USE AND MISUSE OF MEDICATIONS IN THE TREATMENT OF DIZZINESS

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ABSTRACT
This review discusses the pharmacological treatment of dizziness, focusing particularly on the vertigo subtype of dizziness. Classes of medications useful in the treatment of vertigo include anticholinergics, antihistamines, benzodiazepines, calcium channel blockers, and dopamine blockers. These medications often have multiple actions. They may modify the intensity of symptoms (eg, vestibular suppressants) or they may affect the underlying disease process (eg, calcium channel blockers in the case of vestibular migraine). Most of these agents, particularly those that are sedating, also have a potential to modulate the rate of compensation for damage. This consideration has become more relevant in recent years, as vestibular rehabilitation physical therapy is now often recommended in an attempt to improve compensation. Accordingly, therapy of vertigo is optimized when the prescriber has detailed knowledge of the pharmacology of medications being administered as well as the precise actions being sought.

Specific regimens of drug therapy can be tailored for four major etiological classes of vertigo. Otolological vertigo includes disorders of the inner ear such as Ménière’s disease, vestibular neuritis, benign paroxysmal positional vertigo (BPPV) and bilateral vestibular paresis. In both Ménière’s disease and vestibular neuritis, vestibular suppressants such as anticholinergics and benzodiazepines are used. In Ménière’s disease, salt restriction and diuretics are prescribed in an attempt to prevent flare-ups. In vestibular neuritis, shorter durations of vestibular suppressants are now recommended in an attempt to promote compensation. Drug treatments are used as an adjunct to physical therapy for BPPV and bilateral vestibular paresis. Central vertigo includes entities such as migraine and stroke. Prophylactic agents (L-channel calcium channel blockers, tricyclic antidepressants, beta-blockers, anticonvulsants) are the mainstay of treatment for migraine-associated vertigo. In persons with stroke or other structural lesions of the brain stem or cerebellum, an eclectic approach incorporating trials of vestibular suppressants and physical therapy is recommended. Psychogenic vertigo includes disorders such as panic, anxiety disorder, and agoraphobia. Benzodiazepines and antidepressants are the most useful agents for this condition. Undetermined and ill-defined causes of vertigo make up a large remainder. An empirical approach to treating these patients involves incorporating trials of medications of general utility such as benzodiazepines, physical therapy, and trials of medication withdrawal. When
appropriate, physical therapy and psychiatric consultation are suggested.

**NEUROPHYSIOLOGY OF DIZZINESS AND VERTIGO**

Dizziness is a general term that may encompass symptoms caused by diverse etiologies such as low blood pressure and drug side effect. This chapter will more specifically address *vertigo*, a common subtype of dizziness, defined as the illusion of rotational motion. Most vertigo is *otological* and is caused by dysfunction of the rotational velocity sensors of the inner ear, the semicircular canals. Other types of vertigo exist, however, and in this regard it is helpful to consider how the brain processes motion signals. Normal persons continuously process three types of sensory input: vestibular (inner ear), visual, and somatosensory. These three streams of information are combined in the brain to form an estimate of orientation and motion of the head and body. The three streams are also compared centrally, and when a mismatch between two or more senses occurs, vertigo can be perceived.

From this systems-physiology perspective, sources of vertigo include all possible combinations of sensory disturbances related to motion as well as central malfunction of the comparison mechanism. Practically, however, because the visual and somatosensory senses mainly produce position-coded signals, vertigo is only rarely a consequence of visual or somatosensory malfunction. An example of “visual vertigo” might be vertigo that is associated with an oculomotor disturbance accompanied by nystagmus. Nevertheless, the common varieties of visual disturbance, diminished vision, double vision, or disorders of the accommodation system usually do not create vertigo. Similarly, vertigo is only occasionally associated with somatosensory dysfunction as in cervical vertigo. Central vertigo is more frequent but still uncommon with respect to otological vertigo, as will be later discussed in more detail.

When treating vertigo, one must also consider *motion sickness*, which is the malaise and nausea that may follow real or illusory sensations of motion. Vertigo and motion sickness are not synonymous. For example, carnival rides frequently elicit illusory rotational sensations, but motion sickness can often be avoided. Also, the symptoms of motion sickness usually persist longer and tend to be more disturbing than the inciting vertigo. While vertigo is reliably experienced by normal persons experiencing similar sensory disturbances, susceptibility to motion sickness varies remarkably. The pharmacology of vertigo and motion sickness are clearly distinct.

Finally, when planning treatment one must consider *recovery and compensation*. Every vestibular stimulus, whether the result of natural motion or disease, has the potential to initiate a process of compensatory adaptation. The pharmacology of compensation is distinct from that of vertigo and motion sickness and, in fact, agents that relieve vertigo, nausea, or motion sickness may block compensation. Two key concepts regarding compensation need to be considered when planning therapy of vertigo: (1) Promotion of central compensation is desirable during the process of recovery from persistent vestibular imbalance such as after a severe bout of vestibular neuritis. (2) Prevention of unneeded and counterproductive compensation may be desirable after a transient vestibular imbalance such as might be caused by Ménière’s disease.

**NEUROCHEMISTRY OF VERTIGO**

At least four major neurotransmitters of the vestibular system are involved in the three-neuron arc between the vestibular hair cells and the oculomotor nuclei that drives the vestibulo-ocular reflex. A host of other neurotransmitters also
modulate that function. Table 9-1 provides a summary of what is known. *Glutamate* is the major excitatory neurotransmitter. *Acetylcholine* (ACH) is both a peripheral (inner ear) and central agonist (vestibular nucleus) affecting muscarinic receptors. However, peripherally ACH appears to be involved only in the brain stem efferent hair cell synapse, which has an uncertain functional significance. Centrally, ACH is more important. Five subtypes of ACH receptors are presently known. The receptors found in the pons and medulla, presumably those involved with dizziness, are almost exclusively of the M2 subtype. *γ-Aminobutyric acid* (GABA) and *glycine* are inhibitory neurotransmitters found in connections between second-order vestibular neurons and oculomotor neurons. Stimulation of the two types of GABA receptors, GABA-A and GABA-B, have similar effects on vestibular pathways, but specific GABA-B agonists such as baclofen decrease the duration of vestibular responses in animal models. Little is known about the effects of glycine-receptor agonists or antagonists on vestibular responses.

