

## Review Article

## Current Concepts

## TINNITUS

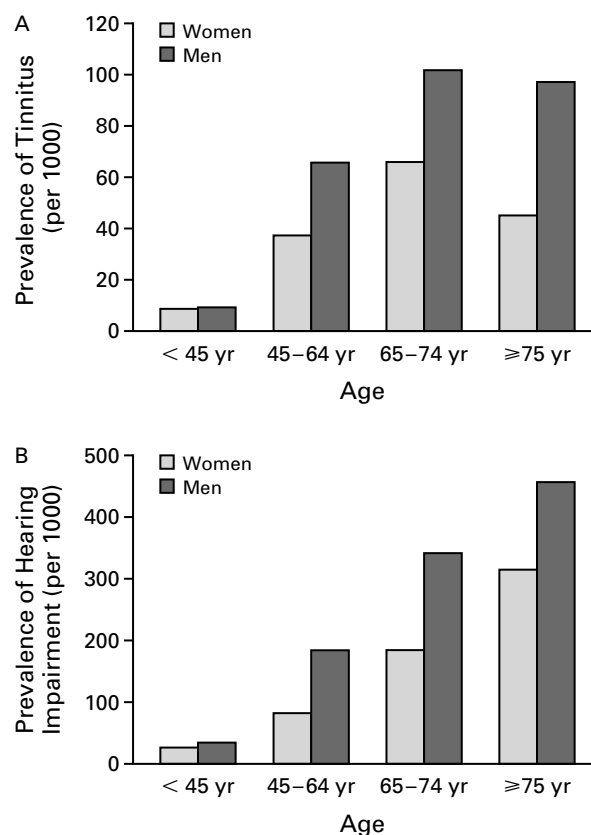
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**T**INNITUS is a common yet poorly understood disorder. Data from the National Center for Health Statistics show that tinnitus is more common in men than women and increases in prevalence with advancing age (Fig. 1). It is frequently associated with hearing impairment.<sup>1</sup> Almost 12 percent of men who are 65 to 74 years of age are affected. Whites are more frequently affected than blacks, and the prevalence in the South is almost twice that in the Northeast.<sup>1</sup> Tinnitus may be present in children, although they rarely make this symptom known.<sup>2</sup> Many patients with tinnitus believe that they have a serious medical problem. This is rarely the case. Most treatments are unsuccessful, and attempts to develop evidence-based therapies have been thwarted by a poor understanding of the pathophysiology of tinnitus. In spite of these limitations, in many cases, tinnitus can be managed satisfactorily.

The successful approach to the patient with tinnitus begins by differentiating objective from subjective tinnitus (Table 1). The failure to make this distinction may lead to diagnostic and management errors. Patients with objective tinnitus are hearing real sounds. Pulsatile sounds are reported by about 4 percent of unselected patients with tinnitus<sup>3</sup> and are usually caused by vibrations from turbulent blood flow that reach the cochlea. An astute observer will link the rhythm of the pulsations, which may be heard on auscultation, to the cardiac cycle. Some causes of pulsatile tinnitus are listed in Table 1. A history taking and physical examination, followed by neuroradiologic

imaging, may identify a treatable cause.<sup>4</sup> Clicking or low-pitched buzzing may indicate palatal myoclonus or contractions of the tensor tympani or stapedius muscle.<sup>5</sup> Occasionally, spontaneous vibrations of the outer hair cells of the cochlea may produce audible sounds known as spontaneous otoacoustic emissions. Such sounds are common but are rarely perceived.<sup>6</sup> The detection of spontaneous otoacoustic emissions requires special equipment and may not be included in a routine audiologic examination.

Subjective tinnitus, which we refer to as tinnitus, is the false perception of sound in the absence of an acoustic stimulus. Common causes are listed in Ta-



**Figure 1.** The Prevalence of Tinnitus (Panel A) and Hearing Impairment (Panel B).

Values are based on responses to the question "Do you have tinnitus or ringing in the ears [or] deafness [or] other trouble hearing?" included in the National Center for Health Statistics survey of noninstitutionalized Americans.<sup>1</sup>

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TABLE 1. CAUSES OF SUBJECTIVE AND OBJECTIVE TINNITUS.

