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Vertigo and H4 Antagonist Effect on Vestibular Symptoms

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Abstract

Vertigo is a condition when a patient feels that the objects around him are moving, and this condition can lead to falls and serious incidences. Vertigo has various etiologies including central, peripheral, psychogenic, and medication-induced vertigo. The most common cause is benign paroxysmal positional vertigo (BPPV) then Meniere's disease and labyrinthitis should be in the differential diagnosis. Ruling out serious conditions such as stroke is important. Various treatment options are used for vestibular symptoms and vestibular rehabilitation shows a positive result. Management of vertigo is the same for a long time despite the partial effect, unwanted side effects due to some drugs, and the need for multiple medications to relieve the symptoms in some patients. More effective treatment with lesser side effects needs to be used. Recently some *in vivo* trials come into view that H4 antagonist such as SENS-111 is effective in treating vestibular symptoms. These medications work by blocking the action of histamine, a chemical messenger involved in the immune response. More clinical trials and research need to be done on this type of treatment and other treatment options as this will lead to positive transformation in the future.

Subject Areas

Pharmacology

Keywords

Vertigo, Dizziness, Peripheral Vertigo, Central Vertigo

1. Introduction

Dizziness is a wide non-specific term used to describe a group of variant symptoms, sometimes referred to as the sensation of movement of surrounding objects when they are not moving [1]. One of the most frequent primary complaints in the emergency room is vertigo or dizziness, three subgroups of etiologies can be identified: neurotological (vestibular), medical (particularly cardiovascular and metabolic), and psychiatric illnesses [2]. Dizziness includes many sensations such as vertigo, lightheadedness, disequilibrium, and oscillopsia [1]. The causes of vertigo are different but the most common one is benign paroxysmal positional vertigo (BPPV), Meniere's disease, labyrinthitis and other less common causes including stroke, brain tumors, brain injury, multiple sclerosis, migraines [3]. Some studies reflect that there is a relation between vertigo and sleep apnea. The cumulative incidence of vertigo was substantially higher in patients with sleep apnea than in those without it [4], and there is possibly an association between the stress of the COVID-19 pandemic or immunization by vestibular disorders and vestibular migraine [5]. Vertigo is the experience of spinning while still in one place. Common symptoms include nausea or vomiting, falls, unsteadiness (postural instability), mental problems, and walking difficulty [6]. Vertigo sufferers usually experience recurrent attacks, which frequently reduce their quality of life. Additionally, possible symptoms include hearing loss, blurred vision, difficulty speaking, and a decreased state of consciousness [6] [7]. When a patient presents with dizziness, the evaluation can be challenging for the doctor and the patient themselves because of the broad differential diagnosis. Additionally, symptoms can be difficult to describe, and even though a single cause is not always identifiable, addressing the underlying cause can alleviate, if not resolve, dizziness symptoms and reduce the risk of falls [8]. In general, a competent diagnostic evaluation entails taking a step-by-step, in-depth medical history, doing a thorough physical examination, and ordering further tests as needed depending on clinical indicators [9]. The first step in separating the periphery causes of vertigo from the central ones is to take a thorough medical history. Even though this method has significant drawbacks, evaluating vertigo's intensity, timing, and causes may be beneficial [10]. For instance, individuals with sudden, severe, isolated vertigo may have a cerebellar stroke or acute vestibular neuritis/labyrinthitis. In contrast, individuals who have spontaneous episodic vertigo may also experience repeated, stereotyped transient ischemic attacks (TIAs) in addition to being impacted by vestibular migraine (VM) [10]. Positional vertigo in adults, often caused by benign paroxysmal positional vertigo (BPPV), may also have a central cause, particularly if it is chronic and accompanied by nystagmus. [11] The peripheral vestibular system contains histamine H4 receptors, [12] and specific inhibition of these receptors reduces the symptoms of vertigo in rats with unilateral vestibular injuries. A translational *in vivo* model of unilateral vestibular loss was used to assess the effects of SENS-111, a selective oral H4 receptor antagonist, on vertigo symptoms. This drug has a

strong affinity for both animal and human receptors [12]. This article aims to review the different common causes of vertigo and review its mechanisms; also we will go through different anti-vertiginous drug options and their possible side effects in addition to non-drug therapy. Furthermore, the effect of the new drug option on vestibular symptoms.

