Pharmacological options for Motion Sickness in children

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Abstract
Motion Sickness (MS) increases its epidemiological weight due to greater willingness to travel and to the diffusion of cinematic videos, video games and virtual reality technologies with strong kinetic stimuli. On the other hand, the pathophysiological mechanisms are identified as a sensory mismatch between vestibular, visual and proprioceptive inputs, and are not well understood. This sensory mismatch is particularly present in the pediatric age, also due to non-contemporary development and maturation times of these receptors/analyzers. On this basis, drug therapy for these patients has a purpose predominantly symptomatic and/or preventive. For paediatric age it deserves further study, since limited experiences exist in the literature and therapeutic choices are often based on experiences in an adult population. In this work we report the main drugs and nutraceuticals that can be used for MS, about the indication and doses for the paediatric age, with the most recent considerations in the literature.

Motion Sickness, also called Kinetosis, is a common phenomenon that almost everyone experiences throughout their life, including children. Its pathophysiology is related to a sensory mismatch between actual versus expected invariant patterns of vestibular, visual, and somatosensory inputs, leading to an activation of vestibule-autonomic pathways involved in producing nausea and vomiting (Viola P.et al.,2022). MS is caused by a variety of motion environments (e.g., cars, boats, planes, tilting trains, funfair rides, space, and virtual reality), and given a sufficiently provocative motion stimulus, in the presence of a functioning vestibular system (Leung, A. K et al., 2019, Golding, J. F et al, 2015, Golding, J. F.,2006). Once the triggering factors cease, the symptoms usually resolve completely within 24 hours (Leung, A. K., 2011). Children under 2 years of age appear to be resistant to MS because they use the visual system only to a limited extent for dynamic spatial orientation and for self-motion perception and therefore are subject to a limited number of visual-vestibular perceptual conflicts (Brandt, T. et al.,1976). In a recent interesting study, the roll vection-induced tilts of the visual and postural vertical exhibited a similar age-dependent course with the greatest effects in the youngest (2-7 years; median of 20°) and the least effects in the oldest age group (13-17 years; median of 9-10°), the latter of which exhibited the highest susceptibility to MS (Schnabel, L. et al 2022). The disease has a high prevalence in female children aged between 7 and 12 years (Henriques, I. F. et al., 2014, Dobie, T. et al., 2001). The clinical characteristics of the disease include emesis, nausea, vertigo and dizziness, asthenia, paleness, and headache (Golding, J. F.

et al., 2016). Common comorbid conditions that may contribute to pediatric MS include migraine disorders, vestibular impairment, otitis media, and motor delay (Lipson, S. et al, 2020). There is a large literature on MS in adults, reporting a prevalence of 13.4%, in children, on the other hand, MS is not well characterized although its prevalence appears to be higher (about 43%) (Henriques, I. F. et al., 2014). In addition, also the treatment for MS has not been well investigated. Pharmacologic treatment for MS includes cyproheptadine, meclizine, ondansetron, scopolamine, promethazine, cinnarizine, flunarizine, *Griffonia simplicifolia*/Magnesium complex.

Cyproheptadine is an antihistaminic drug, effective in prophylaxis of pediatric migraine due to its anticholinergic and anti-serotoninergic properties which may also reduce MS. It appears to be a promising treatment for MS, due to its relatively favorable side effect profile and safety. Lipson et al. reported a treatment response to cyproheptadine in all children (5 patients) with improvement in MS after treatment. Furthermore, Cyproheptadine can be used in children who are too young to take more commonly prescribed MS therapies, such as meclizine or ondansetron (Lipson, S., et al., 2020). In children from 2 to 6 years it is suggested to start with 2 mg (½ tablet or 5 mL of syrup) two or three times a day, and then to adapt the dosage to the individual size and response. Any additional daily dose that may be required, should be given before a night's rest. The total daily dosage should not exceed 12 mg (Agenzia Italiana del Farmaco. 2016).

