

Letters to the Editor

RE: MYTHS IN NEUROTOLOGY, REVISITED: SMOKE AND MIRRORS IN TINNITUS THERAPY

To the Editor: We read with dismay and alarm Dr. Matthew L. Howard's editorial in the November 2001 issue (*Otol Neurotol* 2001; 22:711-4). We strongly disagree with his conclusions that "No reliable, acceptable studies (meaning randomized, double-blind, cross-over studies with statistically significant results) seem to favor any of these therapeutic modalities..." (p. 712). We maintain that, however well intentioned, Dr. Howard is quite simply incorrect in his findings. We base our disagreement on three main points: 1) Dr. Howard's principle that a treatment is useless unless it has been proven in clinical trials is in error; 2) He has not shown diligence in reviewing the many clinical trials that have shown positive therapeutic results for many differing therapies for tinnitus; and 3) His seeming unwillingness to share information about all therapies for tinnitus, regardless of the evidence, does a disservice to those patients suffering from tinnitus and to the medical community as a whole, because patients deserve to know all available information.

Whether health professionals want to realize this or not, anecdote is the cornerstone of most "conventional" medical wisdom. Surprisingly, few of our currently accepted therapies have undergone rigorous randomized clinical trials. There are many commonly accepted medical practices for which double-blind, placebo-controlled studies have either not been conducted at all or show contradictory results. For instance, what double-blind, placebo-controlled study shows that needle aspiration of a peritonsillar abscess is more effective than incision and drainage? What study shows that intranasal saline irrigation is more effective than good household humidity? These studies do not exist, yet these practices are very common. Even more fundamental is the misconception that pharmacological treatment of disease is based on "evidence" from double-blind, placebo-controlled trials. A particular drug may be tested alone and approved for a given condition in an evidence-based study, but the moment that drug is mixed with one or more other drugs outside of the test conditions, the original "evidence" is no longer applicable—the patient is now an anecdote (or

guinea pig, if you will). Just as we have millions of anecdotes related to "alternative" therapies, so do we have millions of anecdotes related to poly-pharmacy. In fact, the "appropriate" prescribing by physicians of multiple pharmaceuticals to treat illness is one of the leading causes of death in this country. It is obvious that this is the result of patients taking untested combinations of drugs that in some cases cause death. Thus, it can be said that the majority of the modern day medical practice is based on anecdotal situations; it is not evidence based. A likely scenario for a physician in modern day medicine is, "I tried something; it worked, so I did it on 20 more people and now we have a new treatment."

Dr. Stephen M. Nagler correctly pointed out in his response (*Otol Neurotol* 2002;23:239-242) "We must teach (our patients) that just because treatments such as tinnitus masking, cognitive behavioral therapy, and Tinnitus Retraining Therapy cannot by their nature be evaluated by double-blind, randomized, prospective studies as can a pill—does not mean that they are ineffective" (p. 239).

Clinical studies of the kind Dr. Howard requires can be very contradictory. For many years we have advised the use of steroids as well as antivirals for the treatment of sudden sensorineural hearing loss (SSHL). This is based upon several excellent studies that have suggested that SSHL may have a viral etiology (1,2,3). Next, a formal study was conducted showing that antivirals may improve the results of SSHL (4). Those physicians interested in going that extra mile for the patients likely adopted the practice of using antivirals years before this study validated our suspicions. Still there were likely many physicians who would not dream of using their common sense, knowledge, and experience to treat patients with SSHL. These are the very protective physicians who need "solid" proof before adding a therapeutic regimen. The Stokroos study added that proof, and now we can all feel vindicated, as there is validity to what we are doing (4). Then 2002 arrived, and another excellent randomized, double-blind, placebo-controlled prospective multicenter clinical trial found that using antivirals for SSHL provided no more benefit than steroid alone (5). There was a period of some 15 years that it was thought that margarines were much better for us than butter, however science reared its ugly head again noting that the trans-fats in margarines are far more damaging than the saturated fat found in butter. Americans responded by significantly reducing their intake of margarine and butter sales surged. Since, 1981 I have advised that my patients take a supplement of 400 mcg of folic

¹The author's unscientific, anecdotal observation is that 85% of the peri-tonsillar abscesses for which aspiration is recommended are in fact not abscesses at all. This may well be another example of unproven treatment in common use, just like Ginkgo biloba.

acid to lower homocysteine levels and reduce the risk of coronary artery disease (CAD). Four hundred mcg of folic acid was at least eight times the recommended dietary allowance. Even in the early 1980's there were many animal and human studies to show the benefits. It wasn't until Rimm et al in 1998 completed a 14-year study on 80,082 women showing that 400 mcg plus additional B6 significantly reduced the risk of CAD that the recommended dietary allowance was increased from 50mcg/d to 400 mcg (6). What we must realize is that the only thing constant is change. Many more examples exist to exemplify the inexactness in science, and we must, therefore, keep a very open mind. This in no way negates the importance of healthy skepticism, but a closed mind impedes growth of knowledge and our ability to care for our patients.