TYPE	CAUSES
<b>Subjective tinnitus</b>	
Otologic	Noise-induced hearing loss, presbycusis, otosclerosis, otitis, impacted cerumen, sudden deafness, Meniere's disease, and other causes of hearing loss
Neurologic	Head injury, whiplash, multiple sclerosis, vestibular schwannoma (commonly called an acoustic neuroma) or other cerebellar–pontine-angle tumors
Infectious	Otitis media and sequelae of Lyme disease, meningitis, syphilis, and other infectious or inflammatory processes that affect hearing
Drug-related	Common side effect of many drugs, such as salicylates, nonsteroidal antiinflammatory drugs, aminoglycoside antibiotics, loop diuretics, and chemotherapy agents (e.g., platins and vincristine)
Other	Temporomandibular-joint dysfunction and other dental disorders
<b>Objective tinnitus</b>	
Pulsatile	Carotid stenosis, arteriovenous malformations, other vascular anomalies, vascular tumors (e.g., of the glomus jugulare), valvular heart disease (usually aortic stenosis), states of high cardiac output (anemia and drug-induced high output), and other conditions causing turbulent blood flow
Muscular or anatomical	Palatal myoclonus, spasm of stapedius or tensor tympani muscle, patulous eustachian tube
Spontaneous	Spontaneous otoacoustic emissions

ble 1. Many people have episodes of tinnitus that last seconds or minutes or are transient and associated with exposure to loud sounds or drugs such as aspirin. These people rarely seek medical attention. In a series of more than 500 patients, a mean ( $\pm$ SD) of  $5.4 \pm 8.6$  years elapsed between the onset of symptoms and a request for medical attention.<sup>3</sup> At that time, 60 percent thought they had a serious problem and 55 percent thought they might become deaf.<sup>3</sup>

In this same group, 22 percent reported that the sounds were equal in both ears, 34 percent reported having unilateral sounds, and most of the others reported a lateral dominance.<sup>3</sup> Lateralized tinnitus is common and rarely a sign of a tumor. Sounds were most commonly described as ringing (by 37.5 percent of patients), buzzing (by 11.2 percent), cricket-like (by 8.5 percent), hissing (by 7.8 percent), whistling (by 6.6 percent), and humming (by 5.3 percent).<sup>3</sup> Most of these patients reported a high pitch, and 34 percent said that their tinnitus rated 8 or higher on a 10-point loudness scale, on which 10 was very loud.<sup>3</sup> Reliable, objective measures of the loudness and pitch of tinnitus are difficult to obtain.<sup>7</sup> In spite of patients' perception that the sounds were loud, hearing tests showed that the sounds occurred at intensities that were just barely greater than the softest sound audible at that frequency.<sup>8</sup> Pitch-matching studies generally show that the pitch of tinnitus corresponds to the frequency at which hearing loss becomes clinically significant (typically above 3000 Hz).<sup>8</sup>

