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Pharmacologic Treatment of Persons with Dizziness

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Dizziness is a general term that may encompass symptoms from diverse causes, such as low blood pressure and drug side effects. This article more specifically addresses vertigo, a common subtype of dizziness, defined as the illusion of rotational motion. Most vertigo is otologic and caused by dysfunction of the rotational velocity sensors of the inner ear, the semicircular canals. There are other types of vertigo, however, and 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 also are compared centrally and when there is a mismatch between two or more senses, vertigo can be perceived.

Neurophysiology of dizziness and vertigo

From this systems physiology perspective, possible sources of vertigo include all possible combinations of sensory disturbances related to motion and central malfunction of the comparison mechanism. Practically, however, because the visual and somatosensory senses produce mainly position-coded signals, vertigo rarely is a consequence of visual or somatosensory malfunction. An example of visual vertigo is vertigo associated with an oculomotor disturbance accompanied by nystagmus. Nevertheless, the common varieties of visual disturbance (diminished vision,

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double vision, and disorders of the accommodation system) usually do not create vertigo. Similarly, vertigo only occasionally is associated with somatosensory dysfunction, as in cervical vertigo. Central vertigo is more frequent but still uncommon with respect to otologic vertigo (discussed later).

When treating vertigo, motion sickness also must be considered, 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 often can be avoided. Also, the symptoms of motion sickness usually persist longer and tend to be more disturbing than the inciting vertigo. Again, although vertigo is experienced reliably by normal persons experiencing similar sensory disturbances, susceptibility to motion sickness varies remarkably. Also, the pharmacology of vertigo and motion sickness clearly are distinct.

Finally, when planning treatment, recovery and compensation must be considered. Every vestibular stimulus, the result of either 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 agents that relieve vertigo, nausea, or motion sickness may block compensation [1,2]. There are two key concepts regarding compensation that need to be considered when planning therapy for vertigo. First, promotion of central compensation is desirable during the process of recovery from persistent vestibular imbalance, such as after a severe bout of vestibular neuritis. Second, prevention of unneeded and counterproductive compensation may be desirable after a transient vestibular imbalance, such as might be caused by Meniere's disease.

Neurochemistry of vertigo

There are at least four major neurotransmitters of the vestibular system involved in the three-neuron arc between the vestibular hair cells and the oculomotor nuclei that drive the vestibuloocular reflex. There also are a host of other neurotransmitters that modulate function. Table 1 summarizes

Table 1
Neurotransmitters of the vestibular system

Neurotransmitter	Peripheral role	Central role
Glutamate	Excitatory for afferent synapse	Excitatory
ACH	Excitatory for efferent synapse	Excitatory
GABA	Inhibitory	Inhibitory
Glycine	Unclear	Inhibitory
Dopamine	Unclear	Excitatory
Norepinephrine	Unclear	Modulator
5-Hydroxytryptamine subtypes 1 and 2	Unclear	Excitatory
Histamine	Unclear	Inhibitory (?)

what is known. Glutamate is the major excitatory neurotransmitter [3]. Acetylcholine (ACH) is a peripheral (inner ear) and central agonist (vestibular nucleus) affecting muscarinic receptors. Peripherally, however, ACH seems involved only in the brainstem efferent–hair cell synapse, which has an uncertain functional significance. Centrally, ACH is more important. There are five known subtypes of ACH receptors. The receptors found in the pons and medulla, presumably those involved with dizziness, almost exclusively are of the M2 subtype [4]. γ-Aminobutyric acid (GABA) and glycine are inhibitory neurotransmitters found in connections between second-order vestibular neurons and oculomotor neurons [5]. Stimulation of the two types of GABA receptors, GABA-A and GABA-B, have similar effects on vestibular pathways [6], but specific GABA-B agonists, such as baclofen, decrease the duration of vestibular responses in animal models [7]. 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 pharmacologic management of vertigo. Histamine is found diffusely in central vestibular structures. Centrally acting antihistamines modulate symptoms of motion sickness [8]. There are three histamine receptor subtypes—H1, H2, and H3. All subtypes of histamine receptors affect vestibular responses [3]. H3 agonists also inhibit histamine, dopamine, and ACH release. Norepinephrine is involved centrally in modulating the intensity of reactions to vestibular stimulation [9] and it 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: anticholinergics, antihistamines, and benzodiazepines (Table 2). Calcium channel blockers also are used for vestibular suppression, although their use for this purpose is not accepted universally.

