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Evaluating Treatments for Ménière's Disease: Controversies Surrounding Placebo Control

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Abstract

Although double-blind experimental designs are considered the gold standard for documenting treatment effectiveness, many treatments for Ménière's disease have not been evaluated using this methodology. Particularly with a disease characterized by exacerbation and remission, carefully controlled, long-term studies are required. The nature of the placebo effect is described in this article, and the concept of debonafide effect introduced. Ideally, patients should be given treatments supported by evidence-based medicine that have the lowest possible risk of side effects. However, risk minimization may dictate using treatments that have not been proven effective and may evoke debonafide effects.

Key Words: Debonafide effect, Ménière's disease, placebo effect

Sumario

A pesar de que los diseños experimentales a doble ciego se consideran el estándar de oro para documentar la efectividad de un tratamiento, muchas terapias para la enfermedad de Ménière no han sido evaluadas utilizando esta metodología. Con una enfermedad caracterizada particularmente por exacerbaciones y remisiones se requieren estudios cuidadosamente controlados y a largo plazo. Se describe en este artículo la naturaleza del efecto placebo y se introduce el concepto del efecto debonafide. Idealmente, los pacientes deberían recibir tratamientos apoyados por una medicina basada en evidencia que tengan el más bajo riesgo posible de efectos secundarios. Sin embargo, la minimización del riesgo puede dictar la utilización de tratamientos que no han demostrado ser efectivos y que pueden provocar efectos debonafide.

Palabras Clave: Efecto defonafide, enfermedad de Ménière, efecto placebo

Diseases as devastating as Ménière's compel experimentation with new and innovative treatments. Evaluating treatment effectiveness is complicated by the exacerbating/remitting cyclic nature of Ménière's disease. In order to be a definitive study, long-term evaluations with careful, contemporaneously recorded symptom diaries are required. Treatment effectiveness must be contrasted to placebo control, to traditional treatments, and/or to no-treatment (Gates, 2004). As in many areas of medicine, not all Ménière's disease studies meet these rigorous conditions. Endolymphatic shunt surgery, once considered the treatment of choice when traditional medical treatment was not adequate, and still advocated by some (e.g., Huang, 2002), was found to be no more effective thant simple mastoidectomy (Bretlau et al, 1984, 1989). This "sham surgery" study highlighted the importance of proper experimental design in evaluating the effectiveness of treatments for Ménière's disease, but as will be discussed at the conclusion of this article, the alternatives may have higher risks, with no better clinical

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outcome.

This article will review the placebo effect and the controversies surrounding use of the placebo control in evaluating treatment effectiveness. Evidence for a placebo or debonafide effect in Ménière's disease treatment, and discussion of its appropriate exploitation, follow.

THE PLACEBO EFFECT AND EVALUATION OF TREATMENT OUTCOMES

Type I research is, by definition, experimentation in which subjects are randomly assigned to one or more treatment group(s) or to a placebo control group. Time-series designs, where subjects serve as their own controls, alternating between receiving no treatment and treatment, can also be type I research studies, if adequate controls are in place. Double blinding should be part of the experimental control: neither the experimenter nor the patient would be aware of the group assignment (Johnson and Danhauer, 2002). If the control treatment has the potential to worsen the disease, or patient report of symptoms, it is particularly important to include a no-treatment group. Sherman and Massoud (2001) provided an illustration of this concept in their study of particle repositioning maneuvers for patients with benign paroxysmal positional vertigo. At the two-week follow-up, the Dix-Hallpike maneuver was negative for 60% of those receiving no treatment, 83% of those receiving treatment, and 15% of those who received a sham maneuver, the repositioning maneuver for the opposite ear, which likely worsened the condition.

The treatment effect is generally considered to be the difference between the treatment and control group (or control phase) performance. This "subtractive" model posits that the true treatment effect is the benefit experienced by those receiving the study treatment minus the benefit received by those in the placebo control group. This assumes that the treatment and placebo effects are distinctly different, nonoverlapping, discrete effects. While the simplicity of this assumption is compelling, it may not be accurate (Kiene, 1996a). In part, it depends upon the definition of "placebo effect."