Not as well understood are the mechanisms of action of several other neurotransmitters known to be important in the pharmacological management of vertigo. *Histamine* is found diffusely in central vestibular structures. Centrally acting antihistamines modulate symptoms of motion sickness. There are three histamine-receptor subtypes: H1, H2, and H3. All subtypes of histamine receptors affect vestibular responses. H3 agonists also inhibit histamine, dopamine, and acetylcholine release. *Norepinephrine* is involved centrally in modulating the intensity of reactions to vestibular stimulation and also facilitates compensation. *Dopamine* facilitates vestibular compensation. Selective agents for *serotonin*-receptor subtypes modulate some types of nausea.

### DRUGS TO SUPPRESS VESTIBULAR FUNCTION

Vestibular suppressant and antiemetic drugs are the mainstay of treatment of vertigo. Vestibular suppressants are drugs that reduce nystagmus evoked by a vestibular imbalance or reduce motion sickness. Conventional vestibular suppressants consist of three major drug groups: the anticholinergics, the antihistamines, and the benzodiazepines (Table 9-2). The use of calcium channel blockers for vestibular suppression will also be discussed, although their use for this purpose presently is not universally accepted.

#### Anticholinergics

Agents that inhibit muscarinic receptors such as scopolamine (Transderm-Scop) increase motion tolerance. Agents with central anticholinergic effects are most important in treating vertigo. Anticholinergic drugs that do not cross the
blood-brain barrier are ineffective in controlling motion sickness. Nevertheless, some anticholinergics that do not cross the blood-brain barrier to a great extent (eg, glycopyrrolate [Robinul]) are reported useful for vestibular suppression in Ménière’s disease. Unlike antihistamines, which will be discussed subsequently, pure anticholinergics are ineffective if administered after symptoms have already appeared.

All anticholinergics conventionally used in the management of vertigo have prominent side effects, including a dry mouth, dilated pupils, impaired accommodation (focusing), and sedation. Scopolamine and atropine are nonspecific muscarinic-receptor antagonists. Hopefully, agents selective for vestibular subtypes of muscarinic receptors (probably M2) will eventually be developed or discovered among the presently available pharmacopoeia, as these agents may provide vestibular suppression with fewer side effects.

Centrally acting anticholinergics also affect compensation, producing a reversible overcompensation if administered after compensation to a vestibular imbalance has been attained. Thus, an anticholinergic given to a person who has fully compensated for a previous vestibular lesion might induce dizziness as well as initiate an anticomparatory response. Anticholinergics most likely also slow the rate of compensation. For these reasons, as well as because of prominent side effects, conventional practice is to avoid chronic administration of anticholinergics for vertigo in persons with peripheral vertigo.

The transdermal preparation of scopolamine (hyoscine, Transderm-Scop) deserves special comment. The transdermal delivery method has a great advantage in that it bypasses the stomach,

### TABLE 9-2 Vestibular Suppressants (Alphabetical Order)

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Dose*</th>
<th>Pharmacological Class</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>0.25 mg to 0.5 mg BID</td>
<td>Benzodiazepine</td>
<td>Mildly sedating, drug dependency</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>2 mg to 10 mg (1 dose) given acutely orally, IM or IV; 2 mg BID for chronic dizziness</td>
<td>Benzodiazepine</td>
<td>Sedating, respiratory depressant, drug dependency, precaution in glaucoma</td>
</tr>
<tr>
<td>Dimenhydrinate (Dramamine)</td>
<td>50 mg every 4 to 6 hours</td>
<td>Antihistamine, anticholinergic</td>
<td>Same as meclizine</td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>0.5 mg BID</td>
<td>Benzodiazepine</td>
<td>Mildly sedating, drug dependency</td>
</tr>
<tr>
<td>Meclizine (Antivert, Bonine)</td>
<td>12.5 mg to 50 mg every 4 to 6 hours; Chewable tabs TID if nauseated</td>
<td>Antihistamine, anticholinergic</td>
<td>Sedating, precaution in prostatic enlargement</td>
</tr>
<tr>
<td>Scopolamine (Transderm-Scop)</td>
<td>0.5 mg patch every 3 days</td>
<td>Anticholinergic</td>
<td>Topical allergy, precaution in glaucoma, tachyarrhythmia, prostatic enlargement</td>
</tr>
</tbody>
</table>

BID = 2 times a day; IM = intramuscular; IV = intravenous; TID = 3 times a day.

*Doses are all those used routinely for adults and will generally not be appropriate for children.

making it effective in situations where gastric absorption may be erratic such as when patients have nausea or emesis. The main problem is skin irritation, which usually precludes long-term usage. Anticholinergic side effects such as dry mouth and trouble focusing also limit use. Overdosage problems can be managed by cutting the patches in half. Occasionally patients become dependent on scopolamine and develop withdrawal symptoms (usually nausea and vertigo) when the patches are discontinued. This can be managed by substitution of an oral formulation of hyoscine, followed by slow withdrawal.

**Antihistamines**

While the precise role of histamine in central vestibular processing is uncertain, use of centrally acting antihistamines can prevent motion sickness and reduce the severity of its symptoms. All the antihistamines in general use for control of vertigo also have anticholinergic activity. Commonly used agents include meclizine, dimenhydrinate, and diphenhydramine. Newer antihistamines that do not cross the blood-brain barrier are not used to treat vertigo.

**Benzodiazepines**

These drugs are GABA modulators, which act centrally to potentiate GABA and suppress vestibular responses. There are at least three benzodiazepine receptors: (1) Ω-1 (cerebellum, hippocampus, and globus pallidus), (2) Ω-2 (spinal cord, superficial colliculus, and caudate), and (3) Ω-3 (peripheral). The Ω-1 receptor is most likely to be relevant for vertigo.

In small doses, benzodiazepines are extremely useful for the management of vertigo. Addiction, impaired memory, increased risk of falling, and possibly impaired vestibular compensation are drawbacks associated with their use. It should be noted, however, that impairment of vestibular compensation by benzodiazepines, if it occurs at all, has never been shown to be clinically relevant.

