Therapeutic interventions in vertigo management

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ABSTRACT

Vertigo is a condition associated with a spectrum of symptoms and ~30% of general population experience vertigo in their life time. In spite of being of high clinical importance, the management of vertigo is quite challenging. Though the literature supports the availability of various therapeutic interventions used in vertigo treatment, their effectiveness depends on accurate diagnosis, appropriate use of intervention, and physician’s awareness of the overlap between vestibular, autonomic, and psychological aspects of vestibular pathology. Unfortunately, several drugs act as tranquilizers and impede the process of vestibular compensation. Betahistine, a histamine analogue, is one of the most commonly used anti-vertigo drugs worldwide and has been supported by many clinical trials. There have been several oral communications in international conferences on the efficacy of using betahistine in several clinical vertiginous syndromes. The current review assesses the use of betahistine 48 mg twice daily for three months as an efficient and well-tolerated treatment for vertigo. Additionally, it highlights the low incidence of side effects even at high doses of betahistine and suggests that it may be considered as the first-line of treatment for vestibular dysfunction.

Keywords: Betahistine, Benign paroxysmal positioning vertigo, Peripheral Vertigo, Vestibular dysfunctions, Vestibular compensation, Meniere's disease

INTRODUCTION

Vertigo is a term that refers to an illusion of self or environmental motion, typically described as spinning or whirling.¹ It is a basic clinical presentation associated with various diseases with different etiologies such as disorders related to inner ear, brainstem, cerebellum or psychology.² Vertigo affects a large number of individuals in general population. The lifetime prevalence of vertigo is ~30% worldwide with an associated comorbidity of 3.2%.¹,⁴ The overall prevalence of vertigo was reported to be 0.71% in an adult rural population from Chandigarh, India.⁵

Vertigo presenting as a symptom can have either central or peripheral cause. Benign paroxysmal positioning vertigo (BPPV) is the most frequent form of peripheral vestibular disorders with a lifetime prevalence of 1-2.4% in the general population.⁶,⁷ BPPV is generally observed to result from canalolithiasis which is caused by otoconia, i.e., calcite crystals. These crystals are removed from the utricle, followed by free movement in the semicircular canals.² The reported female-to-male predominance ratio of vestibular dysfunction is about 5:1.¹⁹ A study conducted in 17,718 patients at a German Center for Vertigo and Balance Disorders reports the five most common forms of vertigo diagnosed at their center as BPPV, somatoform phobic vestibular vertigo, central vestibular syndromes, vestibular migraine, and Meniere’s disease (MD) (Table 1).²

The classical symptoms of vertigo include dizziness, imbalance, migraine, nausea, vomiting, sweating, pallor, spatial disorientation, and diarrhea.¹⁰ Light-headedness or
Vertigo can severely affect the individual’s quality of life, who becomes relatively incompetent to undertake normal work or social activities, has persistent sleep for several hours, and an off-balance sensation lasting for several days. Vestibular dysfunction in adults may result in serious handicap with considerable psychological morbidity. Most of the patients tend to recover within a few weeks, while some may show incomplete recovery. Diagnosis and identification of co-morbid systemic disorders, such as hypertension, vascular disease, type 2 diabetes mellitus and autoimmune syndromes is indispensable as they may affect vestibular compensation if proper treatment is not given. Successful therapeutic management depends on accurate diagnosis, appropriate interventional approaches, and physician’s awareness of the overlap between vestibular, autonomic, and psychological aspects of vestibular pathology.

Based on the current knowledge on vertigo and its management, the present review attempts to highlight the various non-pharmacological and pharmacological therapeutic interventions used in the management of vertigo. Further, it brings out the awareness about the best and effective treatment practices for early control of this debilitating condition.

**THERAPEUTIC MANAGEMENT OF VERTIGO**

The initial step in vertigo management is to reassure and explain the nature of the symptoms to patients, and give proper hydration if necessary. The systematic rehabilitation plan for each patient should be based on the diagnosis. The plan includes detailed elucidation to ensure appropriate understanding and total compliance with the program. The five main pillars of management intervention are as follows: 1. General medical evaluation with treatment of associated comorbid conditions, 2. Vestibular rehabilitation with physiotherapy and management of BPPV, 3. Psychological intervention, 4. Pharmacological intervention, and 5. Surgery.