Meclizine, a first-generation antihistamine (non-selective H1 antagonist), with central anticholinergic action, is used to manage and treat nausea, vomiting, and dizziness caused by MS and vertigo. It inhibits the signals through histamine neurotransmission, from the nucleus of the solitary tract and the vestibular nuclei to the chemoreceptor trigger zone and vomiting center, located in the medulla (Wibble, T et al., 2020, Houston, B. T. et al 2022). Meclizine is approved by FDA for children over 12 years, at the dosage of 25 to 50 mg, one hour before embarkation or triggering situation; additional administration is possible once every 24 h. The drug has not received approval for children under 12 years of age because safety and efficacy have not been established (National Institute of Diabetes and Digestive and Kidney Diseases. 2017). Meclizine administration is chewable or non-chewable by oral tablets. Chewable tablets must be crushed or completely chewed before swallowing. The drug can be taken without regard to food. Meclizine's half-life is about 6 hours, the onset of action is about 1 hour, and the duration of action is approximately 8 to 24 hours (Qazi, F. et al., 2017). Although the drug appears to have a good effect against MS through vestibular modulation, its effectiveness has been questioned (Boussageon, R., et al., 2017). Common adverse drug reactions include drowsiness, urinary retention, dry mouth, headache, fatigue, and vomiting (Weerts et al., 2014). On rare occasions, there have been reports of blurred vision and anaphylactic reactions. Caution is needed in patients with glaucoma and asthma due to its anticholinergic properties (Verhamme et al., 2008; Yayla et al., 2015).

Ondansetron is a selective 5-HT3 serotonin-receptor antagonist used in the prevention of nausea and vomiting induced by surgery, chemotherapy, or radiotherapy, with minimal effect on nausea and vomiting due to MS (Shinohara et al., 2019). Ondansetron is used in pediatric populations in the acute therapy of cyclic vomiting syndrome, but little information is available on its efficacy (Liu et al., 2019). Ondansetron central effects are mediated by the antagonism of 5HT-3 serotonin receptors in the area postrema located on the fourth ventricle floor. Ondansetron peripheral action is on 5-HT3 receptors in the vagus nerve, responsible for nausea and vomiting triggered by the gastrointestinal tract. Routes of administration include oral, intramuscular (IM), and intravenous (IV). Oral formulations are available in dissolving tablet and soluble film forms. Standard dosing to prevent postoperative nausea and vomiting

includes 8 mg every 12 hours orally or 4 mg given intravenously. Pediatric dosing is 0.15 mg/kg with a maximum of 16 mg per dose; however, only few data about the pediatric population are available (Patel et al., 2019).

Scopolamine is used to manage and treat postoperative nausea and vomiting and is also prescribed for the treatment and prevention of MS, with FDA labelled indications. This drug derives from the plants of *Datura Stramonium*, *Scopolia Carniolica*, and *Hyoscyamus Niger*. These plants produce toxic compounds called belladonna alkaloids as a protective mechanism (Kassel et al., 2018; Riad et al., 2022; Spinks et al., 2011). It inhibits G protein-coupled post-ganglionic muscarinic receptors for acetylcholine, and acts as a non-selective muscarinic antagonist, producing both peripheral antimuscarinic properties and central sedative, antiemetic, and amnestic effects (Zhang et al., 2017). The vomiting center in the medulla oblongata contains a high amount of M1, H1, NK1, and 5-HT3 receptors. Scopolamine exerts its action by primarily affecting the M1 receptor, even if the H1 receptor could be also involved (Pergolizzi et al., 2012). Scopolamine is commonly used as a 1 mg transdermal patch applied behind the ear, on the mastoid, at least 4 hours prior to movement exposure, with effects lasting approximately 72 hours. Transdermal scopolamine should not be used in children under the age of 10 because its safety has not been established. The most reported side effects of scopolamine patch use are blurred vision, dilated pupils, dry mouth and dermatitis at the site of application (Zhang et al., 2016; Takov et al., 2019). Less frequently reported side effects are related to anticholinergic toxidrome: flushed skin, tachycardia, agitation, confusion and delirium. Acute angle glaucoma, ipsilateral mydriasis, and cycloplegia have rarely been reported. The two major contraindications are allergy to belladonna alkaloids and angle-closure glaucoma. Scopolamine causes mydriasis, the dilated iris prevents fluid drainage from the anterior chamber resulting in increased anterior chamber pressure (Lin et al., 2014; Lin et al., 2011; Hamill et al., 1983). Scopolamine can also be administered orally and IM, it acts within 30 minutes, for a period of 4–6 hours. The recommended oral and IM dose for children is 0.006 mg/kg, with the possibility of increasing to double the dose orally; intramuscular injection can be repeated every 6–8 hours, if necessary (Brainard et al., 2014, Simmons et al.,2010) suggest that intranasal scopolamine in young adults is efficacious for the treatment of MS in susceptible individuals with no significant cognitive or sedative effects. Toxicity is rare with transdermal administration; according to some authors, 10 mg per day orally can be lethal for children. Overdose causes an anticholinergic syndrome with tachycardia, hallucinations, hyperthermia and dryness of the membranes. Physostigmine can serve as an antidote in such severe cases.

