*Review Article*

# Betahistine as a treatment for vertigo: A systematic review of randomized controlled trial

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**Abstract**

**Background:** Vertigo is the subtype of dizziness and impair patients' health-related quality of life. Betahistine is generally well-tolerated as an anti-vertigo drug. **Objective:** This systematic review aimed to identify the effectiveness of betahistine in vertigo patients. **Methods:** Systematic research was done by using PubMed and Cochrane. with following terms to search: "vertigo medication", "betahistine", "betahistine dihydrochloride", "betahistine mesilate", and "betahistine in vertigo". The quality of randomized controlled trial (RCT) study is assesed by using Jadad score by and **t**he selected studies were reviewed by using PRISMA checklist as the guidance. **Results:** There were 2669 citation from PubMed and Cohcrane. After adjusting for inclusion and exclusion criteria, the final result was a total 6 RCT studies included in this review. One study was discarded because lack of quality as an RCT study, thus remained 5 studies. All selected studies were RCT published in English within the last 10 years, involved subjects with vertigo. Each study was compared betahistine to: different dose of betahistine, diuretics, promethazine, dietary salt restriction, or Semont's maneuver. **Conclusion:** Among 5 studies, 4 studies prove betahistine is an effective drug in vertigo treatment.

***Keywords***: betahistine, vertigo, systematic review

## Introduction

Dizziness is a term used by patients to describe various sensations such as lightheadedness, imbalance, illusory feelings of movement and disorientation (Murdin et al., 2013). Vertigo is the subtype of dizziness, defined as an illusory sensation of motion of either the self or the surroundings in the absence of true motion (Bhattacharyya et al., 2017). Vertigo is a symptom not a diagnosis. There are many disorder or disease with vertigo as the main symptom. Table 1 summarized the differential diagnosis of vertigo.

The origin of vertigo may involve some anatomy structures. The maintenance of the sense of balance and spatial orientation depends on input from the vestibular labyrinth, visual system, and proprioceptive nerves arising from tendons, muscles, and joints. The vestibular nuclei, which are in the medulla and lower pons, receive input from the vestibular labyrinth via the vestibular branch of cranial nerve VIII and from the cerebellum. The vestibular nuclei, in turn, send efferent fibres to the cerebellum, the medial longitudinal fasciculus, and the vestibulospinal tract (Mehndiratta and Kumar, 2010). Thus, the etiology of vertigo may arise from inner ear, brainstem, cerebellum, or may be of psychic origin (Strupp et al., 2013) and can be defined as peripheral vertigo and central vertigo based on the involved anatomy structure.

Another differential diagnosis of peripheral vertigo, based on REVERT Registry, is peripheral vestibular vertigo of unknown origin or pathophysiology (PVVP). From total 4294 subjects, at least 832 subjects considered as PVVP (Agus et al. 2013). Additional differential diagnosis of central vertigo i.e.: vestibullar migraine (Rea, 2010), stroke, transient ischemic attack (Gnerre et al., 2015), and vertebrobasilar ischemia (Li et al., 2011). Vertigo may also triggered by psychiatric disorder, such as anxiety disorder (Kerber and Baloh, 2011).

Vertigo impair patients' health-related quality of life (QoL) (Duracinsky et al., 2007). Vertigo are common in the general population with lifetime prevalences of about 7 % (Lempert and Neuhauser, 2009). Based on a neurotologic survey of the general population, 1 year vertigo prevalence 4.9% (Neuhauser and Hannelore, 2007). Based on a

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**Table 1**. Differential Diagnosis of Vertigo(Zatonski et al., 2014)

| Cause of Vertigo | Duration of Symptoms | Hearing Disorders | Central/Peripheral Vertigo |
|---|---|---|---|
| BPPV | Seconds | No | Peripheral |
| Vestibular neuritis | Days | No | Peripheral |
| Perilymph fistula (PLF) | Seconds | Yes | Peripheral |
| MD | Hours | Yes | Peripheral |
| Labyrinth concussion | Days | Yes | Peripheral |
| Labyrinthitis | Days | Yes | Peripheral |
| Acoustic neuroma | Months | Yes | Peripheral |
| Ischemic causes | Seconds hours | Not usually | Peripheral or central, depending on the place of ischemia |
| Migraine | Hours | No | Central |
| Cerebellum's damage/tumor | Months | No | Central |
| Multiple sclerosis | Months | No | Central |

BPPV: Benign Paroxysmal Positional Vertigo, MD: Meniere's Disease

research by Bisdroff et al. (2013), the 1 year prevalence for vertigo was 48.3% from 2987 adults.