**NON-PHARMACOLOGICAL INTERVENTIONS FOR VERTIGO**

Vertigo should be managed via appropriate strategies so as to attain adequate control over functional activities such as eye coordination, head, and body movements. This may further result in appropriate focus, stability, and posture with no adverse symptoms. Vestibular rehabilitation therapy (VRT) is a non-pharmacological exercise-based treatment strategy for vertigo management. VRT helps in the recovery of vestibular mechanisms such as vestibular adaptation, eye-movement coordination, somatosensory cues, postural stabilization, and other habitation. The key exercises are head-eye movements with various body postures and activities, maintaining balance with less or no support in various orientations of the head and trunk while performing various upper-extremity tasks, repeating the movements provoking vertigo, and exposing patients gradually to various sensory and motor environments. VRT improves quality of life and postural balance. Yet, in some cases such improvement may also need additional pharmacologic treatment. Other measures include dietary restriction, lifestyle adaptations and stress reduction techniques.

Psychological disorders may result in incomplete recovery of vertigo. Initial assessment and examination of the patient’s psychological and avoidance behavior, together with the study of his mood change can be helpful in getting a better understanding of his problems. The presence of avoidance behavior makes patient-compliance with the VRT program unlikely.

**PHARMACOLOGICAL INTERVENTIONS FOR TREATMENT OF VERTIGO**

The ideal antivertiginous drug would prevent vomiting and dizziness, and promote vestibular compensation. The most common group of drugs used in the treatment of vertigo are diuretics, antiemetics, histamine analogues, antihistamines, steroids, antivirals, antimicrobials, calcium channel blockers, antidepressants, anti-convulsants, and aminopyridines. Antiemetics can be administered orally (if feasible), intramuscularly, as a suppository or via buccal membrane. The pharmacological management of vertigo is determined after recognizing the underlying reason behind vertigo. The most commonly observed reasons to initiate vertigo treatment are as follows:

- Acute vestibular related clinical presentation.
- Causes of vestibular symptoms such as MD and epilepsy (This involves disease specific treatment).
- Any chronic vestibular disorder such as central vestibular symptomatology (This requires non-specific but empirical treatment strategy).

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**Table 1: Forms of vertigo and their prevalence among 17,718 patients of a German center for vertigo and balance disorders.**

<table>
<thead>
<tr>
<th>Forms of vertigo</th>
<th>Prevalence N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign paroxysmal positional vertigo</td>
<td>3036 (17.1)</td>
</tr>
<tr>
<td>Central vestibular syndromes</td>
<td>2178 (12.3)</td>
</tr>
<tr>
<td>Phobic vestibular vertigo</td>
<td>2661 (15.0)</td>
</tr>
<tr>
<td>Vestibular migraine</td>
<td>2017 (11.4)</td>
</tr>
<tr>
<td>Meniere’s disease</td>
<td>1795 (10.1)</td>
</tr>
<tr>
<td>Vestibular neuritis</td>
<td>1462 (8.3)</td>
</tr>
</tbody>
</table>