Dr. Howard is accurate when he states that there is no cure for tinnitus. However, he ignores much, if not most, of the literature when he states there are no clinical trials supporting positive therapies for tinnitus. It is obvious from the literature there are many treatment modalities that can be effective in reducing tinnitus symptoms for many patients. He overlooked several major studies on the effects of Ginkgo biloba on tinnitus. One double-blind, placebo-controlled study, conducted in Paris in 1986 by ten ENT specialists showed "...the Ginkgo biloba extract treatment improved the condition of all the tinnitus patients, irrespective of the prognostic factor" (7). Another investigator in Germany combined the results of clinical trials investigating the effects of tinnitus treatment with Ginkgo biloba extract Egb 761. "The results of eight controlled studies on tinnitus due to cerebrovascular insufficiency or labyrinthine disorders of varying genesis show a statistically significant superiority of treatment with the Ginkgo biloba extract Egb 761 as compared with placebo" (8). Still, another study conducted in Czechoslovakia evaluated the outcome of using a combination of Egb 761 and soft laser therapy. "An improvement in tinnitus was audiometrically confirmed in 50.8% of patients: 10 dB in 18; 20 dB in 22; 30 dB in 10; 40 dB in 6; and 50 dB in 5" (9).

The German Commission E is considered the world's foremost authority on the use of herbal medicinals. It was formed as a division of the German Federal Health Administration in 1986 and issued its, by now famous, Commission E Monographs in English in 1998. These monographs are the regulatory "Bible" for herbal medicinals in Germany. They detail the properties, side effects, therapeutic benefits, and recommended dosages of the many herbs it has studied. The commission evaluated 38 double-blind, placebo-controlled trials of Ginkgo biloba before determining its effectiveness for various medical conditions and now recommends pharmaceutically pure Ginkgo biloba for the treatment of tinnitus in the dosage of 480 mg per day (10).

Dr. Howard cites one study on Ginkgo biloba for tinnitus as proof that it is ineffective (11). The authors of the so-called Birmingham study used an extract that was recommended by the German Commission E, however

they ignored the Commission E recommendation on dosage. "The extract and dose of Ginkgo biloba were chosen on the basis of the results of previous trials in which this dose (150 mg/day) of this extract had been reported to be effective in treating cerebral insufficiency". The study was unable to even reproduce these previous results, let alone reduce tinnitus symptoms. This indicates a serious flaw in the methodology. To begin with, the study used less than 1/3 the dosage recommended by the German Commission E. Secondly, they initiated and maintained contact with the subjects of the trial using postal questionnaires exclusively. This method does not provide the level of patient support and does not require the veracity of patients that a more controlled study would provide. The fact that the dosage was far less than in other positive studies, coupled with the remote control methodology, leaves a large margin of uncertainty as to whether the findings have any validity.

The lead author of this letter has a database of over 5,000 tinnitus patients at the Henry Ford Health System. In his experience, high dosage of pharmaceutically pure Ginkgo biloba extract—240 mg taken twice daily—is an effective treatment in a significant number of his patients. Clearly, it does not alleviate the tinnitus in everyone, but it is certainly worth considering this for a 3-4 month trial, if not otherwise contraindicated.

There are many other treatments that exist that may improve the symptom of tinnitus in some patients. An example includes zinc (12,13). There is a high concentration of zinc in the inner ear, and deficiencies have been shown to cause tinnitus. Elderly tinnitus patients are more prone to be zinc deficient, and it has been shown that 1/3 of elderly people with tinnitus have had positive results using this supplement (14). Calcium, magnesium (15,16), and the B-complex vitamins (17,18) have also improved tinnitus for many patients.

Many other treatments have also shown promise in reducing the symptom of tinnitus. A German study of the use of neurofeedback for tinnitus was conducted in 2001. Neurofeedback is a form of biofeedback linked to aspects of the electrical activity of the brain such as frequency, location, or amplitude of specific EEG activity. It has been successfully used in patients with closed head injury, hyperactivity disorder, and epilepsy. The results showed "After 15 sessions of training, 24 patients with a duration of their tinnitus for an average of 1 year showed significant increase of alpha-amplitudes while 16 patients with duration of their tinnitus on an average of 7 years showed a decrease of beta-amplitudes without any change in alpha-activity. After the training all patients had a significant reduction of the score in the tinnitus questionnaire of Gobel and Hiller. In a control group of 15 persons without tinnitus we didn't see any changes of alpha or beta-amplitudes during the same training" (19).

A Swedish study on acupuncture for tinnitus conducted in 1998 concluded that "acupuncture was found to yield immediate relief, both in terms of loudness and disturbance of the tinnitus, and significant improvement

in Quality of Life for three months after the conclusion of treatment" (20).

There are many physicians and scientists working diligently to find an allopathic/osteopathic medical solution for tinnitus. The lead author has been testing patients with an IRB approved protocol using a micro catheter inserted directly into the ear and anchored to the round window. He has been using a combination of medications that are delivered through the micro catheter to perfuse the round window. It is the hope of this study to find some medical strategy that may help mitigate tinnitus symptoms (21).