Furthermore, vertigo prevalence differed based on differential diagnosis of vertigo. Von Breven et al. (2007) state the prevalence of BPPV was more common in older adults, with a prevalence of 3.4% in individuals over age 60, and the cumulative lifetime incidence was almost 10% by age 80 (von Brevern et al., 2007). The prevalence rate for MD range from 3.5/100000 to 513/100000 (Alexander and Harris, 2010). Other study mention the prevalence of MD is 190/100000 (Harris and Alexander, 2010). Retrospective cohort study in patients reffered to a tertiary care balace clinic showed 19.7% patients were diagnosed BPPV, 12.7% MD, 5.8% vestibular paroxysmia, 7.2% bilateral vestibulopathy, 14.4% vestibular migraine, and 40.6% psychogenic vertigo (Grill et al., 2014). BPPV and MD are the most common vertigo diagnosis.

Betahistine is an oral preparation of a histamine precursor (Philips and Prinsley, 2008). Betahistine acts as a partial agonist at $H_1$ receptors and a powerful antagonist at $H_3$ receptors of the inner ear (Alcocer et al., 2015). Two salt formulations of betahistine are currently available i.e.: betahistine dihydrochloride and betahistine mesilate (Kameshwaran and Sarda, 2017). Betahistine is generally well-tolerated as an anti-vertigo drug without any sedative effect (Gananca et al., 2009). Many previous studies concern on betahistine as the main treatment on betahistin. To identify the effectiveness of betahistine in vertigo patients, we reviewed a randomized controlled trial (RCT) study.

## Methods

### Data Sources

Systematic research was done by two reviewer. The database was using PubMed and Cochrane. We use the following terms to search: "vertigo medication", "betahistine", "betahistine dihydrochloride", "betahistine mesilate", and "betahistine in vertigo". The guideline selection process showed in figure 1. It was made based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) four-phase flow diagram (Liberati et al., 2009).

### Study eligibility, criteria, participants, and intervensions

Characterized of included studies i.e.: (i) the study was conducted in the last 10 years (between 2007 to 2017), (ii) English as the main language, (iii) the studies performed in human only, (iv) the subjects had vertigo, (v) betahistine was the main drug assesed in the study, and (vi) the study was identified the effectiveness of betahistine in vertigo patients. Any diagnosis of vertigo was included in this review. Betahistine may be betahistine dihydrochloride or betahistine mesilate. Betahistine may compared to different dose of betahistine, other drugs, or canalith repotition maneuver. The result must be concern on comparison of efficacy between groups or measure the effectiveness of betahistine. The study excluded if: (i) not a randomized controlled trial (RCT) study and (ii) the full text was not available. Eligibility assessment was performed independently by two review authors.

### Appraisal process

The quality of RCT is assesed by using Jadad score by two appraiser. Studies are scored according to the presence of three key methodological features of clinical trials. Jadad score has 5 items. One point is added if the study fullfil each item, so maximum score is 5 (Berger and Alperson, 2009). The study will be excluded if the score is less than 3.

### Review process

The selected studies were reviewed by two review authors using PRISMA checklist as the guidance. PRISMA checklist consists of 27 essential item to make a transparent systematic review and meta-analysis (Liberati et al., 2009). One review author extracted data from included studies and the second review author checked the extracted data. Disagreements were resolved by discussion between two review authors. Variables for which data were sought i.e: authors, year of publications, number of subjects, diagnosis of vertigo, type of intervention (betahistin compared to other drugs or maneuver), and outcome. The outcome was described the efficacy of betahistine compared to other drug or maneuver, measure by relative risk (RR) or p value.

## Results

There were 2669 citation from PubMed and Cohcrane.