Lorazepam is a particularly useful agent because of its effectiveness and simple kinetics. Lorazepam has no active metabolites. Addiction, the biggest problem, can be avoided by keeping the dose to no more than 0.5 mg twice a day. Lorazepam can also be taken sublingually (1 mg) for an acute attack of vertigo. Similarly, low doses of diazepam (Valium) (2 mg twice a day) can be quite effective. Relatively little information is available about addiction potential and efficacy of clonazepam (Klonopin), but it appears as effective a vestibular suppressant as lorazepam. It is also usually prescribed in a dose of 0.5 mg twice a day and recently became available as a sublingual preparation. The author prefers to avoid use of alprazolam (Xanax) for vestibular suppression because of the potential for a difficult withdrawal syndrome. Long-acting benzodiazepines are usually not helpful for relief of vertigo. Selective Ω-1 benzodiazepine-receptor agonists are available as sleep-inducing preparations (eg, zolpidem [Ambien]). Their role, if any, in the treatment of vertigo remains to be established. They also are significantly more costly than older and less specific drugs.

**Calcium channel blockers** have utility in the treatment of dizziness (Table 9-3). Two examples of this group, flunarizine and cinnarizine, are popular antivertiginous agents outside of the United States. Flunarizine has also been reported to be effective in the prevention of motion sickness. Nimodipine has been reported as possibly effective in Ménière’s disease, and L-channel calcium channel blockers are effective drugs to prevent migraine, a common cause of dizziness. Several possible reasons may explain why calcium channel blockers might be of help in the
management of vertigo. Calcium channel blockers may be vestibular suppressants. Practically, some calcium channel blockers such as verapamil have strong constipating effects, which may be helpful in managing diarrhea caused by vestibular imbalance. These drugs also often have anticholinergic and/or antihistaminic activity. Many calcium channel blockers, especially flunarizine and cinnarizine, also have dopamine antagonist characteristics.

**DRUGS TO SUPPRESS EMESIS**

**Antiemetics**

Table 9-4 lists the drugs that are commonly used for control of nausea in vertiginous patients. The choice of agent depends on considerations of the route of administration, the side effect profile, and cost. The oral agents are used for mild nausea. Suppositories are commonly used in outpatients who are unable to absorb oral agents because of gastric atony or vomiting. Sublingual administration of antiemetics is also useful. Injectables are used in the emergency department or inpatient settings.

Some antihistamines commonly used as vestibular suppressants have significant antiemetic properties (eg, meclizine). When an oral agent is appropriate, meclizine is generally the first to be used because it rarely causes adverse effects more severe than drowsiness. Phenothiazines such as prochlorperazine (Compazine) and promethazine (Phenameth, Phenergan) are effective antiemetics, probably because of their dopamine-blocking activity, but they also act at other sites. For example, promethazine is also an H1 blocker. Because these drugs can induce significant side effects such as dystonia, they are considered second-line drugs whose use should be brief and cautious. Similarly, butyrophenones such as haloperidol can be used as antiemetics, but have similar cautions. Droperidol given sublingually is a very effective treatment of emesis, but its use is not recommended due to the possibility of cardiac arrhythmia.

<table>
<thead>
<tr>
<th>TABLE 9-3</th>
<th>Calcium Channel Blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug (Brand Name)</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Cinnarizine (Stugeron) (Not USFDA approved)</td>
<td>25 mg 3 times a day</td>
</tr>
<tr>
<td>Flunarizine (Sibelium) (Not USFDA approved)</td>
<td>10 mg at bedtime</td>
</tr>
<tr>
<td>Nimodipine (Nimotop)</td>
<td>30 mg 2 times a day</td>
</tr>
<tr>
<td>Verapamil</td>
<td>120 mg slow release, at bedtime</td>
</tr>
</tbody>
</table>

USFDA = US Food and Drug Administration.

*Doses are all those used routinely for adults and will generally not be appropriate for children.

Drugs that speed gastric emptying such as metoclopramide (Reglan) and powdered ginger root may be helpful in managing emesis. Metoclopramide, a benzamide derivative, is a dopamine antagonist that speeds gastric emptying, as well as a central antiemetic. It is ineffective in preventing motion sickness. Domperidone, a mainly peripherally acting dopamine-2-receptor antagonist, has antiemetic activity due to peripheral gastrokinetic as well as central action on the chemoreceptor trigger zone. It has similar efficacy to metoclopramide combined with a more favorable safety profile. Sulpiride, a substituted benzamide derivative, is also a dopamine-2 antagonist. Sulpiride has antidepressant, antipsychotic, antivertigo, and antiemetic effects, and resembles the neuroleptics in its side effect profile. Neither domperidone nor sulpiride is approved by the US Food and Drug Administration (USFDA).

5-Hydroxytryptamine 3 (5-HT3) antagonists such as ondansetron (Zofran) are sometimes effective in prevention of vomiting in human vestibular disorders, although animal studies suggest that they should be ineffective. This

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Usual Adult Dose*</th>
<th>Pharmacological Class</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granisetron (Kytril)</td>
<td>1 mg PO, 1 mg IV</td>
<td>5HT3 antagonist</td>
<td>Headache</td>
</tr>
<tr>
<td>Meclizine (Antivert, Bonine)</td>
<td>12.5 mg or chewable 25 mg q 4 to 6 hours PO TID</td>
<td>Antihistamine, anticholinergic</td>
<td>Sedation, precautions in glaucoma, prostate enlargement</td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>10 mg PO TID or 10 mg IM</td>
<td>Dopamine and 5HT antagonist</td>
<td>Restlessness or drowsiness; extrapyramidal</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>4 mg to 8 mg PO, 8 mg sublingual, 4 mg to 16 mg IV</td>
<td>5HT3 antagonist</td>
<td>Headache, diarrhea, fever (all are very rare)</td>
</tr>
<tr>
<td>Palanosetron (Aloxi)</td>
<td>0.25 mg IV</td>
<td>5HT3 antagonist</td>
<td>Headache, constipation</td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>5 mg or 10 mg IM or PO q 6 to 8 hours or 25 rectal q 12 hours</td>
<td>Phenothiazine</td>
<td>Sedation; extrapyramidal</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>25 mg PO q 6 to 8 hours or 25 mg rectal q 12 hours or 12.5 mg IM q 6 to 8 hours</td>
<td>Phenothiazine</td>
<td>Sedation; extrapyramidal</td>
</tr>
<tr>
<td>Thiethylperazine (Torecan)</td>
<td>10 mg PO, up to TID or 2 mL IM, up to TID</td>
<td>Phenothiazine</td>
<td>Sedation extrapyramidal</td>
</tr>
<tr>
<td>Trimethobenzamide (Tigan)</td>
<td>250 mg PO TID or 200 mg IM TID or 200 mg rectal TID</td>
<td>Similar to phenothiazine</td>
<td>Sedation; extrapyramidal</td>
</tr>
</tbody>
</table>