2. Differential Diagnosis

2.1. Common Peripheral Causes

2.1.1. Benign Paroxysmal Positional Vertigo

BPPV is defined as a transient sensation of movement of the surrounding, associated with vertical or horizontal nystagmus along with vertigo, and these symptoms exacerbate with a specific head movement [13]. Severe cases of BPPV could be accompanied by transient vomiting and nausea that lasts not more than 1 min and the patient will not complain of typical cochlear symptoms such as tinnitus and hearing loss [14]. BPPV is the most common cause of peripheral vertigo. 24.1% of all hospital visits with a complaint of dizziness or vertigo are due to BPPV [11]. BPPV could be primary which is also called idiopathic, or secondary in nature. Idiopathic nature represents the most common cases, and the pathophysiology is not well clear [15]. Otoconia which are the crystals of calcium carbonate in the utricle and saccule in the vestibular system detached from their place and enter the semicircular canal (SCC) and move into the endolymph or attach to the Capula in the ampulla and cause excitation or inhibition of the hair cells discharge there [16]. In the ear, there are 3 semicircular canals which are the anterior, lateral/horizontal, and posterior SCC. Although any of the 3 semicircular canals can be affected, the most common SCC affected is the posterior semicircular canal followed by the horizontal canal [17]. In secondary Benign paroxysmal positional vertigo, there is a cause identified [13]. In a review by Yetiser [13] most common secondary causes of BPPV are aging of the vestibular labyrinth due to an increase in age, head trauma, migraine, Meniere's disease, vestibular neuronitis, the gravitational impact of sleeping position especially following bedrest restrictions as after surgeries, diabetes and vitamin D deficiency, however, estrogen deficiency in postmenopausal women reported in some studies. The diagnosis of BPPV is done by the Dix-Hallpike maneuver to observe for nystagmus. Treatment consists of non-surgical procedures such as the canalith repositioning procedure (CRP) which is also called the Epley maneuver, with the aim repositioning of the displaced crystals from the affected canal to their original location [18]. Epley's maneuver and Semont's liberatory maneuver are effective for Posterior canal BPPV while barbecue rotation or the Gufoni maneuver has been demonstrated to be effective for horizontal canal BPPV [17]. Despite the fact that CRP maneuvers are effective in relieving vertigo symptoms in those patients, some will have residual symptoms even after the disappearance of typical vertigo and nystagmus [17]. Pharmacological management such as betahistine will result in better symptom control if it is used as an

additive therapy in a patient with posterior BPPV [19]. Moreover, the Reduction of relapse of BPPV symptoms is reached by correction of vitamin D levels in patients with vitamin D deficiency [20]. 69% of anti-psychotics are used for controlling BPPV, chronic diseases, sleeping disorders, and irritable bowel syndrome [21].

2.1.2. Meniere's Disease (MD)

Episodic vertigo, tinnitus, and sensorineural hearing loss are three core symptoms that define Meniere's disease [22]. Meniere's disease also affects the patient's social functioning [23]. Endolymphatic hydrops which is explained as the expansion of the volume found in the endolymphatic spaces and dilatation of Reissner's membrane is the most histological pathology of Meniere's disease [23]. The hydrops could be either due to dysregulation of endolymph production or obstruction of the endolymphatic duct and/or dysfunction of the endolymphatic sac [24]. The sign of endolymphatic hydrops has been confirmed with published studies of the temporal bone [22]. Meniere's disease is an idiopathic disorder but when it happens secondary to other conditions it is called Meniere syndrome, the secondary condition could be infection, genetics, or trauma [25]. Diagnostic categories of Meniere's disease are considered according to the Barany Society described in (**Table 1**) [26].

The diagnosis is often challenging in both primary and secondary care because of the absence of a pathognomonic test [27]. We are far from using MR imaging as a new diagnostic tool for MD and its role is mainly to exclude other diseases such as schwannoma [28]. High dietary intake of salt affects the composition of the endolymph by affecting the concentration of electrolytes in the blood, also high concentrations of alcohol and caffeine can exacerbate the symptoms of MD through vasoconstriction and a decrease in blood supply to the inner ear [25].

Table 1. The two diagnostic categories of Meniere's disease according to the Barany Society.