Anticholinergics

Agents that inhibit muscarinic receptors, such as scopolamine (Transderm-Scop), increase motion tolerance. Agents that have 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 [8]. Nevertheless, some anticholinergics that do not cross

Table 2
Vestibular suppressants

Drug (brand name)	Dose	Pharmacologic class	Adverse reactions
Clonazepam (Klonopin)	0.25 mg to 0.5 mg twice a day	Benzodiazepine	Mildly sedating, drug dependency
Diazepam (Valium)	2–10 mg (1 dose) given acutely orally, intramuscularly, or intravenously 2 mg twice a day for chronic dizziness	Benzodiazepine	Sedating, respiratory depressant, drug dependency, precaution in glaucoma
Dimenhydrinate (Dramamine)	50 mg every 4–6 hours	Antihistamine Anticholinergic	Same as meclizine
Lorazepam (Ativan)	0.5 mg twice a day	Benzodiazepine	Mildly sedating, drug dependency
Meclizine (Antivert, Bonine)	12.5–50 mg every 4–6 hours, chewable tabs three times a day if nauseated	Antihistamine, anticholinergic	Sedating, precaution in prostatic enlargement
Scopolamine (Transderm-Scop)	0.5 mg patch every 3 days	Anticholinergic	Topical allergy, precaution in glaucoma, tachyarrhythmia, prostatic enlargement

Doses are those used routinely for adults and generally are not appropriate for children.

the blood-brain barrier to a great extent (eg, glycopyrrolate [Robinul]) are reported useful for vestibular suppression in Meniere's disease. Unlike antihistamines (discussed later), pure anticholinergics are ineffective if administered after symptoms have appeared [9a].

All anticholinergics conventionally used in the management of vertigo have prominent side effects, including dry mouth, dilated pupils, impaired accommodation (focusing), and sedation. Scopolamine and atropine are nonspecific muscarinic receptor antagonists [4]. It is hoped that agents selective for vestibular subtypes of muscarinic receptors (probably M2) eventually will be developed or discovered among the currently 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 is attained to a vestibular imbalance [10]. Thus, an anticholinergic given to patients who have compensated fully for a previous vestibular lesion might induce dizziness and initiate an anticompensatory response. Anticholinergics probably also slow the rate of compensation. For these reasons, and because of prominent side effects, conventional practice is to avoid chronic administration of anticholinergics for vertigo in persons who have 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, 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 Transderm-Scop and develop withdrawal symptoms (usually nausea and vertigo) when the patches are discontinued [11]. This can be managed by substitution of an oral formulation of hyoscine, followed by slow withdrawal.

Antihistamines

Although 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 [8]. 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

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

In surprisingly small doses, benzodiazepines are useful for the management of vertigo. Addiction, impaired memory, increased risk of falling [12,13], and impaired vestibular compensation are drawbacks associated with their use. Lorazepam is a useful agent particularly because of its effectiveness and simple kinetics. Lorazepam has no active metabolites. Addiction, the biggest problem, can be avoided by keeping the dose to 0.5 mg twice a day or less. Lorazepam also can be taken sublingually (1 mg) for an acute attack of vertigo. Similarly, low doses of diazepam (Valium) (2 mg twice a day) can be effective. Little information is available about addiction potential and efficacy of clonazepam (Klonopin), but it seems as effective a vestibular suppressant as lorazepam. It usually is prescribed in a dose of 0.5 mg twice a day and recently has become available as a sublingual preparation. The authors prefer to avoid use of alprazolam (Xanax) for vestibular suppression because of the potential for a difficult withdrawal syndrome. Long-acting benzodiazepines usually are not helpful for relief of

Table 3
Calcium channel blockers

Drug (brand name)	Dose	Uses	Common adverse reactions
Cinnarizine (Stugeron) (not FDA approved)	25 mg three times a day	Migraine, vertigo	Sleepiness, weight gain
Flunarizine (Sibelium) (not FDA approved)	10 mg at bedtime	Migraine, vertigo, motion sickness	Sleepiness, weight gain
Nimodipine (Nimotop)	30 mg twice a day	Migraine, Meniere's	Headache, flushing
Verapamil	120 mg sustained release at bedtime	Migraine	Constipation

Doses are those used routinely for adults and generally are not appropriate for children. Several drugs listed here are not FDA approved for use in the United States.

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 (Table 3) are useful in the treatment of dizziness. Two examples of this group, flunarizine and cinnarizine, are popular antivertiginous agents outside the United States [14,15]. Flunarizine also is reported effective in the prevention of motion sickness [14]. Nimodipine is reported as possibly effective in Meniere's disease [16]. L-channel calcium channel blockers are effective drugs to prevent migraine [17], a common cause of dizziness. There are several general reasons why calcium channel blockers might be of help in the management of vertigo. Calcium channel blockers may be vestibular suppressants [14,18]. Practically, some calcium channel blockers, such as verapamil, have strong constipating effects, which may be helpful in managing diarrhea caused by vestibular imbalance. Calcium channel blockers also often have anticholinergic or antihistaminic activity [19]. Many calcium channel blockers, especially flunarizine and cinnarizine, have dopamine antagonist characteristics [20,21].