PO = orally; IV = intravenously; 5HT = 5-hydroxytryptamine; q = every; TID = 3 times a day; IM = intramuscular.

*Doses are all those used routinely for adults and will generally not be appropriate for children. Only drugs that are approved for use in the United States are included. Others are discussed in the text.

difference between animal and actual human experience may be related to well-known species differences with respect to emesis. Convenient sublingual dosing forms of ondansetron and related medications are available. While the extremely high price of these agents limits their usefulness in the treatment of vertigo, their lack of sedation can make them very attractive. These agents do not appear to be helpful in preventing motion sickness.

AGENTS THAT AFFECT COMPENSATION

While the manipulation of compensation is not ordinarily considered in clinical practice, it seems reasonable to do so in the interest of improving patient outcomes. If a patient has a permanent vestibular lesion, for instance an acoustic neuroma or a persistent vestibular neuritis, it may be desirable to speed central compensation. On the other hand, one might wish to retard compensation in persons with a transient vestibular lesion such as that often caused by Ménière’s syndrome.

Drugs that cause decompensation (eg, adrenergic agents) or overcompensation (eg, anticholinergics) may induce recurrent vertigo in persons who have compensated for vestibular injury, although they may be well tolerated by persons with no vestibular disturbance.

Compensation is composed of a number of discrete processes, the most important of which include static and dynamic compensation. Static compensation refers to adjustments that restore a balance of central vestibular tone and is manifested by elimination of spontaneous nystagmus and postural deviation. Dynamic compensation refers to adjustments that restore normal vestibular gain and are manifested by loss of oscillopsia and acquisition of more effective postural responses that restore balance after a perturbation. In animals, static compensation occurs much more quickly than dynamic compensation and requires little in the way of sensory input. On the other hand, dynamic compensation, such as vestibulo-ocular reflex (VOR) gain restoration, is a slower process that requires visual experience for its acquisition and is dependent on the central nervous system structures for maintenance. Static and dynamic compensation presumably have a distinct pharmacology.

The resilience of compensation to drug perturbations is another factor. Some drugs cause decompensation (eg, return of a paretic-type spontaneous nystagmus or reduction of VOR gain) or overcompensation (eg, a spontaneous nystagmus directed oppositely to the original paretic nystagmus), which may account for greater drug sensitivity in persons who have compensated to vestibular deficits. In total then, four factors must be known—effects on the speed and stability of both static and dynamic vestibular compensation.

Table 9-5 summarizes what little is known about how drugs used to treat vertigo affect the rate of compensation to vestibular lesions in animal models. Drugs that speed compensation in animals are mainly stimulants, and drugs that retard compensation are mainly sedatives. Most vestibular suppressants are thought to retard compensation, but what little published evidence is available suggests that they have little or no effect. For example, diazepam has not been proven to disturb static or dynamic compensation (Ishikawa and Igarashi, 1984; Martin et al, 1996).

Also in animals, dopamine agonists speed compensation and antagonists slow compensation. What they do in human clinical situations is presently unknown, but adrenergic agonists such as ephedrine and amphetamines are occasionally used in combination with vestibular suppressants. While they are most often used to counteract the sedative effects of vestibular suppressants,
these stimulants may also help by promoting vestibular compensation. Amphetamines have been shown to speed recovery of motor function in stroke. Both adrenocorticotropic hormone and glucocorticoids have been reported to speed static compensation. Alcohol probably impedes and delays dynamic vestibular compensation, but it does not cause static decompensation. Calcium channel blockers such as verapamil or flunarizine also may enhance compensation, but their use is controversial. It seems likely that antihypertensive agents, which act through adrenergic blocking or depleting, may slow vestibular compensation.

Some drugs also affect completed compensation. In particular, in animals cholinergic agonists cause decompensation while anticholinergic drugs cause overcompensation. Glutamate N-methyl-D-aspartate–receptor antagonists cause decompensation. At this writing, very little clinical data regarding the importance of these considerations are available, and what little are available suggest small effects.

**AGENTS OF UNCERTAIN EFFICACY AND/OR MECHANISM**

Many substances, procedures, and devices have been promoted as effective treatments of vertigo, often without clear proof of efficacy. The tendency to attribute curative properties to a bewildering number of medications, devices, and surgical procedures has been particularly evident in the treatment of Ménière’s disease (Ruckenstein et al, 1991; Torok, 1977). It seems likely that most of these agents have minor or no pharmacological efficacy, but rather they are simply placebos. Another possibility, partially borne out by animal data, is that these agents are not vestibular suppressants but rather affect vestibular compensation.

A particularly intriguing member of this group (Table 9-6) is betahistine. Whereas the antihistamines used in...
treating vertigo are usually centrally acting histamine H1-receptor antagonists, betahistine is a weak H1-receptor agonist and a moderate H3 antagonist. It has been suggested that betahistine decouples the negative feedback loop controlling histamine release resulting in central facilitation of histaminergic neurotransmission in the brain. In therapeutic doses, betahistine administration is associated with reduction in the gain of the VOR. In addition, betahistine increases blood flow to the inner ear. However, it is difficult to see how betahistine might act selectively on blood flow to the inner ear, and it seems highly unlikely that vasodilation is the mechanism for putative positive effects on vestibular function. Substantial evidence indicates that betahistine may speed vestibular compensation, which is a surprising finding for a drug that reduces VOR gain. Vertigoheel, a homeopathic remedy, has recently been compared to betahistine and found to be equivalent. As Vertigoheel is presumably a placebo, this study provides evidence that betahistine is a placebo too. In the United States, as of 2004, the USFDA does not recognize betahistine as an effective medication. Nevertheless, worldwide, betahistine is often used in persons with chronic vertigo. Considering the neurophysiological data reviewed above, more clinical study seems warranted.