Definite Meniere's disease	Probable Meniere's disease
≥2 Spontaneous episodes of vertigo each last for 20 minutes to 12 hours.	≥2 Spontaneous episodes of vertigo lasting for 20 minutes to 24 hours.
Documented low-to medium-frequency sensorineural hearing loss in one ear through an audiometer, defining and locating the affected ear in at least one instance prior to, during, or after one of the episodes of vertigo.	Fluctuating aural symptoms (Fullness, tinnitus, hearing loss) in the affected ear.
Fluctuating aural symptoms (fullness, hearing, tinnitus) located in the affected ear.	Not better accounted for by another diagnosis.
Not better accounted for by any other vestibular diagnosis.	

Therefore, restriction of salt, caffeine, and alcohol is considered the first-line treatment [25]. Step-up treatment when recommended will begin with conservative antivertigo treatment such as betahistine then non-destructive techniques for example application of a trans-tympanic steroid and lastly if no relief in symptoms, invasive destructive techniques will be used such as labyrinthectomy [29]. Other medications can be used such as thiazide diuretics, but their use is not commenced in primary care because of their potential side effect of renal dysfunction and electrolyte disturbance [30]. Just In the case of intractable MD, intratympanic gentamycin is used [31]. However, the risk of hearing loss is shown in many studies, but it depends on the dose used and intervals [32].

2.1.3. Vestibular Neuritis

Vestibular neuritis also known as vestibular neuronitis is a disease that happened secondary to inflammation of the vestibular portion of the 8th cranial nerve and the patient classically presents with symptoms of vertigo, nausea, and gait imbalance [33]. A few days just before the full onset of vestibular neuritis symptoms, a quarter of patients may present with prodromal dizziness lasting a few minutes that precede the prolonged spontaneous vertigo of vestibular neuritis [34]. The inflammation could be a current viral infection causing inflammation and edema of the nerve [33] or could be due to the reactivation of a latent neurotropic virus, herpes simplex virus (HSV) types 1 and 2, and herpes zoster (varicella) virus are the best-known members of this group of viruses [35]. Some cases of vestibular neuronitis were reported after COVID-19 vaccination which is immune-mediated [36]. Moreover, anterior vestibular artery ischemia is thought also to cause vestibular neuritis [37]. The diagnosis of VN is done by bedside observing of ocular motor findings by Head Impulse, Nystagmus, and Test of Skew (HINTS) which is a three-step bedside examination, so when unidirectional nystagmus observed plus positive head thrust opposite to the direction of the fast phase of nystagmus and no vertical eye misalignment and no other neurological features, therefore the patient will be diagnosed with acute vestibulopathy [35]. Vestibular neuronitis is a benign condition and usually self-limiting [38]. Vestibular suppressant medications such as Promethazine, Meclizine, Diazepam, Lorazepam, and antiemetics are used to control severe vertigo, nausea, and vomiting but they should be limited to the first several days [39]. Some studies demonstrate that patients presented and treated within 24 hours of symptoms onset using oral prednisolone have better restitution of vestibular function than those who are treated after 25 to 72 hours [40]. Patients should be encouraged to resume normal activity as soon as it is safe and possible as this will facilitate prompt and full functional recovery to provide the brain with a full range of vestibular inputs and this could be done by directed vestibular therapy with the assistance of a trained physiotherapist [39].

2.1.4. Labyrinthitis

Labyrinthitis is an inflammation of the membranous labyrinth located in the in-

ner ear [41]. Viral or bacterial infection of the inner ear considers the most common cause of labyrinthitis, and viral infection is considered superior to bacterial sources of infection. The least causes include an inflammatory process of the inner ear, temporal bone trauma, hemorrhage, and tumors [42]. Labyrinthitis ossificans is a condition that happened secondary to labyrinthitis when fibrosis happens in the membranous labyrinth and become filled with ossified material [43]. Thus, patients with ossification often present with irreversible SNHL and vertigo [44]. Presence of sensorineural hearing loss and tinnitus differentiate labyrinthitis from other vestibular conditions such as vestibular neuronitis and benign paroxysmal positional vertigo (BPPV) [45]. The diagnosis of labyrinthitis is mainly clinical, therefore detailed history and a neurological examination in addition to an otological examination are valuable [46]. A progressive clinical recovery is seen when oral prednisone is used daily for one week in association with physiotherapy rehabilitation [41].