Drugs to suppress emesis

Antiemetics

Table 4 lists drugs 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 commonly are used in outpatients who are unable to absorb oral agents because of gastric atony or vomiting. Sublingual administration of antiemetics also is useful. Injectables are used in the emergency room or inpatient settings.

Table 4
Antiemetics

Drug (brand name)	Usual adult dose	Pharmacologic class	Adverse reactions
Granisetron (Kytril)	1 mg by mouth 1 mg intravenously	5HT3 antagonist	Headache
Meclizine (Antivert, Bonine)	12.5 or chewable 25 mg every 4–6 hours by mouth three times a day	Antihistamine, anticholinergic	Sedating, precautions in glaucoma, prostate enlargement
Metoclopramide (Reglan)	10 mg by mouth three times a day or 10 mg intramuscularly	Dopamine and 5HT antagonist	Restlessness or drowsiness extrapyramidal
Ondansetron (Zofran)	4–8 mg by mouth 8 mg sublingual 4–16 mg intravenously	5HT3 antagonist	Headache, diarrhea, fever
Palanosetron (Aloxi)	0.25 mg intravenously	5HT3 antagonist	Headache, constipation
Prochlorperazine (Compazine)	5 mg or 10 mg intramuscularly or by mouth every 6–8 hours	Phenothiazine	Sedating Extrapyramidal
Promethazine (Phenergan)	25 mg by mouth every 6–8 hours or 25 mg rectal every 12 hours or 12.5 mg intramuscularly every 6–8 hours	Phenothiazine	Sedating Extrapyramidal
Thiethylperazine (Torecan)	10 mg by mouth, up to three times a day or 2 ml intramuscularly, up to three times a day	Phenothiazine	Sedating Extrapyramidal
Trimethobenzamide (Tigan)	250 mg by mouth three times a day or 200 mg intramuscularly three times a day or 200 mg rectal three times a day	Similar to phenothiazine	Sedating Extrapyramidal

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

Some antihistamines commonly used as vestibular suppressants have significant antiemetic properties (eg, meclizine). When an oral agent is appropriate, meclizine generally is the first to be used, because it rarely causes adverse effects more severe than drowsiness. Phenothiazines, such as prochlorperazine (Compazine) and promethazine (Phenameth or Phenergan), are effective antiemetics, probably because of their dopamine blocking activity, but they also act at other sites. For example, promethazine also is an H1 blocker. Because these drugs can induce significant side effects, such as dystonia, they are considered second-line drugs and should be used briefly and cautiously. Similarly, butyrophenones, such as haloperidol, can be used as antiemetics, but have similar cautions. Droperidol given sublingually is

an effective treatment of emesis, but its use is not recommended because of the possibility of cardiac arrhythmia.

Drugs that speed gastric emptying, such as metoclopramide (Reglan) and powdered ginger root, may be helpful in managing emesis [22]. Metoclopramide, a benzamide derivative, is a dopamine antagonist that speeds gastric emptying and a central antiemetic. It is ineffective in preventing motion sickness [23]. Domperidone, a mainly peripherally acting dopamine-2 receptor antagonist, has antiemetic activity because of its peripheral gastrokinetic and central action on the chemoreceptor trigger zone. It has similar efficacy to metoclopramide combined with a more favorable safety profile [24]. Sulpiride, a substituted benzamide derivative, also is 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 Food and Drug Administration (FDA) of the United States.

5-HT_3 antagonists, such as ondansetron (Zofran), sometimes are effective in preventing vomiting in human vestibular disorders, although animal studies suggest that they should be ineffective [25]. This difference between animal and actual human experience may be related to well-known species differences with respect to emesis [26]. Convenient sublingual dosing forms of ondansetron and related medications are available. Although the high price of these agents limits their usefulness in the treatment of vertigo, their lack of sedation can make them attractive. These agents do not seem to be helpful in preventing motion sickness [27].

Agents that affect compensation

Although the manipulation of compensation ordinarily is not considered in clinical practice, it seems reasonable to do so in the interest of improving patient outcomes. If patients have a permanent vestibular lesion, for instance an acoustic neuroma or a persistent vestibular neuritis, it may be desirable to speed central compensation or, alternatively, to retard compensation in persons who have a transient vestibular lesion, such as often is caused by Meniere's syndrome. Drugs that cause decompensation (such as adrenergic agents) or overcompensation (such as anticholinergics) may induce recurrent vertigo in persons who have compensated for vestibular injury, although they may be tolerated well by persons who have no vestibular disturbance.