Ginkgo biloba has been recommended for vertigo and tinnitus. Ginkgo may reduce the viscosity of the blood (literally blood thinning), and it may also be an antioxidant. Ginkgo may speed vestibular compensation in animals. Notwithstanding these encouraging pharmacological reports, a recent study suggests that ginkgo is similar to betahistine in efficacy for vertigo. As betahistine is reportedly indistinguishable from a homeopathic medication (see above), ginkgo is unlikely to be very effective.

Isosorbide is an osmotic diuretic (not the isosorbide dinitrate used as a

<table>
<thead>
<tr>
<th>Table 9-6: Selected Agents of Uncertain Efficacy and/or Mechanism</th>
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<tbody>
<tr>
<td><strong>Drug (Brand Name)</strong></td>
</tr>
<tr>
<td>Betaistine (Serc) (Not USFDA approved)</td>
</tr>
<tr>
<td>Ginkgo biloba (Herbal preparation)</td>
</tr>
<tr>
<td>Baclofen</td>
</tr>
<tr>
<td>Amantadine</td>
</tr>
<tr>
<td>Piracetam (Not USFDA approved)</td>
</tr>
</tbody>
</table>

TID = 3 times a day; BID = 2 times a day; USFDA = US Food and Drug Administration.  
*Doses are all those used routinely for adults, and will generally not be appropriate for children.

vasodilator) that has been advocated in Ménière’s disease. Two unblinded trials in Japan reported successful control of Ménière’s disease in 60% to 80% of patients (Kanda et al, 1993; Nozawa et al, 1995). These results are uncomfortably close to placebo, which will induce remission in about 60% of patients with Ménière’s disease within 6 months of initiation of treatment (Torok, 1977).

Pentoxifylline (Trental) has been reported useful in the treatment of “vascular inner ear disease.” Pentoxifylline also is a weak anti–tumor necrosis factor (TNF) inhibitor. TNF plays a key role in inner ear inflammation, and for this reason pentoxifylline might have some efficacy for autoimmune inner ear disease.

Baclofen and amantadine, both centrally acting agents used generally in conditions unrelated to vertigo, are sometimes advocated for vertigo. Baclofen is most commonly used in patients in whom the diagnosis of microvascular compression of the eighth nerve is being considered. Baclofen has also been used to reduce the intensity of upbeat and downbeat nystagmus. Baclofen improves symmetry of vestibular responses in hemi-labyrinthectomized rats and may have some role in the treatment of vestibular imbalance. Amantadine is also used in an attempt to promote compensation, by its analogous use in persons with traumatic brain injury.

DL-leucine, an amino acid, is sometimes used for treatment of vestibular imbalance. It has been suggested that leucine restores symmetry of central vestibular neurons. No formal studies of efficacy of any of these drugs for vestibular disorders in humans have been reported.

A sodium channel blocker, phenytoin (Dilantin), has been reported to protect against motion sickness 2 times more effectively than the combination of scopolamine/dextroamphetamine (Chelen et al, 1990; Knox et al, 1994). Phenytoin is not generally used for this purpose, perhaps because of its complicated pharmacokinetics and cerebellar toxicity. Nevertheless, more study of phenytoin and related agents seems warranted.

A potassium channel blocker, 3,4-diaminopyridine, has at least a temporary effect in reducing downbeating nystagmus. The mechanism of this effect is tentatively attributed to increased excitability of cerebellar Purkinje cells. While unlikely to be a placebo, this compound is not USFDA approved. More study seems warranted.

**TREATMENT OF INDIVIDUAL CONDITIONS**

**Benign Paroxysmal Positional Vertigo**

BPPV is the single most common type of vertigo, accounting for roughly 20% of all vertigo cases. BPPV is diagnosed by combining a history of positional vertigo with a typical nystagmus pattern that appears on positional testing. Physical maneuvers using sequential manipulation of the position of the head with respect to gravity are the most effective treatments for BPPV (Epley, 1996). Drugs are not nearly as helpful for BPPV as physical treatments, but antiemetics such as meclizine or ondansetron (Zofran) are helpful in patients whose vertiginous spells are followed by nausea.

**KEY POINTS:**
- Worldwide, betahistine is often used in persons with chronic vertigo.
- Drugs are not nearly as helpful for benign paroxysmal positional vertigo as physical treatments, but antiemetics such as meclizine or ondansetron (Zofran) are helpful in patients whose vertiginous spells are followed by nausea.
nausea than posterior canal BPPV, and antiemetics such as prochlorperazine suppositories may be needed in this situation.

Vestibular suppressants that have little antiemetic activity (eg, diazepam [Valium, Valrelease, Zetran], lorazepam [Ativan]), are generally unable to reduce severe symptoms to acceptable levels. They may, however, be helpful in persons with phobic positional symptoms, again as an adjunct to exercises intended to desensitize them.

**Ménière’s Disease**

Ménière’s disease is the second most common cause of vertigo of otological origin. Spells of hearing decline, monaural fullness, roaring tinnitus, and vertigo are characteristic. While Ménière’s disease is classically attributed to dilatation (endolymphatic hydrops) and periodic rupture of the endolymphatic compartment of the inner ear, this mechanism has come into question for several reasons. First, while about 10% of the population has endolymphatic hydrops on autopsy, only about 0.2% of the population has Ménière’s disease (Rauch et al, 1989; Wladislovsky-Waserman et al, 1984). Also, considerable evidence implicates immune disturbances in Ménière’s disease and periodic release of cytokines as a more plausible explanation. Whatever the cause, medical management of Ménière’s disease largely consists of managing symptoms and, when this fails, referral for consideration of surgical management (Case 9-2).