2.1.5. Eustachian Tube Dysfunction

Eustachian tube or pharyngotympanic or auditory tube has a complex anatomy, and it is important in regulating middle ear homeostasis [47]. Eustachian tube failure is a failure in maintaining middle ear pressure equal to that of the nasopharynx, mucociliary transport of clear inflammatory products and secretions from middle ear and Eustachian tube to nasopharynx, and protection of middle ear from potential hazard such as pathogens and secretion coming from nasopharynx and loud sounds [47]. ETD can cause ear tightness, pain and discomfort or fullness, hearing loss and tinnitus in one or both ears which could be either intermittent or constant [48]. Many pathologies and factors can contribute to ETD which could be singular or in combination together such as microbial, immunological, environmental, and genetic factors that contribute to development of otitis media with effusion (OME), tympanic membrane perforation or retraction, and middle ear atelectasis, chronic suppurative otitis media, and cholesteatoma in long term [49]. The most common conditions that contribute to ETD are rhinosinusitis, allergic rhinitis and laryngopharyngeal reflux [50]. The three categories of ETD are obstructive ETD, patulous ETD, and barotrauma ETD [49]. Obstructive Eustachian tube dysfunction (OETD) is the most common [50]. The diagnosis is made through tympanometry and audiometry, patient symptoms and physical examination [51]. Furthermore, examination via otoscopy, endoscopy, Valsalva, and Toynbee maneuver, and Politzer test may give initial guidance to the diagnosis [52]. Treatment of ETD depends on managing the underlying cause of the inflammation [53]. Surgical options for treatment for chronic cases include Laser tuboplasty. Moreover, minimally invasive methods for treating chronic OETD, such as balloon dilation eustachian tuboplasty (BET), are also considered [52].

2.2. Central Vertigo

Brain ischemia of the brainstem, cerebellum or vestibular nuclei is the most

common cause of central vertigo especially in those elder patients with vascular risk factors [54]. On the other hand, demyelination secondary to multiple sclerosis is the most common cause of central vertigo in young patients [54]. Other causes include brain lesions, seizures, migraine, vascular, degenerative, developmental, and paraneoplastic etiologies, and toxins [55]. Toxicity secondary to medication such as phenytoin, carbamazepine, and phenobarbital anticonvulsant is not so uncommon cause [54]. A study by Wang *et al.* found that ages more than 60, hypertension, diabetes, smoking, and past history of stroke are risk factors for central vertigo and the risk of central vertigo was great in patients with 3 or more risk factors [56]. Machine learning (ML) obtained in the triage is a model designed to predict central vertigo with simple clinical data including non-whirling-type of dizziness, elderly, male gender, and present history of stroke was shown to be important factors for predicting central dizziness and it showed moderate accuracy [57]. The onset of vertigo, duration, vertigo related to posture, ear symptoms such as tinnitus or hearing impairment, previous history of the same episodes, history of sick contact, fever, headache, skin rash, vascular risk factors, history of medications and dosage, and any neurological symptoms for example weakness, numbness, diplopia, or dysarthria all are important history that should be obtained [54]. Central vertigo can continue for a long time usually weeks to months and head position changes have minimal effect on it, but this can occur [58]. To identify central causes of acute vertigo and unsteadiness, the HINTS test and STANDING test which include positional maneuver and gait evaluation are used [59]. Moreover, the vestibulo-ocular reflex (VOR) must be reviewed before the HINTS test [60] [61]. However, the oculomotor test is useful in diagnosing central lesions, and its sensitivity range from 54.2% - 66.7% and specificity 43% - 67.1%, but also it requires more caution when examining patients with different comorbidities and older adults [62]. Vertical skew and bidirectional nystagmus in the HINTS test are most suggestive of a central cause of vertigo [63]. In addition, an oculomotor test suggestive of the horizontal axis in the smooth pursuit test, the vertical axis in the saccade test, and the vertical axes in the gaze-evoked nystagmus test needs assessment of central disorders [62]. The gold standard imaging for the diagnosis of central vertigo is computed tomography scan (CT) and magnetic resonance imaging scan (MRI) as any intracranial lesions can be detected [64]. Even though, imaging could be normal in the first 48 hours after symptoms onset [63]. Based on Swartz and Kern's study, patients with migraine are four times more likely to have hyper-intensity of white matter in MRI scans than those without migraine [65]. Sankalia and colleagues' study found that in the first 24 hours of spontaneous vertigo, the HINTS battery was more sensitive than the initial head MRI in diagnosing stroke [66]. Balance rehabilitation and, depending on the syndrome, pharmacological treatments are multimodal approaches for treating patients with central vertigo [67]. Treatment of vertigo due to a certain type of strokes and brain injuries are challenging for some [68]. Vertigo responding to

H1 antagonist does not exclude the central cause [63]. Olanzapine was effective as an anti-emetic for central vertigo [69] and successful with low doses [58].