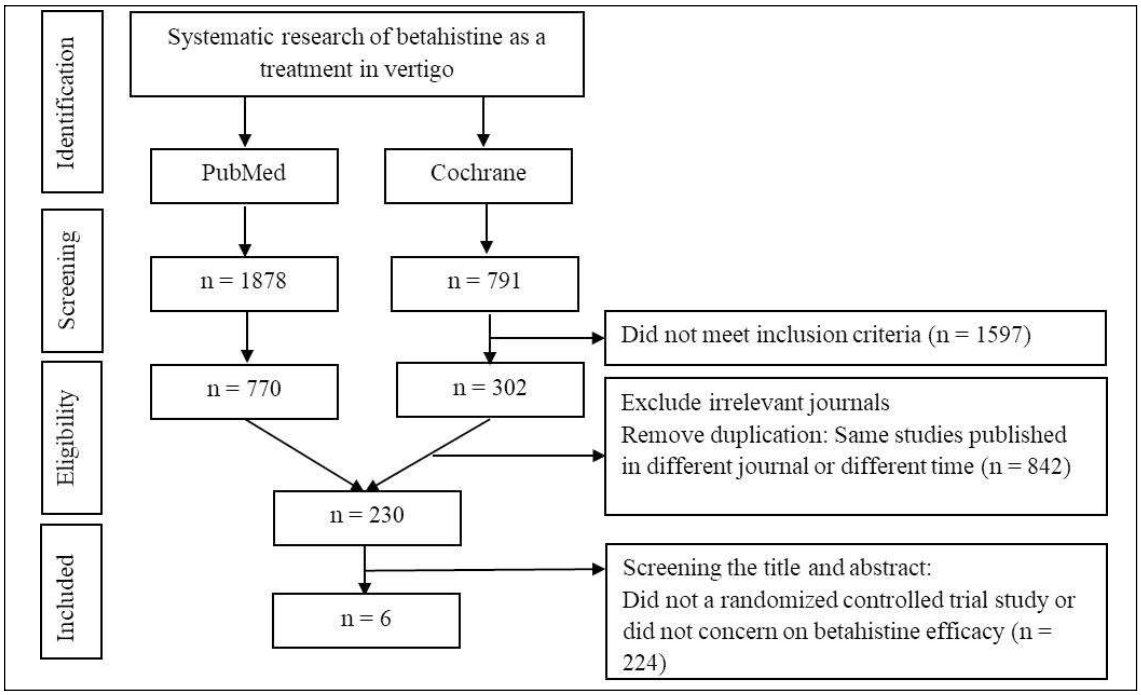


**Figure 1.** Study Selection Process

**Table 2**. Jadad Score

| Author (Year) | Was the study described as randomized? | Was the method used to generate the sequence of randomization described and appropriate? | Was the study described as double blind? | Was the method of double blinding described any appropriate? | Was there a description of withdrawal and dropout? | Total Score |
|---|---|---|---|---|---|---|
| Sokolova et al. (2014) | Yes | Yes | Yes | Yes | Yes | 5 |
| Ashfaq et al. (2015) | Yes | Yes | No | No | Yes | 3 |
| Acharya et al. (2016) | Yes | Yes | Yes | Yes | No | 4 |
| Adrion et al. (2016) | Yes | Yes | Yes | Yes | Yes | 5 |
| Bamaniya et al. (2016) | Yes | Yes | No | No | No | 2 |
| Motamed et al. (2017) | Yes | Yes | Yes | Yes | No | 4 |

After adjusting for inclusion criteria, 1072 remained. Of these, 842 discarded because of the full text was not available, not a RCT study, and/or duplication. About 230 remained journals were screened based on title and abstract. The final result was a total 6 RCT studies included in this review.

Table 2 showed the result of Jadad score for each study. Study by Bamaniya, et al. (2016) was discarded because lack of quality as an RCT study. They did not described the study as double blind and did not mention any withdrawal or dropout. The remained study were further reviewed.

All selected studies were RCT published in English within the last 10 years. The included studies involved subjects with vertigo. The most common diagnosis of vertigo was MD. All intervention received was betahistine compared to different dose of betahistine, placebo, diuretics, promethazine, dietary salt restriction, or Semont's maneuver.

**Discussion**

Study by Sokolova et al. (2014) was conducted in Ukraine. Sokolova, et al. were compare the efficacy and safety of