For the episodic vertigo that is common in Ménière’s syndrome, vestibular suppressants with or without an antiemetic (Table 9-2) are used to treat the acute attack, and no medications are used in the interim. Meclizine, diazepam, clonazepam, and lorazepam are the most useful suppressant agents for mild attacks (see Table 9-2 for doses). Intramuscular promethazine or prochlorperazine and intravenous diazepam are used in the emergency department or inpatient setting for treatment of severe attacks. Otherwise, nausea is managed with sublingual or suppository preparations. However, these are rarely required because most patients have some warning involving a change in hearing or aural sensation, and can take meclizine or a similar preparation before the full-blown attack appears.

No consensus has emerged on the prophylaxis of Ménière’s syndrome and simply treating the symptoms is considered acceptable. No matter what prophylactic treatment is used, remission eventually occurs in 60% to 80% of cases (Ruckenstein et al, 1991; Torok, 1977). Because of the great variability in the course of Ménière’s disease, an adequately powered clinical trial requires

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**Case 9-1**

A 50-year-old man slipped and fell, hitting the back of his head. On arriving in the emergency department, he was unable to sit due to severe vertigo and emesis. Meclizine 25 mg 3 times a day was prescribed, and he was sent home. Three weeks later the patient arrived in the clinic, still complaining of vertigo. After taking a dose of meclizine, an Epley maneuver was performed in the clinic. The positional vertigo was cured and meclizine was stopped.

**Comment.** Vestibular suppressants are far less effective than physical maneuvers for long-term treatment of BPPV. An antiemetic can be very useful, however, to prevent emesis during the treatment maneuvers.
very large numbers, and for the most part, very few of these have been performed.

However, in Ménière’s disease it is common practice to advise dietary salt restriction (1-g to 2-g salt diet) and use of a mild diuretic such as hydrochlorothiazide or the combination of hydrochlorothiazide and triamterene (Dyazide or Maxzide). This regimen may reduce the frequency of attacks and slow the progression of hearing loss. It should be noted that hydrochlorothiazide may cause significant hypotension, especially in the elderly and in those who are already salt restricted. In this situation one may wish to use an every-other-day dose schedule and/or monitor serum electrolytes. The combination form of the drug is scored and can be broken in half.

In patients who cannot tolerate hydrochlorothiazide, diuretics that inhibit carbonic anhydrase such as acetazolamide (Diamox) are occasionally helpful. Carbonic anhydrase inhibitors may also be helpful in persons with episodic ataxia and migraine-associated vertigo, giving them a broader indication. Spironolactone may be used in women with perimenstrual flare-ups. Calcium channel blockers such as verapamil (Calan, Isoptin) or nimodipine (Nimotop) may also be helpful, although very few formal studies of efficacy are available. Patients are also encouraged to avoid caffeine and stop smoking. Some authors recommend a brief course of steroids, especially if a surgical treatment is being considered.

**Vestibular Neuritis**

Vestibular neuritis is a monophasic self-limited condition that presents with vertigo, nausea, ataxia, and nystagmus. These symptoms are brought about by an acute imbalance in vestibular
tone combined with directionally asymmetrical response to head rotation. Although the cause of vestibular neuritis is unknown, many consider viral infection of the vestibular portion of the eighth cranial nerve to be responsible. Mumps and various types of herpes viruses are possible infectious agents.

A peculiar aspect of this condition is that hearing is not impaired; the viral infection is hypothesized to selectively affect the vestibular portion of the eighth nerve or the vestibular ganglion. When hearing is also affected, the syndrome is termed “labyrinthitis.”

Evidence suggests that slightly more than half of patients with vestibular neuritis will recover completely. Severe distress associated with constant vertigo, nausea, and malaise usually lasts 2 or 3 days. Many patients are ready to return to their regular activities after 1 week, and it is likely that in these instances there has been only a transient and incomplete vestibular lesion. However, this author estimates that about 25% of patients may take as long as 2 months to improve substantially (Case 9-3). Subsequent testing in this group often demonstrates a continued unilateral paralysis of vestibular function.

Unfortunately, it is not possible to predict whether a patient will have a transient vestibular imbalance and recover quickly or a permanent loss of function associated with a poorer prognosis. The implication for treatment is that if a permanent vestibular imbalance is made more tolerable by a vestibular suppressant medication, or central repair activity is partially blocked by a benzodiazepine or agent with dopamine-blocking activity, the patient may not recover as rapidly as otherwise. Even bed rest may be unwise since animal studies have shown that immobilization delays recovery from experimental vestibular lesions (Lacour and Tighilet, 2000).

Thus, the conventional treatment strategy for vestibular neuritis involves use of as few medications as possible and to encourage activity as practical. In the first few days of the illness, patients will usually severely restrict their activities as rapid head movements and activities such as sitting up or turning over in bed may cause increased vertigo. Vestibular suppressants and antiemetics are commonly used at this point, prescribed as suppositories if necessary. By the third day, it is usually possible to greatly reduce usage of vestibular suppressants and the patient should be encouraged to increase activity as tolerated.

Recently, Strupp and associates (2004) studied 141 patients with vestibular neuritis. They found that a course

Case 9-3
A 60-year-old woman awoke one morning with severe spinning, nausea, and vomiting. She was unable to walk and had to crawl to the bathroom to vomit. Hearing was unaffected. She was taken to the emergency department by her family, where, after a computerized tomographic (CT) scan was performed, BPPV was incorrectly diagnosed. After treatment with diazepam and prochlorperazine, she was sent home with meclizine and prochlorperazine suppositories. After several weeks, symptoms resolved.

Comment. While this patient was misdiagnosed in the emergency department, treatment was nonetheless appropriate. The CT scan was reasonable as it is generally impossible to exclude a cerebellar infarct in acute vertigo. Recent studies suggest that steroids may be appropriate treatment in this context.
of methylprednisolone, starting with 100 mg/d and tapering to 10 mg/d over 3 weeks, significantly improved the results of caloric testing 1 year following vestibular neuritis. Of those receiving steroids, 60.9% improved, compared with 37.9% of control subjects.