The word "placebo" is derived from the Latin "I shall please," with the dictionary defining placebo as an inert substance given to satisfy the patient. The power of the placebo effect has been recognized since 1955 when Beecher reported that 35% of patients, with a wide variety of disorders, could be effectively treated with placebo alone (Kienle and Kiene, 1996).

The power of suggestion inherent in the placebo holds for side effects as well. Moertel et al (1976) reported that 41% of those taking a placebo reported a side effect of one type or another, with those who responded to placebo providing more reports of adverse effects. Kienle and Kiene (1996) point out that what are considered side effects (headache, nausea, etc.) may be everyday experiences, reported as required by the study design. Therefore, appearance of side effects within placebo-controlled trials may or may not suggest psychological mediation.

However, the "nocebo" effect is well established. Expectation of negative outcome will lead to negative outcome. For example, 80% of hospital patients who were told sugar water was an emetic vomited (Hahn, 1997). The placebo and nocebo responses suggest that expectation of an effect is all that is needed for some patients to experience the effect.

The attention and care associated with the office visit, the practitioner's professional assurance, and the resulting stress reduction, along with the somatic effects of the mind-body connection, may be the root of the placebo effect. However, there are other potential explanations for why clinical patients show improvement that merit discussion and that speak to the need to evaluate treatments against a control group.

First, one should consider the degree to which the placebo effect is spontaneous recovery or regression to the mean (Kienle and Kiene, 1996; ter Riet et al, 1998). Patients typically postpone treatment (or refrain from entering experimental trials) until symptoms become difficult to bear. The body's self-healing properties alone can create a reduction in symptoms in the near term (Kienle and Kiene, 1996). A portion of the placebo effect, and of the treatment effect, may actually be the remission of disease. This is particularly salient in the case of Ménière's, since exacerbation and remission is expected, and the symptoms may "burn out" after a period of time.

Secondly, patient reports are fallible. The "I shall please" root of the word placebo holds

not only in the practitioner appeasing the patient but also in the patient appeasing the practitioner by providing obliging reports (Kienle and Kiene, 1996). If the patient is a part of an open-label drug study, or unknowingly receives an ineffective treatment from a physician, human nature may drive the patient to report that the symptoms have remitted somewhat. The patient does not wish to appear ungrateful for the care provided.

Patient recollection of symptoms may not be entirely accurate. Price et al (1999) found that even just two minutes after experimentation, patient report of the effectiveness of the "strong placebo" increased. The recollection error was related to the pre-experimentation expectation of pain relief. Studies that require patients to track symptoms contemporaneously are less likely to be biased by memory effects.

Even the means of reporting results can affect the study, which illustrates that the size of the placebo effect within an experiment is not invariant. Kiene (1996b) describes the experiments by the German investigators Kohnen and Lienert. In one experiment, double-blinded study volunteers were asked to journal their experiences with a sleep medication or placebo. In the treatment group, 63% reported positive effects, and 17% of the control group did so—a 46% difference in treatment effectiveness. However, in a second experiment, a questionnaire was used. The power of the suggestion apparently increased the effectiveness of both the placebo (now rated effective by 72%) and the experimental medication (83%), narrowing the drug effect to 11%.

It has been suggested that being a subject in an experiment may serve to reduce the reported effectiveness of the drug, while potentially increasing the reporting of relief from the placebo (Kiene, 1996a). If the patient believes that he or she has a 50% chance of receiving the active drug, the patient may moderate his or her report to minimize the error that could occur. Consciously or subconsciously not wishing to appear foolish, the patient who feels much better may report only feeling a little better. This reduces the potential embarrassment that would occur if discovering that the medication was the placebo. Those in a control group may report being somewhat improved, since there is little risk in the statement, which minimizes the self-perceived error that would occur if the patient were receiving an active treatment.

Experimenter subordination and "polite answers" are similar constructs. If the practitioner or experimenter implies an expected answer, then the patient may oblige (Kiene, 1996a; Kienle and Kiene, 1996). The patient receiving, or thinking he or she may be receiving, an active drug wishes to please the experimenter by reporting that it is at least somewhat effective.