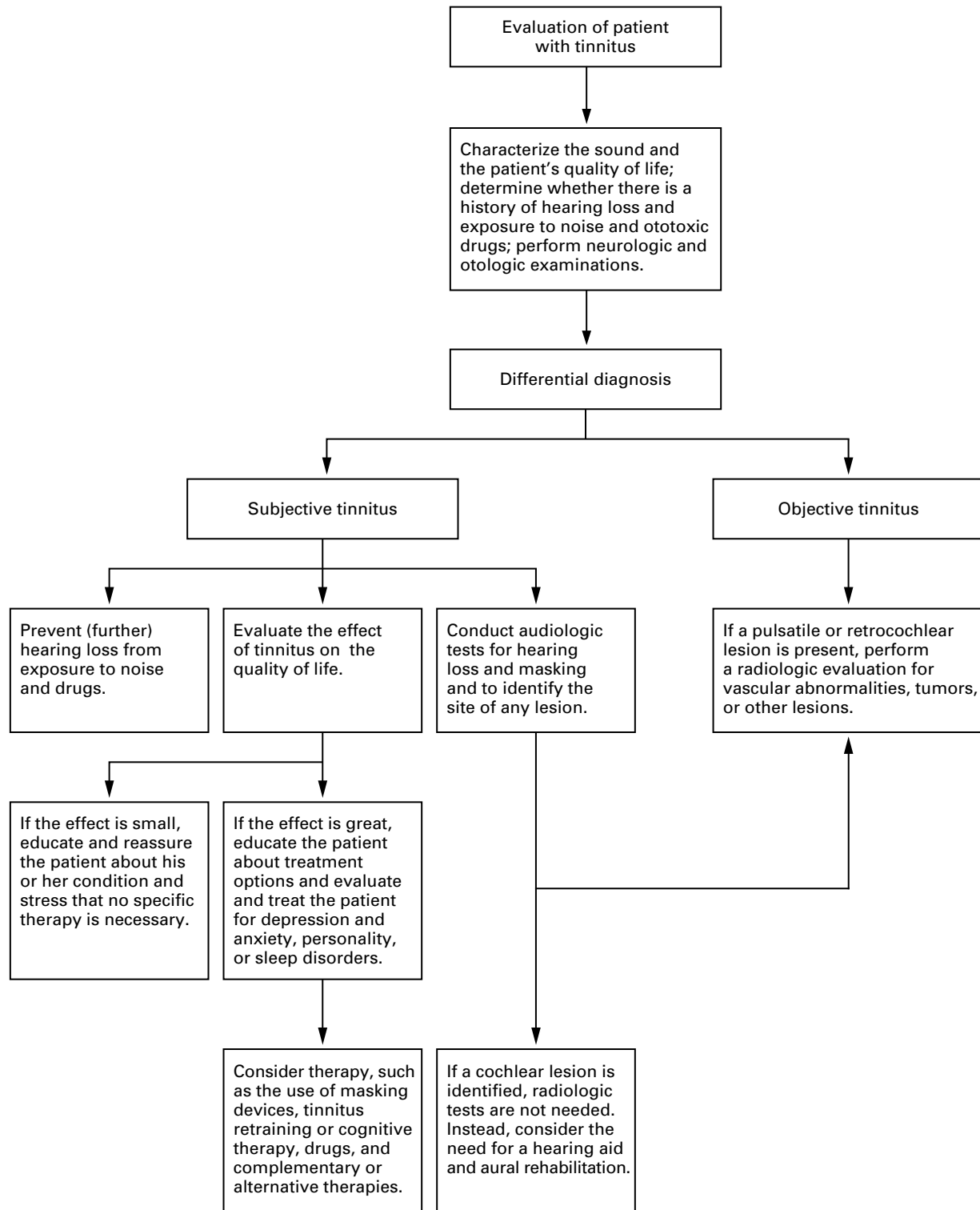
#### CLINICAL APPROACH

The use of a systematic approach to patients, depicted in Figure 2, should help clinicians avoid errors

resulting from a failure to separate objective from subjective tinnitus, identify treatable disorders (such as those listed in Table 1), protect hearing, and treat associated problems such as depression, anxiety, and insomnia. Successful management and a high level of satisfaction on the part of patients are likely to follow a thorough evaluation in which sufficient time is allowed to develop a strong therapeutic relationship.

Since tinnitus is usually a subjective phenomenon, the patient's history and findings on physical examination are particularly important to differentiate objective from subjective tinnitus. A clear description of the sound the patient hears is critical and can be elicited by having the patient answer the following questions: Is the sound constant or episodic, unilateral or bilateral? Was the onset sudden or gradual? How long has it been present? What are the pitch and loudness of the sound? Is there associated hearing loss, vertigo, or pain? Is there evidence of other conditions (listed in Table 1) that are associated with tinnitus? (There is a strong correlation between tinnitus and temporomandibular-joint and other craniomandibular disorders.<sup>9-11</sup>) What else affects tinnitus — background noise, alcohol, stress, or sleeplessness? Is there a history of exposure to loud noise, ear infections, otologic surgery, head injuries, and use of ototoxic drugs? Are there any side effects of tinnitus? How does tinnitus affect daily life and the ability to function?