Table 2: Commonly used therapeutic drugs for vertigo.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose and duration</th>
<th>Mechanism of action</th>
<th>Side effects</th>
<th>Effects on vestibular compensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnarizine</td>
<td>75 mg/day for 3 days</td>
<td>• Selective calcium channel blocker, acts predominantly on the peripheral vestibular labyrinth by affecting local calcium ion flux &lt;br&gt; • Lowers whole blood viscosity, and &lt;br&gt; • Is effective for vertiginous syndrome caused by over-reactivity or unbalanced activity of labyrinthe apparatus in the inner ear &lt;br&gt; • Suppresses the eye movement response or nystagmus</td>
<td>• Sedation &lt;br&gt; • Pedal edema &lt;br&gt; • Extrapyramidal disorders</td>
<td>• Delays vestibular compensation</td>
</tr>
<tr>
<td>Cinnarizine + Dimenhydrinate</td>
<td>Cinnarizine 20 mg+ dimenhydrinate 40 mg/day for 3 days</td>
<td>• Cinnarizine regulates vestibular calcium influx of the labyrinth and improves cerebral circulation &lt;br&gt; • Dimenhydrinate regulates vestibular nuclei and adjacent vegetative centers in the brain-stem &lt;br&gt; • The actions of cinnarizine are reinforced by dimenhydrinate &lt;br&gt; • The fixed combination effectively reduces the vertigo symptoms and decreased the concomitant vegetative symptoms</td>
<td>• Effect on occupation and cognition extra pyramidal side effects &lt;br&gt; • High somnolence</td>
<td>• Delays vestibular compensation</td>
</tr>
<tr>
<td>Betahistine</td>
<td>48 mg/day, 3-6 months</td>
<td>• Increases cochlear and vestibular blood flow &lt;br&gt; • Increases histamine turnover in the central nervous and vestibular system &lt;br&gt; • Increase in the level of histamine in damaged vestibular nuclei reduces inhibition by intact vestibular nuclei by H3 hetero-antagonistic action</td>
<td>• Mild side effects including gastrointestinal complaints, fatigue and altered taste</td>
<td>• Facilitates vestibular compensation</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>10-15 mg/day</td>
<td>• Decreases abnormal excitement in the brain &lt;br&gt; • No effect upon any measure of nystagmic or perceptual vestibular function</td>
<td>• Extrapyramidal symptoms &lt;br&gt; • Drowsiness and dizziness &lt;br&gt; • Dry mouth &lt;br&gt; • Headache &lt;br&gt; • Fever &lt;br&gt; • Muscle stiffness &lt;br&gt; • Irregular heartbeat &lt;br&gt; • Sweating</td>
<td>• Delays vestibular compensation</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg/6 to 8 hours</td>
<td>• Causes inhibition throughout the central nervous system, including activity in the vestibular nerve and vestibular nuclei</td>
<td>• Drowsiness &lt;br&gt; • Dizziness &lt;br&gt; • Respiratory depression</td>
<td>• Delays vestibular compensation</td>
</tr>
</tbody>
</table>

Combination of drugs belonging to the same class, however, is not recommended. Long term use of vestibular suppressants and/or tranquilizers is counterproductive for vestibular compensation. These drugs should be recommended only for truly acute vertigo and stopped as soon as the symptoms of vertigo recede. The prominent side effects associated with the use of anticholinergic agents which are used in the management of vertigo such as dry mouth, dilated pupils, and sedation, especially in elderly people with vertigo also restrict their use.

Calcium channel antagonists may give extrapyramidal side effects in elderly patients. Antihistamines may
cause sedation which is detrimental for the recovery process, and limits their administration in the first three days of acute vestibular loss.\textsuperscript{18,19} Also, there is a consensus that drugs which exert sedative effect on the vestibular system should be used only for the first 24 hours.\textsuperscript{19} The effectiveness and safety of betahistine in different types of peripheral vertigo have been reviewed by various research groups.\textsuperscript{1,2} Betahistine is associated with the benefits of histamine, but, it is not associated with the adverse effects observed with histamine such as headaches, flushing, blurred vision, vomiting, or sedation. Moreover, it exhibits no interference with vestibular rehabilitation. Thus, Vertigo patients who have been on betahistine therapy are not at high risk of fractures due to which they can continue their day to day activities without any modifications and anxiety of having falls.\textsuperscript{11} Acute vestibular symptoms are managed by antiemetic and vestibular suppressant drugs.\textsuperscript{11} Based on the available literature, most commonly used therapeutic drugs are presented in Table 2.\textsuperscript{1,12,15,20,31}

Surgical intervention for vertigo is very rarely required. Specific exceptions to this rule include complications of chronic middle ear disease, neoplasm involving otological structures, and trauma to the middle/inner ear.\textsuperscript{13} Patients with intractable posterior canal BPPV do not present any sign of spontaneous remission. Moreover, they do not respond to repositioning exercises, therefore, they may require surgical treatment options.\textsuperscript{32,33}