If the subtractive model is correct (that the treatment effectiveness is the response rate seen in the treatment group minus the placebo effectiveness rate), then all studies of treatment effectiveness would show the same benefit, plus or minus the expected experimental error rate associated with differing sample sizes. Experimentation suggests this is not true, as was illustrated above by the effect of the type of reporting used.

Further, the patient's expectation of treatment effectiveness (Price et al, 1999; Vase et al, 2003) and reported desire for relief (Vase et al, 2003) are related to the degree to which relief from placebo is reported. Therefore, studies that minimize the expectation of effectiveness are the most likely to show the experimental drug or device as superior to placebo (Kienle and Kiene, 1996).

Even the appearance of the placebo can potentially alter the effect. Medical students given two blue placebo pills, with suggestion that it was a sedative, were more likely to report sedating effects than if given red pills (Blackwell et al, 1972). Placebos administered by injection have been found to be more effective than when given orally, and studies that have contrasted real surgery to sham surgeries also find high placebo effectiveness. The use of a medical device or an "elaborate ritual" increases the placebo effect, and therefore decreases the superiority of the study treatment (Kaptchuk et al, 2000).

Patient experience may also affect the placebo's effectiveness rate. Those who have had prior experience with the class of medication appear to be better able to differentiate between the placebo and the true medication (Rickels et al, 1966, as cited in Kiene, 1996b). Alternatively, experience may boost expectation and increase the placebo effect (Moertel et al, 1976).

Some patients appear to be more susceptible to the placebo effect and are termed "reactors" or "responders." In a placebo washout study, patients are first given a placebo. Those

who react to the placebo are eliminated from the study; the "nonreactors," who are considered more accurate evaluators, then rate the medication effectiveness (Kiene, 1996b; Kaptchuck et al, 2000). This method is not often used but is an intriguing methodology. The washout study design would tend to increase reported effectiveness and further illustrates the limitation of the subtractive model.

To this point, the placebo effect has been described as an experimental error. The term "placebo" has a connotation of deception—something clinicians wish to be avoided in ethical clinical practice. However, alternative and complementary medicine practitioners conceive of holistic healing differently and seek to maximize the healing powers of the mind-body connection. Donnelly (2004) refers to the positive treatment effects, potentially mediated by the endocrine and nervous systems, as "debonafide" effects, from Latin for "derived from good faith." Debonafide is meant to express the powerful, though not fully understood, mind-body connections that mediate healing. Thus, a clinical treatment could be said to have debonafide effects, but it would not be correct to say that a type I experiment elicits a debonafide effect.

Practitioners of alternative and complementary medicine have criticized placebo-controlled experimentation because it typically reduces the patient's good faith and fails to trigger the same holistic healing response. Double blinding reduces the risk of experimenter subordination; however, it is possible that the double-blinded experimental process reduces the therapeutic effects. Within placebo-controlled studies, the patient is generally deprived of the reassurance typically provided along with the treatment. Placebo-controlled experimentation may reduce the healing power that would occur when the treatment is conventionally dispensed (Roberts et al, 1993).

The concept of a debonafide effect has implications for the veracity of the subtractive model. If a given symptom can be treated in two different ways—from stress reduction and the mind-body connection or via medication, without the psychologically mediated endocrine and nervous system involvement—then the subtractive method is invalid.

A conceptual framework is offered for why patients report as they do regarding the effectiveness of a treatment or of a placebo. It is theorized that patients differ in their susceptibility to most of the factors. The change in symptoms reported after an experimental trial can be thought of as being influenced by:

- Change in underlying disease during study period
  This factor is related to the natural course of the disease and whether it remits or exacerbates during the study time frame.
- Susceptibility1 X Positive Reporting Bias (RB)
  Reporting bias refers to the social factors that cause patients to provide an obliging report. Differing patients are variably susceptible.
- Susceptibility2 X Expected Benefit (EB)
  Expected benefit encompasses such concepts whether the study/clinical treatment implies that the benefit will be large or small, and patient's prior experiences. It includes factors that surround the treatment administration that heighten or lessen expectation, such as how elaborate the treatment is, and the clinical mannerisms of the provider. Individuals differ in susceptibility.
- Susceptibility3 X True Benefit (TB)
  True benefit is what we seek to know—how effective the treatment is. Patients with varying psychological and physiological makeup will differ in benefit.
- Susceptibility4 X Negative Experimentation Irritation and Negative Reporting Bias (EI)
  This factor detracts from reported benefit and expectation of benefit, and also varies across patients. Experimental irritation is a lessening of expectation that may occur with either an unskilled practitioner who detracts from the holistic experience or the decrease in expectation that may accompany the knowledge that the experimental treatment may be a placebo. Negative reporting bias is the patient's moderation of a positive report of outcome during experimentation, in order to reduce the embarrassment of reporting an effect if none exists, and can subtract from true benefit.