The physical examination should focus on the head and neck and include a careful inspection of the oral cavity, outer ear, tympanic membranes, cranial nerves (particularly the fifth, seventh, and eighth), and temporomandibular joint and auscultation of the heart, carotid arteries, and periaural region. Clinicians should



**Figure 2.** An Algorithm for the Evaluation of Patients with Tinnitus.

This approach is based on differentiating objective from subjective tinnitus; planned, focused laboratory testing, including audiometry to differentiate cochlear from retrocochlear lesions; education to preserve patients' hearing; and an assessment of the effect of tinnitus on the quality of daily life as a guide to further interventions. Patients with retrocochlear lesions or objective tinnitus may require referral to a specialist, additional audiometric testing, or both.

attempt to associate periodic sounds with the patient's pulse or palatal movements. After specific questioning and manipulations, up to 75 percent of patients with tinnitus indicate that various maneuvers, such as clenching their jaw, cranial pressure, and eye movements affect the loudness of their tinnitus.<sup>12-14</sup>

As shown in Table 1, tinnitus is frequently a symptom of an associated disease process. Although treatment of the disease may not relieve tinnitus, an accurate diagnosis and treatment are important to prevent additional disability. Common conditions associated with subjective tinnitus that may require treatment include impacted cerumen, otitis media and other infectious or inflammatory conditions that affect hearing, Meniere's disease (associated with low-pitched tinnitus), and otosclerosis. Drug-induced tinnitus may disappear after the offending agent is discontinued.

As with other medical conditions, the laboratory tests ordered depend on the results of an analysis of the patient's history and the findings on physical examination. Patients with pulsatile tinnitus should be evaluated for disorders that cause a high cardiac output (e.g., anemia and hyperthyroidism), valvular heart disease (especially disease of the aortic valve), and occlusive cerebrovascular disease (particularly among patients with risk factors for atherosclerosis).

A comprehensive audiologic evaluation is essential. To quantify any hearing loss and identify any treatable conductive component of hearing loss, the test battery should include pure-tone thresholds (air and bone conduction), measures of acoustic impedance (tympanometry, acoustic-reflex thresholds), speech audiometry, and tests for maskability. Unilateral high-frequency hearing loss combined with poor speech discrimination suggests the possibility of a tumor, usually a vestibular schwannoma (commonly called an acoustic neuroma) or a meningioma. Patients with these findings must undergo additional tests to locate the lesion, such as tests of auditory brain-stem evoked responses, tone decay, reflex decay, and measures of vestibular function. Bilateral schwannomas may occur in patients with neurofibromatosis type 2. When indicated by audiometric tests, magnetic resonance imaging with gadolinium enhancement should be obtained.<sup>4</sup> Patients with audiologic evidence of cochlear damage rarely require radiologic evaluations, since the results seldom affect the approach to management.

The exact prevalence of hearing loss among patients with tinnitus is high but difficult to determine. Among patients with normal hearing, typically defined as audiometric (or hearing-level) thresholds that are 20 to 25 dB or less at frequencies ranging from 250 to 8000 Hz, it is likely that many once had better hearing or have impairments at frequencies higher than 8000 Hz.

Further hearing loss must be avoided. Since expo-

sure to noise is a common cause of hearing loss, all sources of noise exposure should be reviewed. Although regulations of the Occupational Safety and Health Administration limit the level of noise exposure in most workplaces, regulations do not apply to all work areas, and additional ear protection may be advisable. Personal listening devices, appliances, and power tools are sources of noise that could cause or exacerbate hearing loss. A wide variety of hearing protectors is available. The choice should be based on the intensity of ambient sounds and occupational or other demands. For example, farmers (whose workplaces are not covered by Occupational Safety and Health Administration regulations) may require earmuff-like devices when they operate machinery, whereas orchestra musicians should be provided with custom-molded devices that fit into the external auditory meatus and are designed to attenuate sounds evenly across a broad range of frequencies. Patients with tinnitus should be instructed to inquire about all otologic side effects of any new drugs that are prescribed.