**Table 3.** Summary of Selected Studies

| Authors (Year) | Level of Evidence/ Study Design | Number of Subjects (Age) | Diagnosis of Vertigo among Participants | Intervention (Lenght of Study) | Outcome |
|---|---|---|---|---|---|
| Sokolova et al. (2014) | Level I/ RCT | 160 (≥45, mean = 58) | Peripheral vertigo not otherwise specified, vertiginous syndrome not otherwise specified | Betahistine 32 mg/day, *Ginkgo biloba* extract EGb 761 240 mg/day, and placebo (12 weeks) | There was no significant differences between 2 groups on severity (p: 0.704), symptoms (p: 0.319) and disability due to vertigo (p: 0.237). |
| Ashfaq et al. (2015) | Level I/ RCT | 70 (>38, mean = 53.4; 53.2) | BPPV | Betahistin 16 mg thrice daily and Semonts maneuver (15 days) | Semont's maneuver was more effective than betahistine (p: 0.006) |
| Acharya et al. (2016) | Level I/ RCT | 97 (mean = 47.86) | MD | Dietary sodium restriction + placebo, amiloride 5 mg + furosemide 40 mg, and betahistine 24 mg (3 months) | Betahistine was effective in reducing the number and severity of vertigo attacks (p <0.001) |
| Adrion et al. (2016) | Level I/ RCT | 221 (21-80, mean = 6.1; 56.1; 54.5) | MD | Betahistine 48 mg, betahistine 144 mg, and placebo (12 months) | Vertigo attack, RR 1.036 for low dose betahistine and RR 1.012 for high dose betahistine compared to placebo. |
| Motamed et al. (2017) | Level I/ RCT | 162 (18-65, mean = 41.8) | No spesific description on vertigo diagnosis | 25 mg promethazine IM injection, placebo, and betahistine 8 mg (1 year) | VAS level 2 and 3 hours after treatment were higher in promethazine group (p: 0.043; 0.039). |

RCT: Randomized Controlled Trial, MD: Meniere's Disease, BPPV: Benign Paroxysmal Positional Vertigo; RR: Rate Ratio; IM: intra muscular

*Ginkgo biloba* extract EGb 761 and betahistine. The subjects criteria in this study must had symptoms of vertigo for at least 3 months and scored at least 3 on a one-to-ten numeric analog scale (NAS) at screening. Evaluation of treatment efficacy and safety were scheduled 4, 8, and 12 weeks after baseline visit.

This study showed no significant differences between the two treatment groups with respect to treatment-related changes. *Ginkgo biloba* extract EGb 761 and betahistine are equally effective in the treatment of vertigo. The size of treatment effects did not vary with age, gender, clinical neurootological findings, or severity of symptoms. However, there are numerically, but not statistically significantly, more improvements in the subjects treated with *Ginkgo biloba* extract EGb 761.

The strength of this study is measure effectiveness of betahistine in two infrequent diagnosis of vertigo. Most of other studies are concern on BPPV or MD because of the high prevalence. In this study, vertigo diagnosis of the subjects were made based on International Classification of Disease 10th edition (ICD-10): peripheral vertigo not otherwise specified and vertiginous syndrome not otherwise specified. The randomization and blinding were described clearly. This study also used a spesific instruments to measure treatment efficacy i.e: Numeric Analog Scale (NAS), Vertigo Symptom Scale (VSS-SF), Sheehan Disability Scale (SDS), and Clinical Global Impressions (CGI) scale. The limitation of this study are 80 subjects per treatment arm the study did not have a statistical power to prove equivalence of the two treatment and the lack of placebo group as "negative" control.

Ashfaq, et al. conducted a research on BPPV treatment by comparing between Semont's maneuver and betahistine. Each group consist of 35 subjects. BPPV diagnosis was confirmed by positive Dix Hallpike test and normal pure tone hearing threholds. The subjects were re-evaluated on the 14th day of treatment. Both treatment groups showed significant improvement after 15 days (p: 0.006), but the rate was higher in Semont's maneuver group. About 89% on Semont's maneuver group were disease free, whereas in betahistine group only 57%. Only 3% in Semont's group remained in severe vertigo, while in betahistine group 11%.

The choice to compare betahistine to Semont's maneuver is no wonder. BPPV is caused by canalolithiasis or cupulolithiasis which producing false signaling during position changes (Ardic and Tumkaya, 2014) and Semont's maneuver is one of canalith repotition maneuvers designed to move the endolymphatic debris from the posterior semicircular canal into the vestibule (Nguyen-Huynh, 2012). Unfortunately, this study did not describe how Semon's maneuver performed and did not identify any subjects' side medication in Semont's maneuver group since it may interfere the results. History of vertigo (severity and number of attack) before the treatment was not clearly describe.

Research by Acharya, et al. was made to identify the first line treatment of MD. The study was conducted by comparing 3 groups: group A was advised to reduced salt intake in their diet, group B was given a combination

amiloride 5 mg and furosemide 40 mg taken every morning, and group C was given betahistine 24 mg at bedtime daily. Vitamin B complex was given to group A as the placebo. Each subject were followed up after 6 weeks.