This framework proposes that the final four factors are all mediated by related patient personality/psychological characteristics. Those who expect, and are susceptible to, improvement through treatment may respond well to the clinical conditions that relieve stress, positively affecting the endocrine and nervous systems. Those who are highly susceptible to expectation may, or may not, tend to place high value on social aspects and moderate responses or tend to provide answers they think will please the study/treatment providers.

The model proposes that an underlying disorder can be treated two ways—through direct physiological changes (e.g., pharmaceutically induced) or via changes in psychological state of the patient that creates changes in the endocrine and/or nervous systems. Therefore, a patient may benefit from a treatment, a placebo, or likely maximally through the clinical combination of the treatment combined with the debonafide effects associated with clinical reassurance.

Figure 1 illustrates hypothetical patient responses to either a treatment or to a placebo, and the benefit reported in each case, illustrating that either active or control treatments may produce patient report of benefit. It illustrates that minimizing expected benefit will increase the size of the treatment advantage. The overlap between the expected benefit and treatment benefit illustrates the theory that some symptoms can be relieved via stress reduction and/or other mind-body connections or by the treatment alone, even in the absence of an expectation of benefit. Patient A has a modest response to placebo, partially from a reporting bias, which is partly moderated by some experimental irritation. Patient B has larger expectation of benefit, creating a larger placebo response. Because of the larger overlap between benefit derived via the mind-body connection and the benefit from the experimental treatment, this patient would show less treatment advantage than would patient A.

This framework has not been tested, and may not be experimentally testable. It is meant to illustrate reasons why the subtractive model would not always reveal the same relative treatment benefit and theorizes that the treatment benefit and the placebo benefit are intertwined.

If we accept that the placebo affect can be enhanced by patient expectation, biased patient reporting, and disease remission, consider the potential magnitude of the debonafide effect during uncontrolled therapeutic administration of novel procedures by enthusiastic health-care professionals. Roberts et al (1993) conducted a meta-analysis of the results of early studies of "innovative" procedures for a variety of medical conditions. All of the procedures were later found to be no more effective than placebo in randomized controlled clinical trials. In total, 6931 patients were tested. Excellent outcome was reported by 40% of patients and good outcome by 30%, with only 30% having poor outcome. This study concludes that with heightened patient expectation, uncontrolled clinical trials can show good patient outcome in 70% of patients.

Some argue that any treatment that has few or no side effects and a 70% relief rate is by definition effective. This point is often made by holistic practitioners and is reinforced by mothers' use of kisses in the safe and effective treatment of their children's bruises. If a procedure is noninvasive, safe, and—as administered by the enthusiastic practitioner—effective, then the patient may be served well, even though the method of relief is via mind-body connections, rather than surgical or pharmaceutical intervention. Relative to Ménière's disease, it could be argued that highly conservative treatments such as sodium restricted diets and/or avoidance of caffeine, alcohol, tobacco, and stress fall into this category. This argument ignores the possibility that a significant portion of the reported effectiveness comes from patients providing obliging reports, and discounts the disabling nature of Ménière's disease, which requires the most effective treatment possible.

However, when treatments pose risks, greater scientific justification is required. Understanding the degree to which a surgical or drug treatment is a debonafide/placebo effect is then crucial. Recommending surgery or using ototoxic drugs poses risks; careful analysis is required.