2.3. Drug-Induced Vertigo

One of the most common reported side effects of medications is ototoxicity [70]. Depending on the site of damage either in the cochlea or vestibular apparatus, drug-induced ototoxicity forms are cochleotoxicity and vestibulotoxicity [71]. Tinnitus and hearing impairment can be resulted due to cochleotoxicity, on the other hand, coordination impairment and dizziness/vertigo resulted from vestibulo-toxicity, and it can happen during using the medication or after [72]. Therefore, the risk of falls will increase [73] and consequently will impact the quality of life [73]. And here is an example of medications that induce vertigo listed in (**Table 2**) [74].

2.4. Psychogenic Vertigo

Despite the fact that common causes of dizziness are vestibular, neurologic, and cardiac disease, it is also important to put in mind that psychiatric disorders are common as well [75]. Vestibular syndromes may be a primary cause of the psychiatric disorder, or psychiatric disorder could be a secondary complication of vestibular disorder [76]. Psychiatric disorders account approximately for 8% - 10%

Table 2. Short list of medications that may cause vertigo.

Medicine Class	Examples
Analgesics	Codeine
Antibiotics	Aminoglycosides, macrolides, minocycline, nitrofurantoin, sulfamethoxazole
Anticonvulsants	Levetiracetam, phenytoin, pregabalin
Anti-inflammatories	Celecoxib, parecoxib, naproxen, prednisone
Antimalarials	Mefloquine, quinine, hydroxychloroquine
Antivirals	Oseltamivir, raltegravir
Anti-Parkinson's drugs	Lisuride
Cardiovascular drugs	Nifedipine, furosemide, indapamide, prazosin, terazosin, glyceryl trinitrate, isosorbide mononitrate, sotalol, timolol
Gastroenterology drugs	Omeprazole, lansoprazole, sucralfate
Rheumatology drugs	Zolendronic acid, alendronate
Phosphodiesterase type-5 inhibitors	Sildenafil, vardenafil
Other medicines	Lithium, haloperidol, benzodiazepines, desmopressin, melatonin

of the primary causes of vestibular symptoms in patients presenting to neuro-otology centers [76]. Vague symptoms description, chronic dizziness, and relieving of dizziness episodes with benzodiazepine use all raise suspicion of psychiatric disorders [75]. In addition, past history of psychiatric disorder can give a clue to the doctor [75]. Le *et al.* study found that psychogenic vertigo has a female predominance [77]. Disorders such as depression, anxiety, and bipolar can present as disorientation, dizziness, or psychogenic vertigo [78] [79].

3. Treatment

3.1. Symptomatic Treatment

The effect of symptomatic treatments to suppress vestibular symptoms such as vertigo is effective in those whose episodes last at least hours or days and those with recurrent symptoms, on the other hand, it's not beneficial in brief vertigo episodes [80]. In addition, symptomatic treatment is given for relieving severe symptoms of vertigo and vomiting which is probably in the first two days [80]. Histaminergic medication such as betahistine is used for vertigo. Betahistine is a potent histamine H3 receptor antagonist and weak H1 receptor agonist [81]. Oral betahistine is a well-known medication used for approximately half a century in Europe, it well known suppresses the severity and the frequency of vertigo, and high doses of it can be tolerated [82]. For Meniere disease (MD), betahistine is used to control symptoms when used for a duration of fewer than 3 months and to prevent further attacks when used for more than 3 months [82]. Mild adverse effects were reported such as nausea, GI distention, and headache [83]. Antihistamines, anticholinergic and benzodiazepines are all vestibular suppressants medication [84]. Lorazepam, diazepam, and clonazepam are examples of benzodiazepines, and meclizine, diphenhydramine, and dimenhydrinate are antihistamines with anticholinergic properties which are all used for vertigo [84]. Antihistamines have fewer adverse effects than anticholinergics, and among all antihistamines, meclizine is the long-acting drug [85]. However, somnolence, dry mouth, blurred vision, mydriasis, urinary retention, headache, and gastrointestinal symptoms are the important adverse effects of dimenhydrinate [86]. Promethazine is a first-generation antihistamine with an antiemetic effect. A study by Saberi and colleagues to investigate the effect of ondansetron and promethazine in acute peripheral vertigo found that both medications are effective in controlling vertigo and nausea, but promethazine was more effective in improving vertigo and ondansetron more effective in resolving nausea and vomiting [87]. Benzodiazepines act on GABA receptors, therefore, suppress vestibular injury [88]. Other treatments include cinnarizine, it's a piperazine derivative with antiserotonergic, antihistaminic, antidopaminergic, and calcium channel-blocking effects [89]. Its effect in treating acute peripheral vertigo was well documented [90]. Drowsiness, weight gain, less frequent GI disturbances, and depression are the adverse effect of cinnarizine [85]. Flunarizine, a derivative of cinnarizine with also calcium-antagonist and antihistamine properties, is used for vertigo and