By comparing pre- and post-treatment, number of vertigo was significantly decreased in group B ($p<0.001$) and group C ($p<0.001$). The severity of vertigo was significantly decreased only on group B ($p<0.001$). Dietary sodium restriction was ineffective in improving any parameter in MD.

This RCT are identify history of vertigo before the treatment by using visual analog scale (VAS). It made the comparison of pre- and post-treatment effectiveness easier. This study not only compared betahistin to other drug but also to non-pharmacology treatment. There are some limitations. Contraindication of diuretic and adverse effent on treatment groups were not described.

Research in German by Adrion, et al. aimed to measure efficacy and safety of betahistine in MD subjects. About 74 subjects received placebo,73 subjects received low dose betahistine (24 mg twice a day), and 74 subjects received high dose betahistine (48 mg thrice a day). This study had a strict re-evaluation at months one, four, six, and nine. At months two, three, five, seven, and eight each subjects had a standardise telephone interviews.

Vertigo attack rate ratio (RR) for low dose betahistine compared to placebo was 1.036 (95% CI: 0.942-1.140) and high dose betahistine compared to placebo was 1.012 (0.919-1.114). Attack rates was significantly decline in each treatment groups, but there were no significant differences across the treatment groups. The percentage of subjects with longlasting or more severe attacks did not significantly differ between treatment groups. The p value for attack duration was 0.348 and for attack severity was 0.390. The data showed that the experimental treatment with low or high dose betahistine did not lead to higher probabilities of attacks compared with placebo.

Excellent description of inclusion and exclusion criteria, randomisation and blinding process, study treatments, and analysis. This study had a spesific MD criteria to choose the subjects. The limitation of this study is using diaries in the patients' natural environment as the source data to measure "MD attacks in a given time periode" as the efficacy end point. It had a risk of having missing or inaccurate information compared to objective measurements.

The most recent study by Motamed, et al. compared the effect and side effects of betahistine and promethazine intra muscular (IM) injection in vertigo. Group A received 25 mg IM injection and group B received 8 mg betahistine. This study measured the vertigo severity changes by using VAS. Post treatment VAS test was done consecutively for each hour up to 3 hours.

There was no significant differences between groups at 1 hour after treatment, but at the second (p: 0.043) and third hours (p: 0.039) the VAS were higher in promethazine group. Clinical symptoms such as tinnitus, nausea, vomiting, and drowsiness, were also compared between both groups. After 1 (p: 0.0298), 2 (p: 0.0412), and 3 (p: 0.0398) hours the prevalence of subjects with no clinical symptoms were higher in betahistine group. Unwanted side effects were observed only in promethazine group. Overall, this study found that betahistine is more effective than promethazine in improving vertigo.

The strength of this study is using a spesific intrument to compare vertigo severity before and after treatment. The limitation of this study i.e: this study did not describe clearly the spesific vertigo diagnosis. It only describe how to select the subjects by performed many physical examination, but there was no report of vertigo diagnosis after performing the examination.

There are some mechanism of betahistine in vertigo. Betahistine may increased inner-ear blood flow with local vasodilation and increased permeability, thereby relieving pressure from the inner ear. It is a very important effect to MD (Yacovino and Luis, 2014). An animal experiments support previous statement, considering that betahistne has been found to enhance cerebral and cochlear blood supply and improve oxygenation of the inner ear, enhance central compensation and reduce nystagmus in humans, probably through an effect on the vestibular nucleii (Desloovere, 2008). Betahistine is almost completely absorbed after oral administration. Its maximum plasma concentration is achieved after one hour of oral administration (Alcocer et al., 2015).

Clinical studies and meta-analyses demonstrated that betahistine is effective and safe in the treatment of many types of peripheral vertigo (Alcocer et al., 2015). OSVaLD study is 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. Many countries involved in OSVaLD study. The study revelaed betahistine 48 mg/day was associated with improvements in multiple measure of health-related quality of life and had a good tolerability profile in patients with recurrent peripheral vestibular vertigo (Bajenaru et al., 2014; Benecke et al., 2010; Kirtane and Biswas 2017; Morozova et al., 2015). Other large study, the Virtuoso Study, stated the same results. Betahistine 48 mg/day in patients with recurrent peripheral vestibular vertigo is associated with improvements in objective measures of health-related quality of life and satisfactory tolerability (Parfenof et al., 2017)

**Conclusion**

Among 5 studies, 4 studies prove the effectiveness of betahistine in vertigo treatment. One study shows Semont's maneuver as a better treatment than betahistine to treat a spesific diagnosis of vertigo, that is BPPV.

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