Compensation is composed of several discrete processes, the most important of which is static and dynamic compensation [28]. Static compensation is defined as adjustments that restore a balance of central vestibular tone and that are manifested by elimination of spontaneous nystagmus and postural deviation. Dynamic compensation is defined as adjustments that restore normal vestibular gain and that are manifested by loss of oscillopsia and acquisition of more effective postural responses that restore balance after a perturbation. In animals, static compensation occurs

more quickly than dynamic compensation and requires little in the way of sensory input [28]. Dynamic compensation, however, such as vestibulo-ocular reflex gain restoration, is a slower process that requires visual experience for its acquisition and is dependent on central nervous system (CNS) structures for maintenance [10]. 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 opposite to the original paretic nystagmus), which may account for greater drug sensitivity in persons who have compensated for vestibular deficits. Four things need to be known: effects on the speed and stability of static and dynamic vestibular compensation.

Table 5 summarizes what little is known about how drugs used to treat vertigo affect the rate of compensation to vestibular lesions in animal models [29,30]. Drugs that speed compensation in animals mainly are stimulants, and drugs that retard compensation are sedatives. Most vestibular suppressants are believed to retard compensation, but what little published evidence is available suggests that they have little or no effect. For example, diazepam is not proved to disturb static or dynamic compensation [31–33].

In animals, dopamine agonists speed compensation and antagonists slow compensation [2,34]. What they do in human clinical situations is unknown, but adrenergic agonists, such as ephedrine and amphetamines, occasionally are used in combination with vestibular suppressants. Although they most often are used to counteract the sedative effects of vestibular suppressants, these stimulants also may help by promoting vestibular compensation. Amphetamines are shown to speed recovery of motor function in stroke [35]. Adrenocorticotrophic hormone (ACTH) [36] and glucocorticoids [37] are reported to speed static compensation. Alcohol probably impedes and delays dynamic vestibular compensation, but it does not cause static

Table 5
Commonly used agents for vertigo that may affect the rate of vestibular compensation

Drug or drug category	Example	Effect on speed of compensation	Effect on level of compensation
Anticholinergic	Scopolamine		Overcompensation
GABA modulator	Diazepam	No effect	
Dopamine blocker	Haloperidol	Slows static compensation	
ACTH	ACTH	Speeds static compensation	
Glucocorticoid	Methylprednisolone	Speeds compensation	
Adrenergic agonist	Amphetamine	Speeds compensation	Decompensates

Adapted from Brandt T. Vertigo. Its multisensory syndromes. London. Springer-Verlag; 1991. (17); p. 48–9.

decompensation [38]. Calcium channel blockers, such as verapamil or flunarizine, also may enhance compensation [39], but this is controversial [30]. It seems likely that antihypertensive agents, which act through adrenergic blocking or depleting, may slow vestibular compensation.

Some drugs also affect completed compensation; particularly in animals, cholinergic agonists cause decompensation, whereas anticholinergic drugs cause overcompensation [40]. Glutamate N-methyl-D-aspartate (NMDA) receptor antagonists cause decompensation [41]. At this writing, there is little clinical data regarding the importance of these considerations [30] and what is available suggests small effects [1,31].

Agents of uncertain efficacy or mechanism

Many substances, procedures, and devices are promoted as effective treatments of vertigo, many without clear proof of efficacy. The tendency to attribute curative properties to a bewildering number of medications, devices, and surgical procedures is evident particularly in the treatment of Meniere's disease [42,43]. It seems likely that most of these agents have minor or no pharmacologic efficacy; rather, they simply are placebos. Another possibility partially borne out by animal data is that these agents are not vestibular suppressants; rather, they affect vestibular compensation. Table 6 lists the most commonly used agents of uncertain efficacy or mechanism.

An intriguing member of this group is betahistine. Whereas the antihistamines used in treating vertigo usually are centrally acting histamine H1-receptor antagonists, betahistine is a weak H1-receptor agonist and

Table 6
Selected agents of uncertain efficacy or mechanism

Drug (brand name)	Dose	Pharmacologic class	Adverse reactions
Betahistine (Serc) (not FDA approved)	4 mg three times a day to 16 mg three times a day	Histamine agonist	Gastric upset, aggravation of asthma, should not use in persons with hepatic dysfunction
Ginkgo biloba	120 to 240 mg per day	Unknown mechanism	Allergy, interaction with blood thinners
Baclofen	10 to 80 mg per day	GABA-B agonist	Gastric upset, weakness
Amantadine	100 mg daily or twice a day	Dopamine agonist	Rash
Piracetam (not FDA approved)	800 mg two or three times a day	Unknown	Anxiety, insomnia, tremor, confusion