migraines [89]. Its adverse effects are similar to cinnarizine in addition to rhinitis and myalgia [91]. Diuretics effect in reducing endolymphatic hydrops in a patient with Meniere disease (MD) has been reported, but the evidence that supports its use is low [92]. However, impaired glucose tolerance and an increase in cholesterol, triglycerides, and calcium levels are adverse reactions of thiazide diuretics such as hydrochlorothiazide [86] [93] [94]. Antipsychotics, such as prochlorperazine, are used now for a long time for vertigo and it is used for up to one week for an acute attack of vertigo management, but extra-pyramidal symptoms should be checked [85]. In the case of refractory vertigo in patients with Meniere's disease, it was suggested that oral prednisone is good antivertigo management [95] and a good treatment for hearing loss in those patients when applied intratempanically [96]. Despite that, oral prednisolone has considerable systemic risks, and some don't recommend it in MD [97].

3.2. Vestibular Rehabilitation

For those who present with chronic vestibular dysfunction with activity limitations, impairments, and participation restrictions, physicians should offer vestibular rehabilitation [98]. Vestibular rehabilitation builds the patient's confidence and strength to maintain the balance through the integration of proprioceptive, visual, and residual vestibular function [99]. The effect of Vestibular rehabilitation studied in Meniere's disease by Liu *et al.* randomized control trial with 66 patients distributed in three groups: a betahistine group, a vestibular rehabilitation therapy group, and a control group with no treatment and found that both betahistine and vestibular rehabilitation reduce risk of falling and can improve quality of life although vestibular rehabilitation was more effective than betahistine [100].

4. Discussion

The pathophysiology of vertigo is still lacking, and comprehensive knowledge is impeded by definitions that are non-standardized [101]. Full detailed history, careful clinical examination, and investigations according to the clinical indications, are all needed for suitable diagnostic evaluation [102]. Taking a precise medical history for a patient presenting with vertigo is considered the first step in distinguishing between peripheral and central causes [103] Asking about the time of vertigo, intensity, and triggering factors may be helpful [104]. For example, when a patient presents with isolated vertigo which is acute and spontaneous in onset the patient might have acute vestibular neuritis/labyrinthitis or cerebellar stroke [103]. On the other hand, if presented with a spontaneous episodic attack of vertigo he might have vestibular migraine (VM) or suffer from recurrent TIA [105]. Positional vertigo in adult indicates mainly that the patient might have benign paroxysmal positional vertigo (BPPV), but if it is persistent and associated with nystagmus gives a clue to central origin [105]. Also, the patient should be investigated regarding the presence of associated symptoms be-