It is important to evaluate the effect of tinnitus on daily life. Surprisingly, the perceived severity of tinnitus is unrelated to measurements of its loudness or pitch.<sup>8</sup> Thus, other methods are required to assess the effect of tinnitus, and questionnaires have been developed for this purpose.<sup>15</sup> The effect of tinnitus is greatest in patients who report physical immobility, sleeplessness, and pain and among those who are depressed or irritable, who are socially isolated, or who have psychiatric symptoms.<sup>16</sup> Treating these problems may reduce the effect of tinnitus, even though the percept is unchanged.<sup>16,17</sup>

## PATHOPHYSIOLOGY

The high incidence of cochlear damage led many to suggest that tinnitus arises in this organ.<sup>18,19</sup> However, an origin in the central nervous system is implied by the observation of tinnitus in patients with complete transections of the auditory nerve. Functional-imaging studies of three disparate groups of patients support the central-origin hypothesis, as illustrated in Figure 3.<sup>12,20,21</sup>

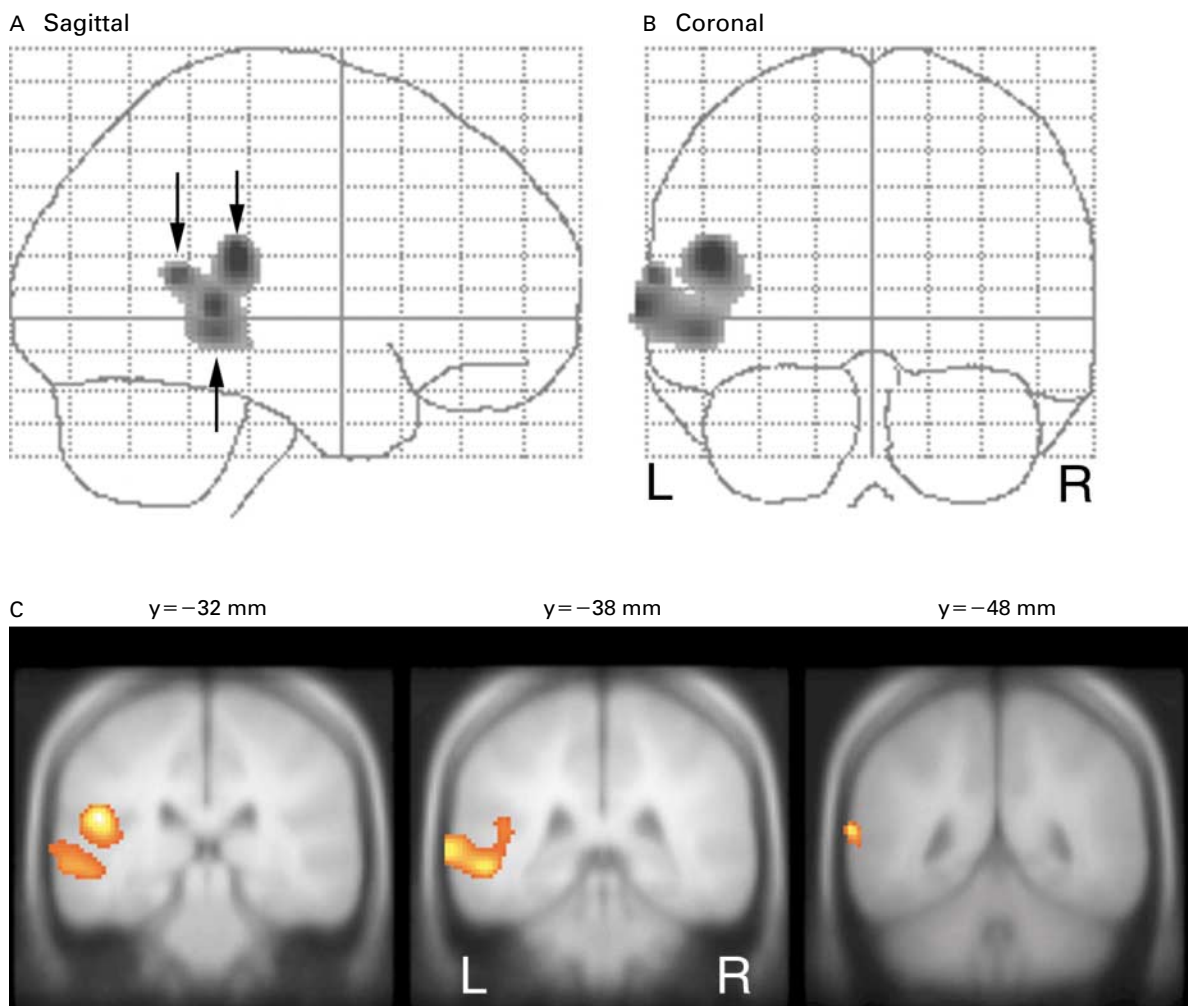
Hearing loss leads to a reorganization of the pathways in the central auditory system.<sup>12,20,22,23</sup> These changes may occur rapidly<sup>24</sup> and lead to abnormal interactions between auditory and other central pathways.<sup>20</sup> Analogous changes in the somatosensory system linked to phantom pain<sup>25</sup> led us to suggest that there are similarities between neuropathic pain and tinnitus.<sup>12</sup> In patients with gaze-evoked tinnitus, lateral eye movements fail to produce the inhibition of the auditory cortex observed in controls.<sup>20</sup> The absence of this phenomenon, called cross-modal inhibition, may contribute to the false perception of sounds.