Doses are those used routinely for adults and generally are not appropriate for children. Several of these drugs are not FDA approved for use in the United States.

a moderate H3 antagonist [44]. It is suggested that betahistine decouples the negative feedback loop controlling histamine release, resulting in central facilitation of histaminergic neurotransmission in the brain [45]. In therapeutic doses, betahistine administration is associated with reduction in the gain of the vestibulo-ocular reflex [45,46]. In addition, betahistine increases blood flow to the inner ear [47]. It is difficult to understand how betahistine might act selectively on blood flow to the inner ear, however, and it seems highly unlikely that vasodilation is the mechanism for putative positive effects on vestibular function. There is substantial evidence that betahistine may speed vestibular compensation [48–50], which is a surprising finding for a drug that reduces vestibular-ocular reflex gain. Vertigoheel, a homeopathic remedy, recently has been compared to betahistine and found equivalent [51]. As Vertigoheel presumably is a placebo, this study provides evidence that betahistine also is a placebo. In the United States, as of 2004, the FDA does not recognize betahistine as an effective medication. Nevertheless, betahistine often is used in persons who have chronic vertigo, and considering the neurophysiologic data (discussed previously), more clinical study seems warranted.

Ginkgo biloba is recommended for vertigo and tinnitus. Ginkgo may reduce the viscosity of the blood (literally, blood thinning), and it also may be an antioxidant. Ginkgo may speed vestibular compensation in animals [52–54]. Notwithstanding these encouraging pharmacologic reports, a recent study suggests that ginkgo is similar to betahistine in efficacy for vertigo [55]. As betahistine reportedly is indistinguishable from a homeopathic medication in effectiveness (discussed previously), ginkgo is unlikely to be effective.

Isosorbide is an osmotic diuretic (not the isosorbide dinitrate used as a vasodilator) that has been advocated in Meniere's disease. Two unblinded trials in Japan [56,57] report successful control of Meniere's disease in 60% to 80% of treated patients. These results are uncomfortably close to those of placebos, as approximately 60% of patients who have Meniere's have a remission within 6 months on placebo [43].

Pentoxifylline is reported useful in the treatment of vascular inner ear disease [58]. Pentoxifylline also is a weak anti–tumor necrosis factor (TNF) inhibitor [59]. 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, centrally acting agents used generally in conditions unrelated to vertigo, sometimes are advocated for vertigo. Baclofen most commonly is used in patients in whom the diagnosis of microvascular compression of the eighth nerve is considered. Baclofen also is used to reduce the intensity of upbeat and downbeat nystagmus [60]. Baclofen improves symmetry of vestibular responses in hemilabyrinthectomized rats [61,62] and may have a role in treatment of vestibular imbalance. Amantadine also is used in an attempt to promote compensation, by analogy with its use in persons who have traumatic brain injury [63].

DL-leucine, an amino acid, sometimes is used for treatment of vestibular imbalance. It is suggested that leucine restores symmetry of central vestibular neurons [64]. There are no formal studies of efficacy of any of these drugs for vestibular disorders in humans.

Piracetam, a cyclic derivative of GABA, is a member of a family of nootropics. According to Nicholson, nootropics facilitate learning and retrieval of information and protect the brain from physical and chemical intoxication [65]. Piracetam mainly is recommended for central vertigo [66–68]. Side effects are believed minor but may include anxiety, insomnia, tremor, and confusion. Piracetam is not FDA approved.

A sodium channel blocker, phenytoin (Dilantin), is reported to protect against motion sickness two times more effectively than the combination of scopolamine and dextroamphetamine [69,70]. Phenytoin generally is not 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 [71]. The mechanism of this effect tentatively is attributed to increased excitability of cerebellar Purkinje's cells. Although unlikely to be a placebo, this compound is not FDA approved. More study seems warranted.

Treatment of individual conditions

Drug treatment of benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is the single most common type of vertigo, accounting for approximately 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. Currently it is believed that BPPV is caused by the presence of free otoconia or canaliths, within the semicircular canals, dislodged from the otolith organs by trauma, infection, or degeneration (see Fig. 1). The debris moves to the lowest part of the posterior canal with changes in head position and causes vertigo and nystagmus as they tumble. Symptoms can be intense but fortunately brief, because dizziness occurs only when the debris shifts position. Some patients are conditioned by the reliable appearance of vertigo in particular positions and develop a phobia related to sleeping on the back or on one side. This syndrome should not be confused with phobic postural vertigo, which is a combination of phobic avoidance, postural unsteadiness, and episodic dizziness [71a].

