuclei, the archi-cerebellum, and to other brainstem, autonomic, and hypothalamic areas. Unnatural or conflicting motion stimuli sensed mainly by the vestibular labyrinth, but also by the eyes, and proprioceptors, travel to the vestibular nuclei, then through the cerebellum to the vomiting center located in the parvicellular reticular formation of the medulla oblongata and to diverse areas of the CNS, explaining the different symptoms and signs of MS. Anticholinergic drugs that do not cross the blood-brain barrier are ineffective in the control of MS (8).

The drugs can be divided into the categories: antimuscarinics, H1 antihistamines, and sempathomimetics. All anti-MS drugs can produce unwanted side effects such as drowsiness, promethazine being a classic example. Transdermal scopolamine or the calcium channel antagonist cinnarizine, are less sedating drugs than others (1).

#### **Anticholinergics/ Scopolamine**

Scopolamine is a belladonna alkaloid that acts like atropine. This drug acts on muscarinic receptors (10). Scopolamine is the most effective anti-MS agent presently available, is non-selective for the 5 types of muscarinic receptors found in CNS. It inhibits vestibular input to the vestibular nuclei and probably acts directly on vomiting center. The zamifenacin, M3 and M5 muscarinic antagonist was found to be as effective as scopolamine in human subjects tested on a rotating chair. A transdermal scopolamine has been developed to provide effective MS prophylaxis and to avoid considerable side effects of buccal and parenteral administration. Because the effect of transdermal scopolamine is obtained to 6 to 8 h postapplication, the combined administration of 0.3 or 0.6 mg of oral scopolamine can be used during the first hours of a voyage until the transdermal patch takes effect, with no significant adverse effects. Repeated or prolonged use of transdermal scopolamine may increase the risk of undesirable side effects. Scopolamine nasal spray is an effective, fast and safe treatment method (8).

The scopolamine patch is attached to the skin behind the ear in a hairless area and delivers 0.5 mg of scopolamine at a fairly consistent rate over 3 days. The patch must be applied well in advance, however, since an effective drug concentration is not achieved until 6 to 8 hours after application. This delay can be reduced to an hour or less by simultaneously administering a single dosage, the patch may not be suitable for children.

Common side effects of topical scopolamine include dry mouth, drowsiness, blurred vision, sore-throat, confusion, disorientation, memory loss, restlessness.

Scopolamine tablets can be (0.4 mg of scopolamine per tablet) prescribed dosage is 1 to 2 tablets every 8 hours needed. It must be taken 1 hour before exposure to motion to reach an effective concentration. Oral scopolamine is twice as effective as topical form in preventing MS. Side effects of scopolamine can be eliminated by adding 5 to 10 mg of the symphatomimetic medication d-amphetamine (10).

#### **Antihistamines**

Histamine increases the firing rate in afferent nerves from the ampullae of the semicircular canals. This effect is antagonized by various H1 receptor antagonists used as anti-MS agents (8). First generation H1 antihistamines are effective against MS, but second generations are ineffective (13). Dimenhydrinate (Dramamine) appears to be the most effective antihistamine. The usual adult dosage is 50 mg, which typically produces some drowsiness and minor dizziness. It is most recommended when driving or working around machinery, but can be a good choice for long exposure to mild -to-moderate motion. Cyclizine is less effective at the usual dosage of 50 mg, but causes less drowsiness and dizziness and is often used to avoid travel sickness in children or very mild-short-term exposures to motion in adults.

Meclizine has a slower onset and longer duration (12 to 24 hours) of action than the other antihistamines side effects include drowsiness, dry mouth, blurred vision and dizziness (10).

#### **Monoamine Antagonists/ Agonists**

Dopamine D2 and D3 receptors are known to play a role in nausea and emesis. Competitive D2 receptor antagonist metoclopramide, administered through intravenous or intramuscular injection but not oral route, alleviated overall symptoms and restored gastric emptying after the initiation of MS. The effectiveness of dopamine antagonists may depend on the administration route and timing. Oral administration of the 5-HT3 receptor antagonists, Ondansetron, has no preventive effect against sea sickness or experimental MS. 5-HT1B/1D receptor agonist, rizatriptan, prevents the development of MS in migranious patients (13).

#### **D-Amphetamine and Ephedrine**

D-amphetamine has been shown to protect against MS when used alone and to act synergistically when combined with scopolamine or promethazine. It reduces the sleepiness and performance decrement produced by scopolamine (10).

#### **Others**

Neuroleptics including barbiturates, diazepam, and baclofen as well as phenytoin were found to be effective in prevention of MS (13).

Phenytoin has anti-motion sickness potential,

although its complex pharmacokinetics and side effects limit practicality. Betahistine has been proposed to have anti-motion sickness properties but a number of studies indicate that its action is too weak to be effective for practical purposes. Chlorpheniramine is an antihistamine synthesized many years ago which has anti-MS actions without major side-effects. The anti-psychotic Droperidol is shown to have useful anti-MS action and may merit further study, but its practical value may be off set by side-effects.

Corticosteroids, such as dexamethasone, attracted some interest as a potential anti-MS agents over fifteen years ago, but evidence for their value is indirect (1). Flunarizine, antihistamine and calcium channel blocker, has been used for treatment of vertigo and migraine. It is proposed in the prevention of MS (8).

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