Promethazine is a phenothiazine derivative with antidopaminergic, antihistamine, and anticholinergic properties, used to treat allergic conditions, nausea, vomiting, and as prophylactic therapy for MS with FDA-approved indications (Southard et al., 2022; Page et al., 2009). It is most effective when given 30 minutes to 1 hour before the triggering event. Promethazine has several routes of administration, including oral, rectal, intramuscular, and intravenous. Promethazine hydrochloride syrup, tablets, or rectal suppositories are administered at 12.5 to 25 mg twice daily for children. In paediatrics, dosing adjustments are needed in function of both patient weight and clinical indication (Shupak et al., 2006). Adverse drug reactions include sedation, confusion and disorientation. Promethazine can cause blurred vision, xerostomia, dry nasal passages, dilated pupils, constipation and urinary retention due to its anticholinergic activity. Extrapyramidal symptoms including pseudo-parkinsonism, acute dystonia, akathisia and tardive dyskinesia are due to its antidopaminergic activity (American Geriatrics Society Beers Criteria® Update Expert Panel et al., 2019). It is contraindicated in chil-

dren under 2 years of age due to the risk of potentially fatal respiratory depression. The main feature of promethazine toxicity is CNS depression, tachycardia, respiratory depression, and delirium (Starke et al., 2005; Southard et al., 2022).

Cinnarizine is a piperazine derivative, has antihistaminic, antiserotoninergic, antidopaminergic, and calcium channel–blocking properties. It is currently used for the treatment of nausea, vomiting, vertigo, and the prevention and treatment of MS. It reduces both frequency and severity of migraines in children, particularly when it is associated with vestibular symptoms (Ashrafi et al., 2014; Oskoui et al., 2019). For adults a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. The recommended dose for cinnarizine in children who are older than 5 years is 6.25 mg to 12.5 mg 3 times daily, and it is not approved for children who are younger than 5 years. Overdose can cause alterations in consciousness ranging from somnolence to stupor and coma, vomiting, extrapyramidal symptoms, convulsion and hypotonia (Kirtane et al., 2019; Turner et al., 2006).

Flunarizine is the difluorinated derivative of cinnarizine with antihistamine and calcium-antagonist properties. This drug has been used in the past in the treatment and prevention of MS (Lee et al., 1986). Its efficacy in the prevention of MS remains to be addressed.

Esposito et al. (2015) evaluated, in 254 prepubertal children, the efficacy and safety of the *Griffonia simplicifolia*/Magnesium (50 and 200 mg, respectively) as a prophylactic treatment for MS. *Griffonia simplicifolia*, containing high concentrations of 5-hydroxy-l-tryptophan, might be effective for serotonin-related disorders, including MS. The *Griffonia*/magnesium complex was orally administered for 3 months to group A, while no therapy was administered to group B. At the end of the study, group A showed a significantly lower prevalence (36% vs. 73%; $p < 0.001$) and severity (evaluated through the visual analogical scale) of MS symptoms than group B (2.59–0.14 vs. 6.91–2.08; $p < 0.001$). No adverse drug reactions were recorded, except sporadic diarrhea and stomachache, during the first 2 days of treatment (3.14% of the subjects in group A). These results suggest that *Griffonia*/magnesium complex is a potential treatment for MS (Esposito et al., 2015; Di Mizio et al., 2021).