**BETAHISTINE: PHARMACOLOGY AND MECHANISM OF ACTION**

Betahistine is the most frequently chosen anti-vertigo drug worldwide.\textsuperscript{22} Chemically 2-[2-(methylamino)ethyl]pyidine, betahistine is almost completely absorbed after oral administration. Its maximum plasma concentration (Cmax) is achieved after one hour of oral administration. Food intake merely slows down the absorption process, but does not impair the total absorption of the drug.\textsuperscript{3} Two salt formulations of the drug are currently available – betahistine dihydrochloride and betahistine mesilate. Chemical structure and molecular weight comparisons suggest that for delivery of an equivalent dose, a patient would need to take fewer tablets of betahistine dihydrochloride than of betahistine mesilate, taking currently available formulations and maximum recommended doses into account.\textsuperscript{34,35} Betahistine hydrochloride is an oral preparation of a histamine precursor which acts as a partial agonist at H1 receptors and a powerful antagonist at H3 receptors of the inner ear.\textsuperscript{1} It increases cochlear and vestibular blood flow as well as cerebral blood flow.\textsuperscript{22,23,36} It increases histamine synthesis centrally within tuberomammillary nuclei of the posterior hypothalamus, which results in histamine release within vestibular nuclei by antagonizing H3 autoreceptors. This mechanism is coupled with betahistine’s less specific effects on regulation of alertness (through cerebral H1 receptors) to promote and facilitate central vestibular compensation.\textsuperscript{37} The main result of betahistine therapy obtained to date is linked to its facilitating vestibular compensation. The efficacy of this drug in vertigo therapy is derived from its action on histamine receptors.

**BETAHISTINE: DOSE, DURATION AND EFFICACY**

**Meniere’s disease (MD)**

Betahistine has shown considerable efficacy at the standard dose range of 8–48 mg daily for treatment of MD and other types of peripheral vertigo.\textsuperscript{28,39} Initial (8–16 mg thrice daily) and maintenance (24–48 mg daily) doses are adjusted according to the response to treatment.\textsuperscript{1,39} Many studies have shown that the daily dose of betahistine (48 mg) for three months is an effective and safe treatment option for treatment of peripheral vertigo.\textsuperscript{1,39,42} As per Alcocer et al, betahistine at dosage of 48 mg daily for three months has shown an excellent safety profile for treatment of vertigo in more than 40 years of its clinical use.\textsuperscript{1} The efficacy of betahistine (48 mg/day for 3 months) was greater than that of cinnarizine (75 mg/day) in reducing time to compensation after vestibular neurectomy for MD.\textsuperscript{39} Djelilovic-Vranic et al also noticed that betahistine (48 mg) produced better effect in terms of symptoms reduction in MD than cinnarizine within one month of treatment.\textsuperscript{20} Comparing the efficacy and tolerability of betahistine (16 mg, twice daily) with cinnarizine (25 mg, twice daily) in the treatment of otogenic vertigo, a study reported that the treatment with betahistine led to significantly greater improvement in mean vertigo scores and is better tolerated than cinnarizine.\textsuperscript{23} Betahistine has also shown to be efficacious in MD treatment in combination with intratympanic dexamethasone (ITD). Complete vertigo control was higher in patients who were given betahistine 144 mg/day (48 mg TID) than those who were given ITD with placebo.\textsuperscript{41}

**BPPV**

Unlike other anti-vertigo drugs, betahistine helps in increasing the effectiveness of Epley maneuver in vertigo management. Combination of Epley maneuver, and betahistine therapy, has been found to be more effective than Epley maneuver alone or combined with placebo in certain patients.\textsuperscript{38} Use of cinnarizine or other labyrinthine sedatives together with Epley maneuver was, however, found to cause delay in the recovery process. These drugs, as they cause sedation of the labyrinth, attenuate the signals sent by the labyrinth to the brain, which in turn delays the recovery process even if the particle repositioning is achieved by Epley maneuvers.\textsuperscript{41} However, future clinical studies are needed to investigate the benefit of pharmacological treatments in combination with Epley maneuver.\textsuperscript{56} The clinical summary of betahistine use globally and in India is presented in Table 3 and Table 4, respectively.\textsuperscript{20,23,26,38,42,44,47}
Table 3: Review of some clinical studies conducted on the dosage, efficacy and safety of betahistine.