Physical treatments using sequential manipulation of the position of the head with respect to gravity are the most effective treatment of BPPV [72]. Drugs are not as helpful for BPPV as are physical treatments, but antiemetics, such as meclizine or ondansetron (Zofran), are helpful in patients whose

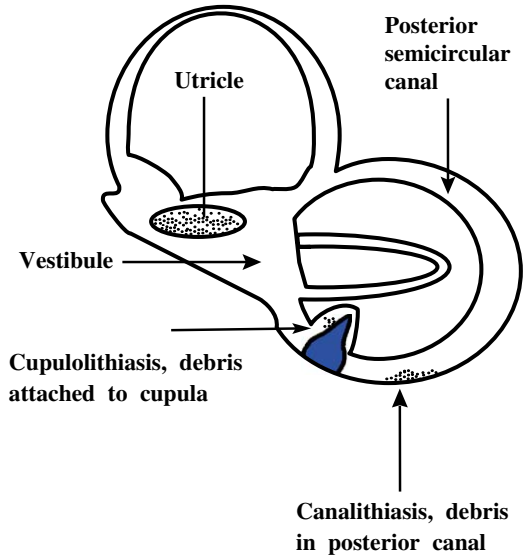

Fig. 1. Mechanisms of benign paroxysmal positional vertigo. (Courtesy of Timothy C. Hain, MD.)

vertiginous spells are followed by nausea. Meclizine also may be an effective and far less expensive adjunct to the specific exercises for this condition. In this situation, it is taken before home exercises in an attempt to prevent motion sickness and nausea. Those patients who awaken from sleep resulting from dizziness may take meclizine nightly until the physical therapy relieves their underlying disorder. Vestibular suppressants that have little antiemetic activity (eg, diazepam [Valium, Valrelease, and Zetran] and lorazepam [Ativan]) generally are unable to reduce severe symptoms to acceptable levels. They may, however, be helpful in persons who have phobic positional symptoms, again as an adjunct to exercises intended to desensitize them.

Drug treatment of Meniere's disease

Meniere's disease is the second most common cause of vertigo of otologic origin. It is typified by spells of hearing decline, monaural fullness, roaring tinnitus, and vertigo. Although Meniere's disease classically is attributed to dilation (endolymphatic hydrops) and periodic rupture of the endolymphatic compartment of the inner ear, this mechanism has come into question for several reasons. First, although approximately 10% of the population has endolymphatic hydrops on autopsy [73], only approximately 0.2% of the population has Meniere's disease [74]. Also, there is considerable evidence for immune disturbances in Meniere's disease [75] and periodic release of cytokines may be a more plausible explanation. Whatever the

cause, medical management of Meniere's disease largely consists of managing symptoms and, when this fails, referral for consideration of surgical management. The surgical management of Meniere's disease is highlighted in elsewhere in this issue.

For the episodic vertigo that is common in Meniere's syndrome, vestibular suppressants with or without an antiemetic (Tables 2 and 3) 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 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. These rarely are required, however, 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.

There is no consensus on prophylaxis of Meniere's syndrome, and simply treating the symptoms is considered acceptable. No matter which prophylactic treatment is used, remission eventually occurs in 60% to 80% of cases [42,43]. Because of the great variability in the course of Meniere's disease, to have adequate power, a clinical trial requires large numbers, and few of these have been performed.

It is common practice, however, to advise dietary salt restriction (1 to 2 g salt per day) and use of a mild diuretic, such as hydrochlorothiazide-triamterene (Dyazide or Maxide). This regimen may reduce the frequency of attacks and slow down progression of hearing loss [54]. Dyazide may cause significant hyponatremia, especially in the elderly and in those who already are salt restricted, and in this situation, an every-other-day dose schedule may be used or serum electrolytes monitored. The Maxide form of the drug is scored and can be broken in half.

In patients who cannot tolerate Dyazide, diuretics that inhibit carbonic anhydrase, such as acetazolamide (Diamox), occasionally are helpful. Carbonic anhydrase inhibitors also may be helpful in persons who have episodic ataxia and migraine-associated vertigo, giving them a broader indication. Spironolactone may be used in women who have perimenstrual flareups. Calcium channel blockers, such as verapamil (Calan and Isoptin) or nimodipine (Nimotop), also may be helpful, although few formal studies of efficacy are available [16]. Patients also are encouraged to avoid caffeine and stop smoking. Some investigators recommend a brief course of steroids, especially if a surgical treatment is being considered [76]. The surgical management of Meniere's disease is highlighted elsewhere in this issue.

Drug treatment of vestibular neuritis

Vestibular neuritis is a monophasic self-limited condition that presents with vertigo, nausea, ataxia, and nystagmus. These symptoms are brought

on by an acute imbalance in vestibular tone combined with directionally asymmetric response to head rotation. Vestibular neuritis is believed caused by a viral infection of the vestibular portion of the eighth cranial nerve. Mumps and 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 also is affected, the syndrome is termed labyrinthitis.