Conclusion

MS can be triggered by direct or indirect stimuli due to mismatches in the visual-vestibular and proprioceptive autonomic pathways. Movement by various means, the use of video games and virtual reality technologies, can generate provocative stimuli for MS. We presented the possibilities of drug treatment by critically analyzing them for some main aspects: the indication and the possibility of administration with respect to age, also suggesting the dosages officially reported. Considering the foregoing, the invitation remains to approach the pharmacological treatment of this problem with caution, keeping in mind the limitations regarding age and the off-label risk, and, at the same time, considering the behavioral and dietary prevention rules to avoid onset of symptoms. Finally, we must also consider the possibility of rehabilitation therapy, even with the same virtual reality tools that proved to be significantly effective and useful for MS (Ugur et al., 2022).

Footnotes

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References

Agenzia Italiana del Farmaco. (2016). Riassunto delle caratteristiche del prodotto: Ciproeptadina (ciproeptadina cloridrato). Agenzia Italiana del Farmaco.

American Geriatrics Society Beers Criteria® Update Expert Panel. (2019). American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society, 67(4), 674–694. https://doi.org/10.1111/jgs.15767

Ashrafi, M. R., Salehi, S., Malamiri, R. A., Heidari, M., Hosseini, S. A., Samiei, M., et al. (2014). Efficacy and safety of cinnarizine in the prophylaxis of migraine in children: A double-blind placebo-controlled randomized trial. Pediatric Neurology, 51(4), 503–508. https://doi.org/10.1016/j.pediatrneurol.2014.05.031

Boussageon, R., Vanderkam, P., Tudrej, B., Manach, C., Huas, C., Rat, C., Frèche, B., & Vaillant-Roussel, H. (2017). Clinical efficacy of acetylleucine, meclizine and betahistine in dizziness: Systematic review and meta-analysis of randomized controlled trials. Exercer, 133, 216–223.

Brainard, A., & Gresham, C. (2014). Prevention and treatment of motion sickness. American Family Physician, 90(1), 41–46.

Brandt, T., Wenzel, D., & Dichgans, J. (1976). Die Entwicklung der visuellen Stabilisation des aufrechten Standes beim Kind: Ein Reifezeichen in der Kinderneurologie [Visual stabilization of free stance in infants: A sign of maturity]. Archiv für Psychiatrie und Nervenkrankheiten, 223(1), 1–13. https://doi.org/10.1007/BF00367449

Dobie, T., McBride, D., Dobie, T., Jr., & May, J. (2001). The effects of age and sex on susceptibility to motion sickness. Aviation, Space, and Environmental Medicine, 72(1), 13–20.

Di Mizio, G., Marcianò, G., Palleria, C., Muraca, L., Rania, V., Roberti, R., Spaziano, G., Piscopo, A., Ciconte, V., Di Nunno, N., Esposito, M., Viola, P., Pisani, D., De Sarro, G., Raffi, M., Piras, A., Chiarella, G., & Gallelli, L. (2021). Drug-drug interactions in vestibular diseases, clinical problems, and medico-legal implications. International Journal of Environmental Research and Public Health, 18(24), 12936. https://doi.org/10.3390/ijerph182412936

Esposito, M., Precenzano, F., Sorrentino, M., Avolio, D., & Carotenuto, M. (2015). A medical food formulation of Griffonia simplicifolia/magnesium for childhood periodic syndrome therapy: An open-label study on motion sickness. Journal of Medicinal Food, 18(8), 916–920. https://doi.org/10.1089/jmf.2014.0113

Golding, J. F. (2006). Motion sickness susceptibility. Autonomic Neuroscience, 129(1–2), 67–76. https://doi.org/10.1016/j.autneu.2006.07.019

Golding, J. F. (2016). Motion sickness. In Handbook of Clinical Neurology (Vol. 137, pp. 371–390).

Golding, J. F., & Gresty, M. A. (2015). Pathophysiology and treatment of motion sickness. Current Opinion in Neurology, 28(1), 83–88.

Hamill, M. B., Suelflow, J. A., & Smith, J. A. (1983). Transdermal scopolamine delivery system (TRANSDERM-V) and acute angle-closure glaucoma. Annals of Ophthalmology, 15(11), 1011–1012.

Henriques, I. F., Douglas de Oliveira, D. W., Oliveira-Ferreira, F., & Andrade, P. M. O. (2014). Motion sickness prevalence in school children. European Journal of Pediatrics, 173, 1473–1482. https://doi.org/10.1007/s00431-014-2351-1

Houston, B. T., & Chowdhury, Y. S. (2022). Meclizine. In StatPearls. StatPearls Publishing.