<table>
<thead>
<tr>
<th>Author, et al</th>
<th>Year</th>
<th>Patients (N)</th>
<th>Indication and study</th>
<th>Dose and duration</th>
<th>Efficacy end points</th>
<th>Safety end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morozova et al</td>
<td>2015</td>
<td>N=204</td>
<td>Vestibular Vertigo Observational study (OSVaLD study)*</td>
<td>• Betahistine: 16 mg thrice a day &lt;br&gt; • Mean treatment duration: 91±5 days</td>
<td>Total DHI score improved by 43 points with betahistine treatment.</td>
<td>Drug was well tolerated with very low incidence of adverse effects</td>
</tr>
<tr>
<td>Lezius et al</td>
<td>2011</td>
<td>N=11</td>
<td>Severe Meniere’s disease Retrospective analysis</td>
<td>• Betahistine-288 and 480 mg/day &lt;br&gt; • Treatment duration: ~ 4.1 ± 1.4 years</td>
<td>Improvement in patients with positive influence on cochlear function &lt;br&gt; Moderate recovery of hearing &lt;br&gt; Ability of verbal communication preserved &lt;br&gt; Number of vertigo attacks significantly lower with the high dosage</td>
<td>Long-term high dosage betahistine prophylaxis is potent and safe &lt;br&gt; No serious adverse events were documented &lt;br&gt; Side effects did not require any change in the treatment strategy &lt;br&gt; Mild side effects, namely gastrointestinal complaints (N=4), fatigue (N=4), and altered taste (N=1)</td>
</tr>
<tr>
<td>Djelilovic-Vranic et al</td>
<td>2012</td>
<td>N=73</td>
<td>Meniere’s disease Observational study for 2 years</td>
<td>• Betahistine: 16 mg thrice daily during hospitalization and subsequently for 8 weeks &lt;br&gt; • Cinnarizine: 75 mg bid for 8 weeks</td>
<td>Decrease in vertigo attacks &lt;br&gt; Cessation of vomiting and nausea &lt;br&gt; Slight improvement in noise tinnitus and hearing impairment</td>
<td>Betahistine is well tolerated without any usual side effects</td>
</tr>
<tr>
<td>Ganaca et al</td>
<td>2009</td>
<td>N=120</td>
<td>Meniere’s disease Randomized, open label study</td>
<td>Betahistine: 16mg thrice daily or 24 mg twice daily Treatment duration: 24 weeks</td>
<td>Significant improvement in clinical outcome level from baseline (p&lt;0.01)</td>
<td>Betahistine is well tolerated &lt;br&gt; Low incidence of adverse effects &lt;br&gt; The most frequently reported adverse events: headache, epigastric disturbance, anxiety and insomnia &lt;br&gt; Decrease in incidence of adverse effects with time</td>
</tr>
<tr>
<td>Strupp et al</td>
<td>2008</td>
<td>N=112</td>
<td>Meniere’s disease Open non-masked trial</td>
<td>• Betahistine-dihydrochloride at two dosages: low dosage (16-24 mg thrice a day) vs high dosage (48 mg thrice a day) &lt;br&gt; • Treatment duration: 12 months</td>
<td>Decrease in mean number of attacks in 3 months &lt;br&gt; Low-dosage: 7.6 (4.5) to 4.4 (2.0) (p&lt;0.0001) &lt;br&gt; High dosage: 8.8 (5.5) to 1.0 (0.0) (p&lt;0.0001)</td>
<td>Treatment well tolerated in both groups</td>
</tr>
</tbody>
</table>

*OSVaLD: Observational Study in Patients Suffering from Recurrent Peripheral Vestibular Vertigo to Assess the Effect of Betahistine 48 mg/day on Quality of Life and Dizziness Symptoms
Table 4: Review of clinical trials in India on the dosage, duration, efficacy and safety of betahistine.