Evidence suggests that slightly more than half of patients who have vestibular neuritis recover completely [77]. 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 a week and it is likely that in these instances there has been only a transient and incomplete vestibular lesion. A substantial proportion of patients may take as long as 2 months to improve substantially, however. On subsequent testing, this group often demonstrates a continued unilateral paralysis of vestibular function.

Unfortunately, it is not possible to determine if patients have either a transient vestibular imbalance and will 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 blocked partially by a benzodiazepine or an agent with dopamine blocking activity, patients may not recover as rapidly as otherwise. Even bed rest may be poorly conceived, because animal studies show that immobilization delays recovery from experimental vestibular lesions [49].

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

Recently, Strupp and associates [78] studied 141 patients who had vestibular neuritis. They found that a course of methylprednisolone, starting with 100 mg per day and tapering to 10 mg per day over 3 weeks, significantly improved the results of caloric testing 1 year after vestibular neuritis. Those receiving steroids improved 60.9% compared with a 37.9% change in control subjects. Similar results are reported in a smaller group of patients [79]. Whether or not this changes the standard of care for vestibular neuritis remains to be seen.

No matter which treatment is chosen, most patients recover subjectively within 2 months. Those who do not usually have a significant fixed vestibular paresis combined with central dysfunction that slows their

compensation. For example, patients who have alcoholic cerebellar degeneration or persons of advanced age may recover 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.

Pharmacologic treatment of bilateral vestibular paresis

Bilateral vestibular paresis presents with oscillopsia, ataxia, and mild vertigo. Typical patients are those treated recently 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 one most commonly encountered). The symptoms of bilateral vestibular paresis, ataxia, and oscillopsia manifest themselves when the patients recover from their infection and try to walk.

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

Medications that reduce symptoms of other forms of otologic 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 also is prudent to avoid medications that have 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 [80]. The authors also advise these patients to avoid loud noises in particular, as they are likely more vulnerable to noise-induced hearing loss than the general population. Theoretically, in persons who have 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 slow or prevent recovery.

Pharmacologic treatment of central vertigo

Vertigo caused by CNS dysfunction, or central vertigo, is unusual. In the emergency department setting or otolaryngology clinic, a central cause of vertigo is identified in fewer than 5% of cases. Even in neurology settings, central vertigo typically accounts for only approximately 20% of diagnoses in patients complaining of vertigo [81]. Central vertigo largely is caused by vascular disorders. In the authors' experience, stroke and transient ischemic attack, usually involving the brainstem or cerebellum, account for one third

of cases. Vertigo attributed to vertebrobasilar migraine causes approximately 15% of cases. A large number of individual miscellaneous neurologic 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 otologic vertigo, in that in central vertigo, prolonged duration of symptoms are common. Although patients who have peripheral vestibular imbalance caused by a structural lesion of the vestibular nerve (eg, vestibular neuritis) typically recover within months, patients who have central vertigo, such as that caused by the 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 who have 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, 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, Isoptin SR, or Verelan), 120–240 mg, often is effective. If patients do not tolerate verapamil (constipation is the most common problem), amitriptyline can be tried. When treating migraine-associated vertigo, amitriptyline (10 mg nightly, gradually increasing to 25 or 50 mg) is favored over other antidepressant medications because of its antihistaminic and anticholinergic activity, which is helpful in suppressing vertigo, whether or not from migraine. It also is inexpensive. Unfortunately, amitriptyline use often is accompanied by the side effects of sedation and weight gain. β-Blockers form a third line of treatment. Depression and impotence are the main reasons some patients are unable to tolerate them. Several anticonvulsants, including sodium valproate, topiramate, and gabatril, also can be used for migraine prophylaxis. At this writing, topiramate (Topamax, 25 mg to 100 mg per day, in divided doses) seems the most useful, as it combines reasonable efficacy with the often useful side effect of weight loss. Sodium valproate (Depakote) has substantial side effects, including tremor and weight gain, that make it less favored.

Another common presentation of central vertigo is in patients who have a known central lesion, in whom the goal is to reduce symptoms of vertigo or ataxia. Benzodiazepines, such as lorazepam, clonazepam, and diazepam, frequently are helpful (see Table 3 for doses), but one must be wary of psychologic addiction and physical dependence [82]. Gabapentin (Neurontin, 100 twice a day to 600 three times a day) often is useful as a suppressant of spontaneous nystagmus. Meclizine, taken in a dose of 25 to 50 mg twice or three times a day, occasionally is 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 [83]. Similarly,

occasional patients who have oculomotor signs localizing to the vestibulocerebellum are helped by acetazolamide (Diamox) therapy [84].

