Evidence-Based Medical Treatment in Peripheral Vestibular Diseases

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Evidence-based medicine grades scientific research articles according to their structural specification. It represents an evidence value that we can count on for clinical applications. In this review, we evaluate our medical treatment algorithm in peripheral vestibular diseases according to evidence-based medicine rules. Benign paroxysmal positional vertigo, vestibular paroxysmia, labryinthis, vestibular neuritis, otosclerosis, autoimmune inner ear disease, Meniere's disease, and migraine-associated vertigo are discussed.

Key Words: Vertigo, dizziness, medical treatment

Introduction
Peripheral vestibular disease is one of the major problems that physicians frequently encounter in all stages of the health system. The discussions and scientific research concerning the differential diagnosis, follow-up and treatment of these diseases continue, and each year, new proposals are put forward. Sometimes, it becomes difficult to decide which treatment would be appropriate for the patients and necessary to review the literature and evaluate new developments. Today, however, medical knowledge production is so vast that the evaluation of this knowledge has already exceeded the limits of one person alone. Thus, selective reading and gaining access to relatively reliable resources have become important. Evidence-based medicine has long been under study and an attractive concept. The scientific studies are classified according to the value of the knowledge they produce and apply on the patients based on this value. Initial studies began in 1970 and were studied by different groups in many different countries (1). The first version of the Oxford Centre for Evidence-Based Medicine system that we used in this article was made in 1998, and the last update was made in 2011 (2).

According to this, various levels were defined for any question that might arise in research studies, and a scale leveled on the only question “Is the treatment effective?” was used (Table 1). For the diseases prevalent in society, we generally use an algorithm whether in writing or not. We sometimes update it. The purpose of this study is to examine peripheral vestibular diseases that we frequently encounter during our everyday practice and the treatment algorithm that we apply in our clinic from an evidence-based medicine aspect (Figure 1-4). In this research, especially compilation and meta-analysis studies and randomized controlled trials were considered, and after each reference number, the value of evidence-based medicine was highlighted.

Clinical and Research Effects

Benign Paroxysmal Positional Vertigo (BPPV)
Benign paroxysmal positional vertigo is a disease that is caused by otoliths leaving utricular macula and free-floating in endolymph in semicircular canals (canalolithiasis) or by adhering to a canal cupula (cupulolithiasis) and producing false signaling during position changes. The basic diagnosis is vertigo that lasts seconds-minutes triggered by changes in positions. Diagnosis and treatment are performed through various maneuvers (Figure 1). The standard clinical approach does not require any medication. For some patients, however, in order to comply with treatment and to reduce dizziness and anxiety, medication might be used during the post-maneuver period.

In order to find an answer to the question “Which one can be more effective, betahistine or maneuver?”, Maslovara et al. (3) divided 96 patients randomly into two groups, and as a scale, they used the Dizziness Handicap Inventory (DHI). They stated that in the first and eighth weeks, the Epley maneuver showed statistically significant higher well-being (Table 1, Level 2 evidence). Güneri et al. (4) reported that adding 1-week betahistine
treatment to repositioning maneuver showed a higher rate of well-being according to the vertigo symptom scale for patients with hypertension, a history of less than 1 month, and symptoms less than 1 minute (Table 1 Level 2 evidence). Jung et al. (5), after randomly dividing 73 patients into 2 groups, gave 2-week low-dose etizolam (anxiolytic), in addition to repositioning maneuver, to one of the groups and reported that the group that was given medication showed a better state according to DHI measurements (Table 1, Level 2 evidence).

**Vestibular Paroxysm**

It is a clinical condition caused by vascular compression on the 8th nerve in the brainstem due to irregular warnings and is characterized by positional vertigo attacks that last seconds and sometimes hearing loss and ringing at high frequencies. It is also referred to as neurovascular cross-compression syndrome (Figure 1). It is diagnosed with magnetic resonance imaging, brainstem audiometry (ABR- auditory brainstem response), and hyperventilation test. The vessel that causes vascular compression in 75% of the patients is the anteroinferior cerebellar artery (AICA) (6).