<table>
<thead>
<tr>
<th>Author et al</th>
<th>Year</th>
<th>Patients (N)</th>
<th>Indication and study</th>
<th>Dose and duration</th>
<th>Efficacy end points</th>
<th>Safety end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodla et al\cite{23}</td>
<td>2011</td>
<td>N=80</td>
<td>Otogenic Vertigo Prospective, comparative, single-center study</td>
<td>• Cinnarizine (25 mg, thrice a day) vs Betahistine (16 mg thrice a day) • Treatment duration: 4 weeks</td>
<td>• 2-fold decrease in intensity of symptoms with Betahistine (p=0.001) and pronounced lowering of vertigo-associated (p=0.009) with Betahistine.</td>
<td>• The drug Betahistine was well tolerated with no serious adverse events reported with both compounds • Two patients having Betahistine reported non-serious adverse events – Headache: one patient – Abdominal pain: one patient</td>
</tr>
<tr>
<td>Baneck e et al\cite{46}</td>
<td>2010</td>
<td>N=1796</td>
<td>Acute Vertigo, Multicenter, open-label OSVaLD* study</td>
<td>• Betahistine 48 mg/day (as 24 mg twice a day or 16 mg thrice day) • Given as monotherapy or as adjunctive therapy • Treatment duration: Three months</td>
<td>• Improvement in quality of life of patients • Improvement in DHI, HADS and SF-36v2 following betahistine treatment – Total DHI score improved 37.2 points – Significant improvements in both HADS-A and HADS-D scores (p&lt;0.001), – Improvements in the distribution profiles of anxiety and depression scores</td>
<td>• Adverse drug reactions in 2.4% patients. • Drug is satisfactorily tolerable</td>
</tr>
<tr>
<td>Bradoo et al\cite{47}</td>
<td>2000</td>
<td>N=29</td>
<td>Severe Meniere’s, Open prospective study as out-patient trial</td>
<td>• Betahistine (16 mg thrice a day) after meals • No other vertigo medication • Treatment duration: 6-weeks</td>
<td>• Frequency of attacks reduced by 61.66% after one week • Baseline (14.66 attacks/week) vs Betahistine-therapy (5.62 attacks/week), p&lt;0.05. • Duration of attacks reduced by 53.18% after one week • Average severity score reduced by 36.9% after 1 week of treatment</td>
<td>• The drug is well tolerated with mild incidence of side-effects • No adverse signs or symptoms were noted in any patient – Gastrointestinal side effects such as gastrointestinal upset, hyperacidity not noted with this dose</td>
</tr>
<tr>
<td>Padgao nkar et al\cite{38}</td>
<td>1999</td>
<td>N=1739</td>
<td>BPPV, Open, multicenter prospective study</td>
<td>• Betahistine: 1-2 tablets (8 mg Betahistine /tablet) daily to all patients • Treatment duration: Six weeks</td>
<td>• Frequency of attacks reduced by 96.6% • Mean duration of attacks reduced by 97.1% • Average severity score reduced by 93.5%</td>
<td>• Betahistine was well tolerated with very low incidence of adverse effects</td>
</tr>
</tbody>
</table>

#VSm: Mean vertigo score; *DHI: Dizziness handicap inventory; **HADS: Hospital anxiety and depression score; +SF-36v2: Short-Form; BPPV: benign paroxysmal positional vertigo; **OSVaLD: Observational study in patients suffering from recurrent peripheral vestibular vertigo to assess the effect of betahistine 48 mg/day on Quality of Life and dizziness symptoms.
Pathophysiology of MD shows a misbalance between the influx and efflux of fluids that leads to an alteration of the endolymphatic pressure, which in turn causes endolymphatic hydrops. It is postulated that betahistine regulates capillary structures in the stria vascularis of the inner ear, reducing the pressure in the endolymphatic space, and facilitating the reabsorption of endolymphatic fluid.  

High doses of betahistine with a long-term follow-up have shown to increase cochlear perfusion resulting in improved efficacy in the treatment of MD.  

Many clinical studies conducted on Indian population have reported and established the standard dose and efficacy of betahistine (discussed in Table 4).  

The multicenter, open-label OSVaLD study (a three-month observational study in patients suffering from recurrent peripheral vestibular vertigo to assess the effect of betahistine 48 mg/day on quality of life and dizziness symptoms) was conducted on 1796 patients in 13 countries including India (23 centers) to assess the efficacy and safety of drug in vertigo management. Data obtained from the OSVaLD study illustrated that treatment with betahistine (48 mg/day) for three months in patients with recurrent peripheral vestibular vertigo is associated with improvements in objective measures of health-related quality of life and satisfactory tolerability. On treatment with betahistine, all the study endpoints, i.e., the Dizziness Handicap Index (DHI; all p<0.001 vs. baseline), Hospital Anxiety and Depression Score (HADS; p<0.001) and the short-form (SF)-36v2 showed a significant improvement and reported betahistine as well tolerated drug.  