Levine hypothesized that a reduction in auditory-

nerve input leads to disinhibition of the dorsal cochlear nucleus and an increase in spontaneous activity in the central auditory system, which is experienced as tinnitus.<sup>26</sup> This mechanism could explain the temporary ringing sensation that may follow exposure to noise,<sup>27</sup> the effects of some drugs such as furosemide, and spontaneous tinnitus in people with normal hearing who are placed in total silence.<sup>28</sup> Other drugs, such as aspirin, increase the spontaneous firing rate of the auditory nerve.<sup>29</sup> The complexity of the changes in the nervous system associated with tinnitus may explain why it is so resistant to treatment.

### THERAPY

Many drugs produce tinnitus (a list is available at <http://www.hearusa.com>), but despite numerous trials, no drugs have been approved by the Food and Drug Administration for the treatment of tinnitus. Many trials have been criticized because of deficiencies in design, including the lack of appropriate controls, inappropriate randomization procedures, and poor choices of end points. In his review of 69 randomized clinical trials, Dobie concluded that “no treatment can yet be considered well established in terms of providing replicable long-term reduction of



**Figure 3.** Neural Sites That Mediate Tinnitus.

Positron-emission tomography shows foci of neural activity in auditory cortical sites in the temporal lobe from a group of patients with tinnitus perceived in the right ear. The unilaterality of the sites suggests a central origin of tinnitus, since real sounds presented to the right ear activated bilateral auditory cortical sites. In Panels A and B, the sites of activation are projected onto coronal and sagittal planes. The arrows on the sagittal projection in Panel A identify the locations of the coronal planes shown in Panel C. In the coronal planes, the colored foci of activation are superimposed on spatially averaged magnetic resonance images. The y values represent the distance of each site from the plane of the anterior commissure. Data are from Lockwood et al.<sup>12</sup> Additional methodologic details have been published elsewhere.<sup>20</sup>

tinnitus impact, in excess of placebo effects.<sup>29,30</sup> In randomized clinical trials, placebo effects are strong and are attributed in part to the attention these patients receive. Further pathophysiologically oriented research may yield criteria that identify subgroups of patients who are responsive to specific therapies.

Reports that lidocaine abolished tinnitus raised hopes that other antiarrhythmic drugs would be effective.<sup>30</sup> Lidocaine must be given intravenously in high doses, has a brief duration of action, exacerbates tinnitus in some subjects, and is associated with marked side effects.<sup>31</sup> In an analysis of seven randomized clinical trials of tocainide, those involving less than 1200 mg per day showed no benefit, while trials employing higher doses were either flawed or showed no benefit.<sup>30,32</sup> Randomized clinical trials of flecainide and mexiletine were marked by adverse drug effects in up to 70 percent of the participants or dropout rates of about 50 percent.<sup>30</sup>