Carbamazepine (Tegretol) or oxcarbazepine (Trileptal), in doses appropriate for neuralgia or epilepsy, can be tried in patients who have an abnormal electroencephalogram or brief paroxysmal symptoms (quick spins) that do not respond to other medications. Oxcarbazepine should be initiated at a lower dose in persons taking benzodiazepines. Gabapentin (Neurontin), a glutamate blocker, also may be used in this situation [85]. Baclofen (Lioresal) is used similarly. In this situation, epilepsy, microvascular compression, or intrinsic brainstem lesions [86] may be treated. Gabapentin also generally is useful as a suppressor of nystagmus. Physical therapy, emphasizing effective use of appliances, such as canes, walkers, and footwear, often is useful.

Pharmacologic treatment of psychogenic vertigo

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

Because of inadequacies of diagnostic methodology, it is difficult to determine the proportion of psychogenic patients in the dizzy population. Some investigators indicate that as many as 50% of all persons who have dizziness have a functional source of complaints [87]. This large percentage, however, results from an algorithm in which patients who have no findings on testing are assigned this diagnosis. This process is fraught with peril, given that it lumps together patients in whom the diagnostic process may have failed with those who have a psychologic origin of symptoms. In the first author's practice, only approximately 15% of patients are assigned the psychogenic diagnosis.

Anxiety and panic is the most common psychiatric diagnosis in persons who have dizziness. Accordingly, benzodiazepines and antidepressants are the mainstay of treatment. As considerably larger doses of benzodiazepine medications are needed for anxiety than for vestibular suppression, and because long-term treatment likely is needed, psychiatric referral can be useful in these cases.

Depression is an unusual cause of vertigo. When it is clear that depression is significant, one of the selective serotonin reuptake inhibitor family, such as sertraline (Zoloft) or paroxetine (Paxil), may be used. These drugs also are useful in obsessive-compulsive tendencies, often found in persons complaining of chronic dizziness. It generally is best to use these agents sparingly, however, as they commonly have nausea as an associated side effect, some may increase tinnitus, and all increase falling [88]. Buproprion (Wellbutrin) and venlafaxine (Effexor) also can be useful in selected patients. Vertigo resulting from somatization and malingering has no drug treatment.

Treatment of undetermined and ill-defined causes of vertigo

Whether or not in the emergency room, otolaryngology clinic, neurology clinic, or general medical setting, variants of unlocalizable diagnoses, such as unknown diagnosis, vasovagal syncope, hyperventilation syndrome, post-traumatic vertigo, and nonspecific dizziness, often are the most common single cause of dizziness reported. Between 38% and 52% of diagnoses fall in this category across many series [81,87,89,90]. The unifying feature to these diagnoses is the lack of abnormality on otologic and neurologic examination.

Treatment necessarily is empiric in vertigo of undetermined origin. In the author's practice, patients are asked to log their symptoms on a calendar. Next, for patients already taking medication, drugs are withdrawn that could affect the vestibular system symptoms recorded for 2 or more weeks. This strategy may identify persons who have ataxia caused by medication. Care must be taken in this situation not to eliminate a medication critical to the patient's well being. For example, when withdrawing an antihypertensive, such as a calcium channel blocker, that has vasodilator properties, angina may be precipitated.

Several drugs then are tried. Daily meclizine may be replaced a small dose of clonazepam or lorazepam, which helps allay patients' anxiety and also may be helpful during exacerbations caused by its vestibular suppressant effect. It generally is difficult to exclude mild Meniere's disease, and salt restriction and a diuretic, such as hydrochlorothiazide-triamterine (Dyazide), may be tried. A trial of migraine prophylaxis with sustained-release verapamil (120–240 each evening) sometimes is helpful in patients who have dizziness and headaches or in patients who have the diagnosis of vestibular Meniere's disease. Carbamazepine or oxcarbazepine is tried for the symptom of quick spins (discussed previously in the section on central vertigo). Gabapentin also is a reasonable drug to try empirically for central vertigo. Betahistine, although possibly a placebo, often is useful.

Patients who do not respond to these regimens are followed at 3- to 6-month intervals and undergo yearly audiometric screenings. Occasionally, small acoustic neuromas or early Meniere's disease evolves into an identifiable clinical presentation. It often is helpful to see patients quickly when there is an acute flare of symptoms, as in this way intermittent conditions that can have normal examinations between flare-ups, such as BPPV and Meniere's disease, sometimes can be diagnosed.

Summary

Pharmacologic treatment of dizziness is complex and generally not entirely satisfactory. Symptoms are caused most often by loss of function in the inner ear, which medications generally are unable to restore. Although there is a substantial armamentarium of drugs that can be used for symptomatic treatment, side effects usually are substantial. Clinicians 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.

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