No matter what treatment is chosen, most patients recover subjectively within 2 months. Those who do not may have a significant fixed vestibular paresis combined with central dysfunction that slows their compensation. For example, patients with alcoholic cerebellar degeneration or persons of advanced age may recover much more slowly. Such patients can benefit from a program of physical therapy incorporating gait training and visual-vestibular exercises. Surgical treatment is not indicated for vestibular neuritis.

Bilateral Vestibular Paresis

Bilateral vestibular paresis presents with oscillopsia, ataxia, and mild vertigo. The typical patient is an individual who was recently treated for a serious infection, most often osteomyelitis or peritonitis. The infection is treated for several weeks with an ototoxic antibiotic (of which gentamicin is the most commonly responsible). The symptoms of bilateral vestibular paresis, ataxia and oscillopsia, manifest themselves when the patient recovers from the infection and tries to walk (Case 9-4).

The long-term prognosis of these patients is good. Although they rarely achieve “normal” performance on functional evaluations, substantial recovery is the rule unless a superimposed cerebellar lesion is present. Most patients return to productive work within 1 year of exposure.

It is important to note that medications that reduce symptoms of other forms of otological vertigo such as the vestibular suppressants generally make symptoms worse in bilateral vestibular paresis. Vestibular suppressants must be eliminated in the management of this condition. It is also prudent to avoid medications with potential vestibular suppressant activity such as calcium channel blockers and those that have central anticholinergic side effects (eg, many of the tricyclic antidepressants). Patients should be warned to avoid subsequent exposure to ototoxic drugs, especially gentamicin and loop diuretics (eg, furosemide [Lasix], bumetanide [Bumex], and ethacrynic acid [Edecrin]). If a loop diuretic is necessary, bumetanide is the least ototoxic.

The author also advises these patients to be careful to avoid loud noises, as they are likely more vulnerable to noise-induced hearing loss than the general population. Theoretically, in persons with some remaining vestibular function, medications that promote central plasticity (such as stimulants)
might be helpful in treating bilateral vestibular paresis, and those that retard compensation (sedatives) might also slow or prevent recovery.

**Central Vertigo**

Vertigo caused by central nervous system dysfunction, or “central vertigo,” is unusual. In the emergency department setting or otolaryngology clinic, a central cause of vertigo is identified in less than 5% of cases. Even in neurology settings, central vertigo typically accounts for only about 20% of diagnoses in patients complaining of vertigo (Drachman and Hart, 1972). Central vertigo is largely caused by vascular disorders. In the author’s experience, stroke and transient ischemic attack, usually involving the brain stem or cerebellum, account for one third of cases. Vertigo attributed to vertebrobasilar migraine causes approximately 15% of cases. A large number of individual miscellaneous neurological disorders such as seizures, multiple sclerosis, and the Arnold-Chiari malformation make up the remainder.

There is a striking difference in the duration of symptoms between central vertigo associated with a fixed structural lesion of the nervous system and otological vertigo in that prolonged duration of symptoms is common in central vertigo (Case 9-5). While patients with peripheral vestibular imbalance caused by a structural lesion of the vestibular nerve (eg, vestibular neuritis) typically recover within months, patients with central vertigo such as that caused by a stroke involving the cerebellum may continue to be distressed by ataxia, nausea, and the illusion of motion for years. Presumably, the persistence of symptoms in patients with central vertigo reflects a defect in the central mechanisms that usually compensate for vestibular lesions.

A combination of headache and vertigo is a common presentation of central vertigo, particularly in women in their mid 30s. In most instances, these symptoms are caused by vertebrobasilar migraine, and a prophylactic drug should be tried. A sustained release preparation of verapamil (Calan SR, Isotin SR, Verelan) 180 mg is often effective. If the patient does not tolerate verapamil (constipation is the most common problem), a trial of amitriptyline can be made. When treating migraine-associated vertigo, amitriptyline (10 mg nightly gradually increasing to 25 mg or 50 mg) is favored over other antidepressant medications because of its antihistaminic and anticholinergic activity, which is helpful in suppressing vertigo whether from migraine, or not. It is also very inexpensive. Unfortunately, amitriptyline use is often accompanied by the

**Case 9-5**

A 35-year-old woman presents with dizziness and headaches. She is dizzy for weeks at a time, although she does not describe a clear-cut spinning sensation but rather vague motion sensitivity. She denies having migraine headaches but does attributes frequent headaches to “sinus.” Her mother had similar dizzy spells, which she “grew out of.” Topiramate 25 mg at bedtime, increasing to 25 mg 2 times a day was prescribed for the patient. After 1 month, her dizziness and headaches were much better, and she was also pleased that she had lost about 5 lbs.

**Comment.** This patient had migraine-associated vertigo. Dizziness and headache in women of childbearing age generally respond to migraine prophylactic drugs.
side effects of dry mouth, sedation, and weight gain. Beta-blockers represent a third line of treatment. Depression and impotence are the main reasons why some patients are unable to tolerate them. Several anticonvulsants, including sodium valproate, topiramate, and tiagabine (Gabitril), can also be used for migraine prophylaxis. At this writing, topiramate (Topamax, 25 mg/d to 100 mg/d in divided doses) appears to be the most useful, as it combines reasonable efficacy with the often-useful side effect of weight loss. Sodium valproate (Depakote) has substantial side effects, often including tremor and weight gain, which make it less favored.

Another common situation is the occurrence of central vertigo in a patient with a known central lesion in whom the goal is to reduce symptoms of vertigo or ataxia. Benzodiazepines such as lorazepam, clonazepam, and diazepam are frequently helpful (see Table 9-3 for doses), but one must be wary of psychological addiction and physical dependence. Gabapentin (Neurontin, 100 mg 2 times a day to 600 mg 3 times a day) is often useful as a suppressant of spontaneous nystagmus. Meclizine taken in a dose of 25 mg to 50 mg 2 or 3 times a day is occasionally successful. Dopamine blockers such as prochlorperazine can be tried. The antiemetic ondansetron may be helpful when central vertigo does not respond to the usual agents. Similarly, occasional patients with oculomotor signs localizing to the vestibulocerebellum may benefit from the use of acetazolamide (Diamox) therapy.