Kassel, L., Nelson, M., Shine, J., Jones, L. R., & Kassel, C. (2018). Scopolamine use in the perioperative patient: A systematic review. AORN Journal, 108(3), 287–295. https://doi.org/10.1002/aorn.12336

Kirtane, M. V., Bhandari, A., Narang, P., & Santani, R. (2019). Cinnarizine: A contemporary review. Indian Journal of Otolaryngology and Head & Neck Surgery, 71(Suppl. 2), 1060–1068. https://doi.org/10.1007/s12070-017-1120-7

Lee, J. A., Watson, L. A., & Boothby, G. (1986). Calcium antagonists in the prevention of motion sickness. Aviation, Space, and Environmental Medicine, 57(1), 45–48.

Leung, A. K. (2011). Motion sickness. In A. K. Leung (Ed.), Common problems in ambulatory pediatrics: Symptoms and signs (pp. 323–328). Nova Science Publishers.

Leung, A. K., & Hon, K. L. (2019). Motion sickness: An overview. Drugs in Context, 8, 2019-9-4. https://doi.org/10.7573/dic.2019-9-4

Lin, C. H., Lung, H. L., Li, S. T., & Lin, C. Y. (2014). Delirium after transdermal scopolamine patch in two children. Journal of Neuropsychiatry and Clinical Neurosciences, 26(2), E01–E02. https://doi.org/10.1176/appi.neuropsych.12120411

Lin, Y. G., Chen, P. H., Chang, F. Y., Wu, L. T., Liao, K. Y., & Wu, T. C. (2011). Delirium due to scopolamine patch in a 4-year-old boy. Journal of the Formosan Medical Association, 110(3), 208–211. https://doi.org/10.1016/S0929-6646(11)60031-4

Lipson, S., Wang, A., Corcoran, M., Zhou, G., & Brodsky, J. R. (2020). Severe motion sickness in infants and children. European Journal of Paediatric Neurology, 28, 176–179. https://doi.org/10.1016/j.ejpn.2020.06.010

Liu, Y., Li, X. J., Liang, Y., & Kang, Y. (2019). Pharmacological prevention of postoperative delirium: A systematic review and meta-analysis of randomized controlled trials. Evidence-Based Complementary and Alternative Medicine, 2019, 9607129. https://doi.org/10.1155/2019/9607129

National Institute of Diabetes and Digestive and Kidney Diseases. (2017). Meclizine. In LiverTox: Clinical and research information on drug-induced liver injury. National Institutes of Health.

Oskoui, M., Pringsheim, T., Billinghurst, L., Potrebic, S., Gersz, E. M., Gloss, D., et al. (2019). Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology, 93(11), 500–509. https://doi.org/10.1212/WNL.0000000000008105

Page, C. B., Duffull, S. B., Whyte, I. M., & Isbister, G. K. (2009). Promethazine overdose: Clinical effects, predicting delirium and the effect of charcoal. QJM: An International Journal of Medicine, 102(2), 123–131. https://doi.org/10.1093/qjmed/hcn153

Patel, P., Paw Cho Sing, E., & Dupuis, L. L. (2019). Safety of clinical practice guideline-recommended antiemetic agents for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric patients: A systematic review and meta-analysis. Expert Opinion on Drug Safety, 18(2), 97–110. https://doi.org/10.1080/14740338.2019.1568988

Pergolizzi, J. V., Jr., Philip, B. K., Leslie, J. B., Taylor, R., Jr., & Raffa, R. B. (2012). Perspectives on transdermal scopolamine for the treatment of postoperative nausea and vomiting. Journal of Clinical Anesthesia, 24(4), 334–345. https://doi.org/10.1016/j.jclinane.2011.07.019

Qazi, F., Shoaib, M. H., Yousuf, R. I., Nasiri, M. I., Ahmed, K., & Ahmad, M. (2017). Lipids bearing extruded-spheronized pellets for extended release of poorly soluble antiemetic agent-meclizine HCl. Lipids in Health and Disease, 16(1), 75. https://doi.org/10.1186/s12944-017-0466-x

Riad, M., & Hithe, C. C. (2022). Scopolamine. In StatPearls. StatPearls Publishing.