The first choice in treatment is pharmacotherapy. Responding to DHI measurements (Table 1, Level 2 evidence). Table 1. The scale that is leveled on the question “Is the treatment effective?” of the Oxford Centre for Evidence-Based Medicine system

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Systematic complication of randomized studies or non-randomized studies</td>
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<tr>
<td>2</td>
<td>Randomized studies or observational studies that reveal dramatic effects</td>
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<tr>
<td>3</td>
<td>Non-randomized cohort studies</td>
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<tr>
<td>4</td>
<td>Case series, case control, or past controlled studies</td>
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<tr>
<td>5</td>
<td>Mechanism-based reasoning</td>
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Hüfner et al. (7) treated most of the 32 patients with carbamazepine (avg. dose of 568 mg/day) or oxcarbazepine (avg. dose 870 mg/day) and reported that the frequency of the attacks decreased by 10%, the severity of the disease decreased by 15%, and the duration was decreased by 11% (Table 1, Level 4 evidence). In the compilation prepared by Huppert et al. (8), vestibular paroxysm patients are recommended to take gabapentin (300–1800 mg/day) or valproic acid (600–900 mg/day) or phenytoin (100–300 mg/day) as a second option (Table 1, Level 5 evidence).

**Labyrinthitis**

It is a clinical condition characterized with dizziness and hearing loss or hearing loss only. It can sometimes be bacterial, viral, or chemical. Antibiotics are used for the treatment of bacterial infections, whereas for the treatment of viral and chemical ones, which we encounter most frequently today, corticosteroids have been used for many years as the main treatment option. However, there are still debates on this issue. Wei et al. reported in their review for the Cochrane database that there is no study that meets all of the criteria and claimed that the evidence concerning corticosteroid use is still unclear (Table 1, Level 1 evidence). However, according to the guideline prepared by the American Academy of Otolaryngology- Head and Neck Surgery working group (10), the first option is to use per oral (PO) corticosteroids. It is recommended to apply hyperbaric oxygen therapy (HBO) within 3 months and intratympanic steroid therapy for the patients who do not respond to the initial therapy in order for recovery (Table 1, Level 5 evidence). Many countries’ guidelines are of the same opinion. The situation does not change when individual studies are concerned apart from guidelines.

Bennett et al. reported in the review that they prepared for Cochrane that there are studies showing that HBO is effective in the acute phase, but there is no evidence for the chronic phase (Table 1, Level 1 evidence). Cvorovic et al., on the other hand, divided the patients who did not respond to PO steroid into 2 groups and gave HBO to one group and intratympanic (IT) steroids to the other. Significant recovery was observed in both groups (Table 1, Level 4 evidence). Wu et al. (13) reported that the use of IT steroid for the purpose of recovery was successful (Table 1, Level 2 evidence). Erdur et al. (14) used steroid drops via ventilation tube for recovery purposes and obtained statistically significant differences (Table 1, level 4 evidence).
Koltsidopoulos et al. (15) used both PO and IT steroid together during the acute phase and received better results among the patients who used only PO steroid (Table 1, Level 2 evidence). Bae et al. (16), on the other hand, argued that IT steroid use alone displayed the same success as other methods during the acute phase (Table 1, Level 4 evidence). The treatment scheme we use in our clinic is shown in Figures 2 and 3.

**Vestibular Neuritis**

Acute vestibular neuritis is a clinical condition characterized by isolated and spontaneous unilateral vestibular loss. It is characterized by dizziness that lasts for days without hearing loss (Figure 2). Although its cause is not known precisely, latent HSV-1 virus, autoimmune reaction, or microvascular ischemic causes have been suggested. Generally, it is clinically diagnosed in the acute phase. In the late-advanced phase, caloric test and vestibular evoked muscle potentials (VEMPs) can provide useful information. Without exception, almost everyone accepts suppressive medication use (dimenhydrinate; 50-200 mg/day, meclizine, 100 mg/g, promethazine, 60-200 mg/g, diazepam, 10-20 mg/g) in the acute phase in order to relieve the patient. However, the etiology of the disease for the treatment is controversial. Karlberg et al. (17) reported that steroid treatment given in the first 3 days accelerated recovery in the long term (Table 1, Level 4 evidence). Strupp et al. (18) had the same results concerning the use of steroids but reported that giving valacyclovir due to the viral hypothesis does not help (Table 1, Level 2 evidence). Despite these studies, systematic reviews state that there is no sufficient evidence on the use of steroids in the acute phase (19, 20) (Table 1, Level 1 evidence).