Benzodiazepines have not been effective in controlling tinnitus or have been used in trials whose results are uninterpretable.<sup>33</sup> In a randomized clinical trial of 40 subjects, tinnitus improved in 76 percent of those who received alprazolam, as compared with 5 percent of those who received placebo.<sup>34</sup> However, the study was criticized because of an absence of a crossover design and possible unblinding attributable to sedation.<sup>35</sup> The use of benzodiazepines should be tempered by reports that tinnitus may recur after the treatment ends and cause a greater level of distress.<sup>36</sup> Four randomized clinical trials of carbamazepine and trials of other anticonvulsants failed to show any benefit.<sup>30,32</sup>

There are many reasons for testing antidepressants, particularly the tricyclics, as a treatment for tinnitus. Depression is relatively common in patients with tinnitus, and tinnitus may be similar to pain syndromes<sup>12</sup> that are often treated successfully with tricyclic antidepressants. The most definitive double-blind randomized clinical trial of nortriptyline included 92 patients with disabling tinnitus, 38 of whom met standard criteria for depression.<sup>37</sup> During drug treatment, 43 percent said the severity of their tinnitus decreased, as compared with 30 percent among those receiving placebo (P not significant). Nevertheless, 67 percent of the patients in the nortriptyline group (dose, 50 to 150 mg per day) indicated that the drug helped them in some way, as compared with 40 percent of those randomly assigned to receive placebo (P=0.008). Factors favoring improvement included the presence of depression, the presence of insomnia, female sex, and the absence of musculoskeletal symptoms.

Many patients try complementary or alternative medical therapies: extracts of *Ginkgo biloba* and acupuncture are among the most popular. A recent study reported no benefit in almost 500 pairs of subjects who were randomly assigned to receive either *G. biloba*

or placebo.<sup>38</sup> An earlier analysis of one unpublished and four published randomized clinical trials of *G. biloba* concluded that the results of trials were favorable, but that a firm conclusion about efficacy was not possible.<sup>39</sup> Differences in the products and end points may explain these variable results. An analysis of six randomized clinical trials of acupuncture for tinnitus failed to demonstrate any efficacy.<sup>40</sup>

Tinnitus retraining therapy has gained popularity, with practitioners reporting improvement in 75 percent of their patients.<sup>41</sup> The rationale for tinnitus retraining therapy is based on a physiological model that links negative emotional associations with tinnitus-related neural activity.<sup>42</sup> Tinnitus retraining therapy centers use a team of physicians, audiologists, and psychologists in a program that combines counseling and low-level broad-band noise generators. This therapy usually takes 1.5 years to complete. The goal is to habituate the patient to the sounds of tinnitus rather than to abolish the sounds. Critiques of tinnitus retraining therapy cite deficiencies related to the choice of control groups, psychologically oriented outcome measures, subject-selection processes, and an inability to separate the effects of the noise generators from those of other components of the treatment.<sup>43,44</sup> Other forms of psychologically based therapy, including hypnosis, relaxation therapy, and biofeedback, have yielded mixed results that, in general, fail to support their use.<sup>30</sup>

Masking devices cover up the unwanted sounds and provide relief for some patients who have a response to masking during the audiologic examination.<sup>45</sup> Variations in the characteristics of tinnitus are not reliable indicators of the likelihood of the success of masking devices.<sup>46</sup> Hearing aids and cochlear implants may also provide relief, but they are usually prescribed to treat hearing loss and not tinnitus.<sup>45,47</sup>

Although there are reports of improvement in tinnitus after microvascular decompression of the auditory nerve,<sup>48,49</sup> the use of surgical treatments, including nerve transection, remains controversial.<sup>48</sup> Self-help groups, affiliated with organizations such as the American Tinnitus Association (<http://www.ata.org>), provide useful information and support for some patients.

There are thousands of Web sites with information on tinnitus, and many patients arrive at the office visit seeking a specific treatment. The pressure to do something may be intense. Clinicians must deal with these expectations without using prescriptions to placate patients. Since no treatment is uniformly effective, a strong doctor-patient relationship is vital. Education and reassurance are powerful tools. Since issues related to the quality of life may be central yet difficult to define or measure with precision, empirical trials of antidepressants, anxiolytics, or complementary or alternative medical therapies may be undertaken after a dis-

cussion of the risks and benefits and the identification of a predefined objective. Many patients can be treated satisfactorily using this approach.

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