The American Tinnitus Association has made a public plea to physicians who treat tinnitus patients. "We have a message to deliver to you. It is from thousands of tinnitus patients. . . . 'Do NOT tell me to go home and learn to live with it.' When people with tinnitus ask for help, please tell them about coping strategies like bio-feedback, foods like those with caffeine that can aggravate the condition, drugs like Xanax, herbs like *Ginkgo biloba* or other nutritional supplements that may help the patient with this often disabling symptom. Tell them about cognitive therapy, tinnitus retraining therapy, and masking that help many people with tinnitus live better lives. To tell your patient, 'learn to live with it,' is not only inhumane and inaccurate, but it is truly a disservice to the patients. It is much more appropriate to say: 'There are many treatment options available. While there are no treatments that work for all patients, through trial and error, most patients are able to achieve a degree of relief from their suffering; some are even able to achieve a great deal of relief'" (22).

We truly believe that physicians were placed in their position to not only treat and teach their patients, but they were also given the awesome responsibility to care for their patients. We will never have all the answers, but when we find treatments that help reduce suffering, don't we owe it to our progeny and our patients to provide that care? When we get sick, we want an informed doctor that reads the literature that educates us about the disease and provides a rationale for treatment. If there is no treatment, then we expect to be made aware of that, and we hope that the doctor may have some other option for us to consider. Most of all, we want that doctor to care for us the way we would care about a family member. If we all did this, the world would be a healthier, happier, and friendlier place.

**Michael D. Seidman, M.D., F.A.C.S.,
and
Barry Keate**

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AUTHOR'S REPLY

To the Editor: I find areas of agreement with the letter written by Dr. Seidman and Mr. Keate. Science is hard, and with many examples, some of which they cite, of multiple studies providing contradictory results so that many years may pass before the benefit, or lack of benefit, from any therapy can be determined with confidence. However, I do not agree with the thrust of their response and believe they have not correctly interpreted the editorial, which is, after all, an expression of opinion.

I see no reason to change my opinion that patients should not be encouraged to pay for treatments without proven value, that anecdote and clinical experience may be used to guide scientific study but are no substitute for it, and that, while a closed mind is harmful, a mind so open that all critical faculties fall out of it is more harm-

ful still. As I pointed out in the editorial, Dr. Nagler's later argument that some therapies "by their nature" cannot be evaluated by double-blind methods amounts to an evasion of responsibility. Further, perhaps the journal of *Otolaryngology-Head & Neck Surgery* will be interested in a commentary on aspiration of peri-tonsillar (1) abscess, but it is out of place here. Endless recitation of unproven treatments in use does nothing to support the argument that unproven treatments are safe, should be in use, or efficacious.

The most important point on which I disagree with the authors is this: They conclude incorrectly that the studies they cite support their thesis. Space and time limits prevent a full commentary on the articles cited. However, the Paperchase abstract of the Holstein article describes a trial of 1 to 3 months and notes better results with those who had tinnitus of recent onset (1). As much tinnitus is self-limited, resolving spontaneously, such a brief trial in a limited number of cases does not answer the objections raised in the editorial. My lack of German prevents me from studying the original. The Hahn article is not a report of a double-blind, randomized study and involves two treatments. Was the benefit obtained from Gingko, the laser, the combination, or neither? The Seidman-Keate letter confirms in my mind the contention I raised in the editorial that the Blondlot or N-ray factor is present in many published studies, including here the studies quoted by Seidman and Keate. The Medline abstract of the Meyer article indicates that it may be a useful addition to the literature, and I certainly did overlook it (2). I am awaiting a copy of the original to study. Although the authors say that "several major studies" were overlooked, they have therefore identified only one that *may* be of value. If it is of value, it must be confirmed by further study. If it is of value, the authors have confirmed my editorial's conclusion that read, "Innovation requires experimentation. Without experimentation, tinnitus will never be treatable. But experimentation must be done in accordance with time-tested principles that will allow confidence in the efficacy of the proposed treatment" (p. 713) (*Otol Neurotol* 2001; 22:711-4). To

date, treatment with Gingko cannot be offered with confidence.

Finally, the authors offer us the oft-repeated exhortation of the American Tinnitus Association that physicians should not tell their patients to "go home and learn to live with it." Instead, we are told, patients should be informed about the "many treatment options available." I urge those who believe this is a rational approach to therapy to consider that for roughly 550 years, literally dozens of treatments for syphilis were in vogue. The 1899 *Merck Manual of Diagnosis and Therapy* lists 80 possible therapeutic agents for syphilis and its manifestations (3). That list does not even include the many folk remedies that were in use: herbs, virgin's urine, religious relics, etc. Now, all those agents have been replaced with the one that works—penicillin (or an alternative for the penicillin-sensitive). In my opinion, there are not "many treatment options available" but multitudes of unproven treatments providing false hope to suffering patients to the detriment of their pocketbooks. A treatment or group of treatments comparable to penicillin for syphilis does not exist, thus explaining the "many treatment option available." Offering non-efficacious "treatment options" to my mind does *not* demonstrate compassion, caring, or good medical practice. Those who disagree are free to do so.

My editorial pleads for a rational approach to treatment, offering only those therapies that are supported by scientific study. Seidman and Keate have not offered good evidence that Gingko meets that criterion.

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