The main application for the treatment of vestibular loss occurring over the chronic phase is the rehabilitation program. There are studies stating that betahistine treatment added to that program is useful (21, 22) (Table 1, Level 3 and 4 evidence).

**Otosclerosis**

Otosclerosis is a bone dystrophy resulting from the otic capsule, where the stapes footplate and inner ear grow. It often causes conductive hearing loss. Dizziness can be observed in any phase of the disease. The patient’s complaints may be in the form of an imbalance, as well as in menieriform crises (Figure 3). The treatment is surgical. But, for the patients with progressive sensori-neural hearing loss or who do not accept surgery, drug therapy can be used for protection.

Studies about treatment options are few and outdated. Shambaugh (23) suggests 60 mg/day of sodium fluoride (NaF) for 2
years (Table 1, Level 5 evidence). Bretla et al. (24) divided 95 patients into 2 groups; one group was given 40 mg/g of NaF, 500 mg/g of calcium (Ca), and 400 IU of vitamin D (vitamin D), and instead of NaF, placebo was given to the other group. After 2 years of observation, they found that the group that was given NaF was in a significantly better state in terms of hearing (Table 1, Level 2 evidence). Felix-Trujillo et al. (25), reported that patients using 40 mg/day NaF preoperatively for 6 months have better postoperative hearing results compared to nonusers (Table 1, Level 3 evidence). There are some studies performed with biophosphonates, but they are as case reports and performed with small patient groups.

Autoimmune Inner Ear Disease
Defined according to the clinical findings, it is a syndrome characterized by idiopathic, bilateral sensorineural hearing loss showing rapid progress (Figure 3). Dizziness can be added to the condition in the form of imbalance. Response to immunosuppressive therapy is considered positive in terms of the diagnosis. It may be due to a systemic autoimmune disease (secondary) and might be caused by the ear (primary), as well. For the diagnosis, systemic immunity tests are usually performed. There is a western blot test available developed for a 68-kDa antigen, a form of HSP-70 that can be activated, but it has not come into widespread use.

The basic treatment is immunosuppression. Despite certain side effects, Alexander et al. (26) proposed long-term (6 months) use of systemic steroids (Table 1, Level 3 evidence). Harris et al. (27), on the other hand, stated that for the patients who benefited from steroid treatment, hearing level is not protected when switched to maintenance therapy with methotrexate (Table 1, Level 4 evidence). In another study, it was reported that IT steroid use as an alternative to systemic steroids yielded good results (28) (Table 1, Level 3 evidence).

Meniere’s Disease
Despite the intervening 150 years, the cause of this clinical condition, showing minutes to hours of dizziness, hearing loss at low frequencies, ringing, and feeling of ear fullness, has not been precisely understood. It can be diagnosed with pure tone audiometry, electrocochleography, and VEMP.

Meniere’s disease is such a very broad subject that Meniere’s disease treatment alone may be a subject to an article. Thus, it will be studied in this article only in terms of evidence-based medicine and the algorithm (Figure 3) that we use in daily practice.