Carbamazepine (Tegretol) or oxcarbazepine (Trileptal), in doses appropriate for neuralgia or epilepsy, can be tried in patients having an abnormal electroencephalogram or brief paroxysmal symptoms (“quick spins”) that have not responded to other medications. Oxcarbazepine should be initiated at a lower dose in persons taking benzodiazepines. Gabapentin (Neurontin), a glutamate blocker, may also be used in these situations. Baclofen (Lioresal) is used similarly. In this situation one might be treating epilepsy, microvascular compression, or intrinsic brain stem lesions. Gabapentin is also generally useful as a suppressor of nystagmus. Physical therapy emphasizing effective use of appliances such as canes, walkers, and footwear is often useful.

### Psychogenic Vertigo

Psychogenic vertigo is caused by an independently diagnosable psychiatric problem such as anxiety, depression, somatization, or malingering. Vertigo of other causes is also often accompanied by an independently diagnosable psychiatric condition such as anxiety, which might be comorbid or reactive.

Because of inadequacies of current diagnostic methodology, it is difficult to determine the proportion of “psychogenic” patients in the dizzy population who present to the clinician or at large in the population. Some authors indicate that as many as 50% of all persons with dizziness have a “functional” source of complaints (Afzelius et al, 1980). However, this large percentage results from an algorithm where patients with no findings on testing were assigned this diagnosis. This process is obviously fraught with peril, given that it lumps together patients where the diagnostic process may have failed with those who do indeed have a psychological origin of symptoms. In the author’s practice, only about 15% of patients are assigned the “psychogenic” diagnosis.

Anxiety and panic are the most common psychiatric symptoms found in persons with dizziness. Accordingly benzodiazepines as well as antidepressants are the mainstay of treatment. As considerably larger doses of benzodiazepine medications are needed for anxiety than for vestibular suppression, and
because these patients will likely need long-term treatment, psychiatric referral can be very useful (Case 9-6).

Depression is an extremely unusual cause of vertigo. When it is very clear that depression is significant, one of the members of the selective serotonin reuptake inhibitor family such as sertraline (Zoloft) or paroxetine (Paxil) may be used. These drugs are also useful in persons with obsessive-compulsive tendencies, which are often found in persons complaining of chronic dizziness. However, it is generally best to use these agents sparingly as they commonly have nausea as an associated side effect, some may increase tinnitus, and all antidepressants increase falling. Buropion (Wellbutrin) and venlafaxine (Effexor) can also be useful in selected patients. Vertigo due to somatization and malingering has no useful drug treatment.

Undetermined and Ill-Defined Causes of Vertigo

Regardless of whether one is practicing in the emergency department, otolaryngology clinic, neurology clinic, or a general medical setting, variants of unlocalizable diagnoses such as “unknown diagnosis,” “vasovagal” syncope, “hyperventilation syndrome,” “posttraumatic vertigo,” and “nonspecific” dizziness are often the most common single “cause” of dizziness reported. Between 38% and 52% of diagnoses fall into this category across many series (Drachman and Hart, 1972). The unifying feature to these diagnoses is the lack of abnormality on otological and neurological examination.

Treatment is necessarily empirical in vertigo of undetermined origin. The author asks the patient to log their symptoms on a calendar. Next, for patients already taking medication, drugs that could affect the vestibular system are withdrawn, and the patient records symptoms over 2 or more weeks. This strategy may identify persons with ataxia caused by medication. One must be very careful in this situation not to eliminate a medication critical to the patient’s well-being. For example, when one withdraws an antihypertensive such as a calcium channel blocker that has vasodilator properties, angina may be precipitated.

Several drugs are then tried. Daily meclizine may be replaced with a small dose of clonazepam or lorazepam, which helps allay the patient’s anxiety. Benzodiazepines also may be helpful because of their vestibular suppressant effect. It is generally difficult to exclude mild Ménière’s disease, and salt restriction and a diuretic such as triamterene/hydrochlorothiazide (Maxzide) may be tried. A trial of migraine prophylaxis with sustained-release verapamil (180

**Case 9-6**

A young woman working at a large accounting firm complained of dizziness and posteriorly located headaches. She found it difficult to describe her symptoms other than that she felt unsteady and had a constant sensation of rocking. She indicated that she ordinarily worked 16-hour days in an attempt to get ahead and become a “partner.” Her symptoms resolved with clonazepam, but she refused to take it as she felt that it just slowed her down too much.

**Comment.** Persons who respond to clonazepam and other benzodiazepines may have anxiety or central or peripheral vestibular disorders. Migraine-associated vertigo generally does not respond to benzodiazepines.
mg each evening) is sometimes helpful in patients with dizziness and headaches or patients with the diagnosis of “vestibular Ménière’s.” Carbamazepine or oxcarbazepine is tried for the symptom of “quick spins” alluded to in the section on central vertigo. Gabapentin is also a reasonable drug to try empirically for central vertigo. Betahistine, while possibly a placebo, may be useful.

Patients who do not respond to the above regimens are followed at 3- to 6-month intervals and undergo yearly audiometric screenings. This is important as occasionally persons with small acoustic neuromas or early Ménière’s disease will evolve into an identifiable clinical presentation. It is often helpful to see the patient quickly when there is an acute flare-up of symptoms, as in this way one can sometimes diagnose intermittent conditions that can have normal examinations between flare-ups such as BPPV and Ménière’s disease (Case 9-7).

**CONCLUSION**

Pharmacological treatment of dizziness is complex and generally is not entirely satisfactory. Symptoms are most often caused by loss of function in the inner ear, which medications are generally unable to restore. While a substantial armamentarium of drugs can be used for symptomatic treatment, side effects are usually substantial. The clinician must keep in mind patient comfort, long-term recovery, adverse effects, and interaction of medications with other treatment modalities such as surgery and physical therapy.

**REFERENCES**


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Paper contradicting common dogma that benzodiazepines impair compensation.


Another paper contradicting common dogma that benzodiazepines impair compensation.


Ten percent of otherwise normal population has hydrops, suggesting that treatments aimed at hydrops may be ill conceived.


A review of the numerous unproven treatments advocated for Ménière’s disease over the years.

Suggests that steroids improve outcome in vestibular neuritis.


The classic paper on numerous unproven treatments for Ménière’s disease.


Basic epidemiology of Ménière’s disease.