cause it could be missed initially or misleading such as headache in vestibular migraine and hypoacusis in anterior inferior cerebellar artery strokes (AICA) [104]. The input from the otolith organs and the three semicircular canals in the peripheral vestibular system gave us the sensation of balance and position, incorporated with visual and proprioceptive information in the vestibular nuclei [101]. These vestibular signals can be disturbed by damage to the sensory hair cell, damage to the neurons, or synaptic uncoupling [101]. Central and peripheral neurons organize this complex process depending on acetylcholine, glutamate, γ-aminobutyric acid, and glycine, all neurotransmitters modulated by adrenaline, noradrenaline, and histamine [106] [107]. Neurotransmission, chemotaxis, inflammation, dilation of capillaries, smooth muscle contraction, production of cytokine and gastric acid secretion all are complex physiologic changes generated by histamine via 4 sub-types of G protein-coupled receptor (GPCR): H1, H2, H3 and H4 receptor [108]. Histamine through H1 receptor in the CNS regulates endocrine hemostasis and energy, memory and cognition and sleeping and awaking cycle [109]. Also, histamine modulates the neurotransmitters release from histaminergic and nonhistaminergic neurons of the central and peripheral nervous system through presynaptic H3 receptors, and through H4 receptor will facilitate some proinflammatory activities [109]. It found that histaminergic system has it roe also neoplasia's such as oral, esophageal, gastric, colorectal, liver, pancreatic, skin, lung, breast, and blood cancers with H_4 receptor rising up as the most convincing candidate for targeting [110]. Findings between 2015 to 2019 showed that the increase in use of antihistamine in general was relevant and use in chronic and sub-acute duration was preferred [111]. Antihistamines should pass the blood-brain barrier to reach the central parts of the vestibular system while the peripheral parts of the vestibular system are protected by blood-labyrinth barrier [112]. A recent meta-analysis evaluated 13 randomized control trials published between 1977-2006 that used placebo and single antihistamine drug which is primarily betahistine and included approximately 900 patients, they reported the value of antihistamine in treating vertigo and confirmed its benefit with an odds ratio of 5.37, 95% confidence interval (3.26 - 8.84) [113]. Diphenhydramine is the most well-known first-generation antihistamine, and it has been available since 1946 and from that time the association of dangerous side effects such as sedation, respiratory depression, coma, and death has been clear [114]. Therefore, this led to creation of less sedating newer second and third generation antihistamines and was available first in Canada in the 1980s [114]. This newer generation also has minor interaction with cholinergic and serotoninergic receptors [109]. Second generation antihistamine is highly selective for H1 receptors that have relatively few sides effect in setting of overdose and because of their limited penetration of the blood-brain barrier under the control of active transporter proteins (ATP-dependent efflux pump, P glycoprotein (Pgp)), they are considered minimally sedating or non-sedating [109]. In spite of that, physician should take caution while prescribing H2 anti-

histamine for those people at risk of delirium and assessment of the patient is advocated [115]. From first- and second-generation antihistamine, bilastine and fexofenadine are considered the least sedating options [116]. Betahistine is the best known among the H_3 receptor antagonists used today [101]. It shows that Combination therapy for vertigo may improve outcomes over only a single drug [113]. H3 receptor antagonism found its selective role in neurons which provided a promising therapeutic approach in peripheral nephropathy and analgesic effect effectiveness [117]. Johnson & Johnson Research and Development discovered the first potent and selective H4 receptor antagonist JNJ7777120 and this discovery was essential for evaluating the role of H4R in pathophysiology, and its immune reaction in inflammation and pruritus [118]. Recently found that H4 receptors have a role in the pathologies of the inner ear and the vestibular system [101]. And a novel oral small molecule SENS-111 is the first H4 receptor antagonist class found, and it has a high binding affinity to both human and animal H4 receptors [101]. Its effect on vertigo and nystagmus induced via caloric irrigation was evaluated in a dose escalation randomized double-blind study in healthy volunteers and concluded that oral SENS-111 is safe as a single once daily use for 7 days with repeated doses up to 250 mg [119]. The safety of SENS-111 is extremely encouraging in the clinical investigation with not reaching the maximum tolerated dose and its side effect was mild to moderate such as headache and back pain and considered transient in comparison with placebo [119] [120] and neither drowsiness nor sedation has been reported [101]. An excitotoxic vestibular loss model for assessing the effect of H4 receptor antagonist (SENS-111) on rats found that when administering human equivalent doses of meclizine and methylprednisolone as single agents this resulted in a minimal reduction of nystagmus one hour after administration of the dose, while when SENS-111 combined with meclizine it showed a beneficial effect on peak acute vertigo, while the combination of SENS-111 and methylprednisolone was also beneficial on vertigo symptoms [12]. In the end, the medical management of vertigo is rarely satisfactory and complicated so accordingly, the interaction of therapeutic modalities with other medications, adverse effects, persistent recovery, and patient satisfaction should be taken into consideration and the need for further trials needed to compare the efficacy of a single drug option and investigate the balance between clinical benefits and risk of adverse effect [113].

5. Conclusion

Vertigo is a common presentation, and the approach to such presentation is complicated and varied. Central causes should be ruled out first by distinguishing red flags in the patient's history and examination. Symptomatic treatment for vertigo is broad, and in many patients, single treatments are not very effective. Future clinical trials on the efficacy of H4 receptor antagonists (such as SENS-111) and other treatment options, including single medication with fewer side effects, are warranted.

Conflicts of Interest

The authors declare no conflicts of interest.

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