A study reported that betahistine (16 mg, thrice daily) helped to reduce average frequency of vertigo attacks by 61.7%. On completing three weeks of therapy, the frequency of attacks was reduced by 95.3% (0.7 attacks per week), which was highly significant (p<0.001). Average duration of attacks was reduced by 53.2% after one week of treatment (baseline: 33.8 minutes vs. treatment: 15.8 minutes, p<0.05). Duration of attacks was further reduced by 93.9% after three weeks of betahistine treatment (baseline: 33.8 minutes vs. treatment: 2.07 minutes). All the patients got total relief from vertigo attacks after 5 weeks of betahistine treatment.  

It was found that both low doses (16 or 24 mg twice daily) and high dose (48 mg twice daily) of betahistine were well-tolerated by the patients. Betahistine has shown acceptable safety profile with mild side-effects. Gastrointestinal complaints (fullness of the stomach and diarrhea), light-headedness, headache, and mild vegetative symptoms were the common side-effects reported. Nonetheless, these side effects did not cause reduction in dosage or a cessation of treatment. However, betahistine is contraindicated for patients with pheochromocytoma. The OSVaLD study, a 3-month multicentre, open-label post-marketing surveillance study of betahistine (48 mg per day) assessing its safety and tolerability, reported 76 adverse drug reactions (ADRs) in 49 patients (2.4%). Out of all, 75 were considered as mild or moderate, whereas, 54 were possibly betahistine related ADRs.  

**EFFECT OF HIGH DOSAGE OF BETAHISTINE**

A study was focused on the effect of long-term high-dose treatment of MD with betahistine on the frequency of the attacks. In an open trial on 112 patients with MD, a higher dosage of betahistine dihydrochloride (48 mg twice daily) and long-term treatment (12 months) was found to be more effective than a low dosage (16-24 mg twice daily) and short-term treatment. Later, a study by Lezius et al., 2011 demonstrated the clinical benefit of high dosages of betahistine dihydrochloride (288-480 mg) in patients with severe MD. The patients who did not exhibit adequate response to dosage of 144 mg/day, were further treated on individual basis with a higher daily dosages of betahistine (288-480 mg) of betahistine dihydrochloride. Hence, it is reported that high dosages were well-tolerated with mild side effects in 46.0% of the patients (Table 3).  

**BETAHISTINE: SAFETY AND TOLERABILITY**

Betahistine is generally well-tolerated as an anti-vertigo drug without any sedative effect. It was found that gastrointestinal, headache, and nausea were possibly betahistine related ADRs. Out of all, 75 were considered as mild or moderate, whereas, 54 were possibly betahistine related ADRs.  

**EFFECT OF BETAHISTINE ON OTHER ASSOCIATED CLINICAL SYMPTOMS**

Betahistine does not only reduce vertigo attacks, but is reported equally efficient in reducing the associated clinical symptoms. On treatment with betahistine, a significant decrease in nausea (96.2%), vomiting (97%), tinnitus (84.3%), and hearing loss (77.9%) was reported in patients with vertigo. Likewise decrease in nausea and relief from headache and hearing loss were also reported in another study. Patients with vestibular disorders also found betahistine (48 mg dose given daily for 120 consecutive days) useful in eliminating tinnitus. However, physicians must familiarize themselves with the safety precautions for any related medication in order to provide appropriate treatment. Research on the effect of betahistine on vertigo and other related comorbidities are still nascent. A recent study assessing the efficacy of oral betahistine in prevention or reversing of hearing deterioration in patients with MD reported betahistine as an effective drug. To understand more on the effectiveness of betahistine in hearing loss of MD, long follow-up studies considering the age, duration of disease, sex and the initial hearing level are recommended.
CONCLUSION

Vertigo has always been a clinical symptom and is referred to various terms such as giddiness, dizziness, imbalance etc. that affect the quality of life. Literature review on clinical studies and recent meta-analyses indicate that betahistine 48 mg daily for three months is effective and a well-tolerated treatment dose. A clear advantage of betahistine is its ease of management with low incidence of side-effects even at doses up to 48mg daily. Significant improvements in the control of vertigo, BPPV and other types of peripheral vertigo have been demonstrated with betahistine therapy. Thus, the current review indicates that the betahistine can be considered as the first line of treatment for vestibular dysfunction and is reportedly safe and well tolerated by a majority of patients.

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REFERENCES