The history of the use of diuretics in the treatment of patients is very old. Coletti (29) studied the proportion of patients using betahistine or acetazolamide that needed vestibular neurectomy and reported that 65% of the patients who had used betahistine and 46% of the patients who had used acetazolamide required an additional treatment (Table 1, Level 3 evidence). Thirlwall and Kundu (30) stated in the study that they prepared for Cochrane that there is no sound evidence to support the use of diuretics in Meniere’s disease (Table 1, Level 1 evidence). In a meta-analysis conducted in 2013, the condition of patients that used betahistine would likely be two times better compared to the patients who had been given placebo (31) (Table 1, Level 1 evidence). IT dexamethasone or gentamicin use is common in patients who do not respond to oral therapy. In a Cochrane review conducted in 2011, it was reported that there is only one sound study that can support the use of diuretics in Meniere’s disease (Table 1, Level 1 evidence). In a meta-analysis conducted in 2013, the condition of patients that used betahistine would likely be two times better compared to the patients who had been given placebo (31) (Table 1, Level 1 evidence). IT dexamethasone or gentamicin use is common in patients who do not respond to oral therapy. In a Cochrane review conducted in 2011, it was reported that there is only one sound study that can support the use of diuretics in Meniere’s disease (Table 1, Level 1 evidence). In a meta-analysis conducted in 2013, the condition of patients that used betahistine would likely be two times better compared to the patients who had been given placebo (31) (Table 1, Level 1 evidence). IT dexamethasone or gentamicin use is common in patients who do not respond to oral therapy. In a Cochrane review conducted in 2011, it was reported that there is only one sound study that can support the use of diuretics in Meniere’s disease (Table 1, Level 1 evidence). In a meta-analysis conducted in 2013, the condition of patients that used betahistine would likely be two times better compared to the patients who had been given placebo (31) (Table 1, Level 1 evidence). IT dexamethasone or gentamicin use is common in patients who do not respond to oral therapy. In a Cochrane review conducted in 2011, it was reported that there is only one sound study that can support the use of diuretics in Meniere’s disease (Table 1, Level 1 evidence). In a meta-analysis conducted in 2013, the condition of patients that used betahistine would likely be two times better compared to the patients who had been given placebo (31) (Table 1, Level 1 evidence).
Migraine-Associated Vertigo

It has been known that migraine headaches and dizziness are associated. In epidemiological studies, these two conditions, which are frequently seen together in the community, are beyond random probability. Other headache types do not show such association. Patients may generally complain about irregular imbalance and dizziness periods. Dizziness may follow headache but may be experienced before, or the patient might have them both at the same time. The dizziness might appear years after the disappearance of migraine headaches. It is diagnosed through anamnesis. It is important for the diagnosis if the patient has a personal or family history of migraine and if the headaches meet the migraine criteria (photophobia, phonophobia, etc.) (Figure 4).

Treatment is carried out in two stages: treatment of acute attack and prophylactic treatment. General vestibular suppressants, antiemetics, and pain relievers can be used in the treatment of acute attack. Despite extensive clinical use and general acceptance of these drugs, there are no sufficiently sound studies conducted with conventional medicine. It is reported in a Cochrane review study (34) that subcutaneous sumatriptan use in the attack period is effective on pain, photophobia, phonophobia, and vestibular symptoms, and there is a significant decrease in terms of pain in 60% of patients in 2 hours (Table 1, Level 1 evidence).

As a long-term precaution, it is recommended all patients avoid all migraine triggers (alcohol, oral contraceptives, nitrates, etc.). Many drugs are used for prophylactic measures. Lepcha et al. (35) reported in the study they conducted with flunarizine, which is a Ca channel blocker, that the drug reduces the frequency and severity of dizziness but shows no change in headache (Table 1, Level 2 evidence). There is also strong evidence for the use of propranolol (60-80 mg/day) and metoprolol (100-200 mg/gram’s) (36, 37) (Table 1, Level 1 evidence). Also, the studies on the use of antiepileptic drugs support the use these drugs. Linde et al. (38), on the other hand, reported in their study that valproic acid reduces migraine pain to almost 50% (Table 1, Level 1 evidence). Another drug that is recommended is topiramate. Placebo-controlled studies conducted in this regard are also effective (39) (Table 1, Level 1 evidence). However, there is no sufficient evidence showing that topiramate is superior to other prophylactic agents.

Conclusion

Dizziness symptom might be associated with many diseases but might also be caused by different systems. The majority of differential diagnoses and treatments is based on clinical information and medical history. Thus, it requires great attention and patience. It is vital to have full confidence while writing a prescription to the patients when planning a course of treatment under the information overload. This is only possible if the clinicians constantly update themselves. In this study, it can be seen that the algorithm that we have examined and used in our clinic is consistent with the results of the current quality work. It is vitally important for all of us to conduct such studies, review evidence, establish consensus committees, and improve the systematic and institutional approach from time to time.

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References

12. Cvorovic L, Jovanovic MB, Milutinovic Z, Arsovic N, Djeric D. Randomized prospective trial of hyperbaric oxygen therapy and in-


35. Lepcha A, Amalanathan S, Augustine AM, Tyagi AK, Balraj A. Flunarizine in the prophylaxis of migrainous vertigo: a randomized controlled trial. Eur Arch Otorhinolaryngol 2013. [CrossRef]