Schnabel, L., Wuehr, M., Huppert, A., Bardins, S., Brandt, T., & Huppert, D. (2022). Age-dependent perturbation of the perceptual and postural vertical by visual roll vection and susceptibility to motion sickness in children. Journal of Neurology. Advance online publication. https://doi.org/10.1007/s00415-022-11017-x

Shinohara, M., Zhao, J., Fu, Y., Liu, C. C., Kanekiyo, T., & Bu, G. (2019). 5-HT3 antagonist ondansetron increases apoE secretion by modulating the LXR-ABCA1 pathway. International Journal of Molecular Sciences, 20(6), 1488. https://doi.org/10.3390/ijms20061488

Shupak, A., & Gordon, C. R. (2006). Motion sickness: Advances in pathogenesis, prediction, prevention, and treatment. Aviation, Space, and Environmental Medicine, 77(12), 1213–1223.

Simmons, R. G., Phillips, J. B., Lojewski, R. A., Wang, Z., Boyd, J. L., & Putcha, L. (2010). The efficacy of low-dose intranasal scopolamine for motion sickness. Aviation, Space, and Environmental Medicine, 81(4), 405–412. https://doi.org/10.3357/ASEM.2668.2010

Southard, B. T., & Al Khalili, Y. (2022). Promethazine. In StatPearls. StatPearls Publishing.

Spinks, A., & Wasiak, J. (2011). Scopolamine (hyoscine) for preventing and treating motion sickness. Cochrane Database of Systematic Reviews, 2011(6), CD002851. https://doi.org/10.1002/14651858.CD002851.pub4

Starke, P. R., Weaver, J., & Chowdhury, B. A. (2005). Boxed warning added to promethazine labeling for pediatric use. New England Journal of Medicine, 352(25), 2653. https://doi.org/10.1056/NEJM200506233522522

Takov, V., & Tadi, P. (2019). Motion sickness. In StatPearls. StatPearls Publishing.

Turner, D., Lurie, Y., Finkelstein, Y., Schmid, T., Gopher, A., Kleid, D., & Bentur, Y. (2006). Pediatric cinnarizine overdose and toxicokinetics. Pediatrics, 117(5), e1067–e1069. https://doi.org/10.1542/peds.2005-2059

Ugur, E., & Konukseven, B. O. (2022). The potential use of virtual reality in vestibular rehabilitation of motion sickness. Auris Nasus Larynx, 49(5), 768–781. https://doi.org/10.1016/j.anl.2022.01.012

Verhamme, K. M., Sturkenboom, M. C., Stricker, B. H., & Bosch, R. (2008). Drug-induced urinary retention: Incidence, management and prevention. Drug Safety, 31(5), 373–388. https://doi.org/10.2165/00002018-200831050-00002

Viola, P., Marcianò, G., Casarella, A., Pisani, D., Astorina, A., Scarpa, A., et al. (2022). The pharmacological treatment of pediatric vertigo. Children, 9(5), 584. https://doi.org/10.3390/children9050584

Weerts, A. P., Pattyn, N., Van De Heyning, P. H., & Wuyts, F. L. (2014). Evaluation of the effects of anti-motion sickness drugs on subjective sleepiness and cognitive performance of healthy males. Journal of Psychopharmacology, 28(7), 655–664.

Wibble, T., Engström, J., Verrecchia, L., & Pansell, T.

(2020). The effects of meclizine on motion sickness revisited. British Journal of Clinical Pharmacology, 86(8), 1510–1518. https://doi.org/10.1111/bcp.14257

Yayla, E. M., Yavuz, E., Bilge, U., Keskin, A., & Binen, E. (2015). Drugs with anticholinergic side-effects in primary care. Nigerian Journal of Clinical Practice, 18(1), 18–21.

Zhang, L. L., Wang, J. Q., Qi, R. R., et al. (2016). Motion sickness: Current knowledge and recent advance. CNS Neuroscience & Therapeutics, 22(1), 15–24. https://doi.org/10.1111/cns.12468

Zhang, X. C., Farrell, N., Haronian, T., & Hack, J. (2017). Postoperative anticholinergic poisoning: Concealed complications of a commonly used medication. Journal of Emergency Medicine, 53(4), 520–523. https://doi.org/10.1016/j.jemermed.2017.05.003