In summary, the "placebo effect" applied to a clinical treatment may be better termed a "debonafide effect" or a "non-specific effect" of treatment. It is proposed that some symptoms can be alleviated *either* through fostering stress reduction and the mind-body connection or through a true treatment effect but optimally through the combined use of both factors. A more elaborate treatment

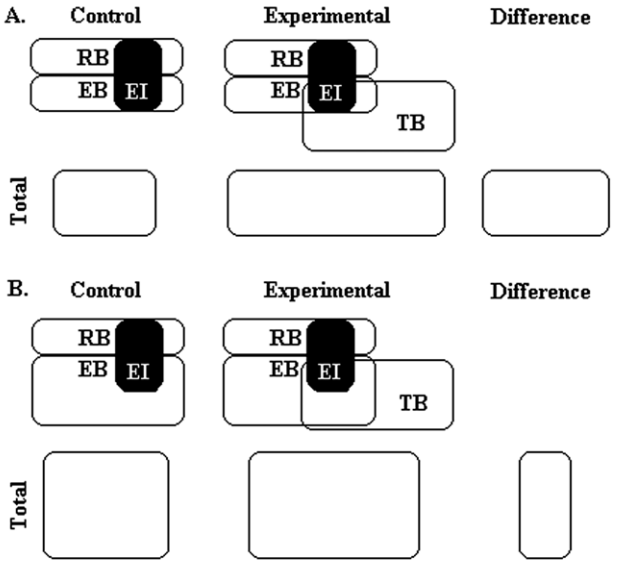

Figure 1. Benefit received by two hypothetical patients (A and B), when in the control group or in the experimental treatment group. The size of the blocks illustrates the effect sizes. RB = Response Bias, the tendency to report positive findings; EB = Expected Benefit; TB = True Benefit; EI = Experimental Irritation, detracts from the report of effectiveness. The total area of the box shows the relative magnitude of the patient's report of improvement. The size of the difference in benefit that the subtractive method would attribute to the treatment is shown on the right. *(A)* This patient is in a well-run clinical trial, which minimizes reporting bias, experimental irritation, and expectation of benefit. *(B)* Illustrates that the difference between the control and experimental treatment benefit decreases when the patient has higher expected benefit. The overlap of EB and TB illustrates that some symptoms could be treated either by the expectation of benefit and its effects on the endocrine and nervous systems or by the administration of the experimental treatment.

applied by a skilled counselor should evoke a maximum debonafide effect. Patients are not unbiased reporters; the means of reporting and psychological/social patient characteristics leading to obliging reports can distort reports of benefit. While some cite 35% as the magnitude of the placebo effect, Roberts et al (1993) found that 70% of patients had good or excellent outcomes in uncontrolled experimentation using treatments that were later found to be equivalent to placebo alone. This suggests that the debonafide effect can be much larger than the oft-cited 35%.

EVALUATION OF TREATMENT OUTCOMES IN MÉNIÈRE'S DISEASE

There is no reason to believe that Ménière's Disease treatment is immune to debonafide effects; therefore, it is reasonable to assume that case studies and retrospective reports will document between 35% and 70% treatment effectiveness, even if the treatment elicits only debonafide effects.

In the treatment of Ménière's, the studied patient's clinical status must also be considered. For many, Ménière's disease "burns itself out," and the debilitating dizziness eventually subsides. The improvement of patients enrolled in uncontrolled treatment studies may be partially attributable to the natural course of the disease (Gates, 2004). In controlled trials, roughly equal numbers of those in the placebo and control group will have cyclic remission, though inclusion of a no-treatment group would best evaluate this factor.

The following reviews the degree to which different treatments for Ménière's have been subject to type I experimentation. The articles by Gates and by Ghossaini and Wazen in this issue also review treatment effectiveness; therefore, this review focuses on experimental concerns and the debonafide effect.

Traditional Pharmacological Treatments

Medical treatment of Ménière's disease typically follows a conservative path. The patient is advised to avoid caffeine, alcohol, tobacco, and stress; may be counseled on salt restriction; and is often prescribed one or more of the conventional medications: a diuretic, a vestibular suppressant, an antiemetic, a vasodilator such as betahistine, or, in Europe, cinnarizine, a calcium antagonist that has vasodilation properties and is used to control motion sickness (Brookes, 1997; Thai-van et al, 2001; Minor et al, 2004; Van de Heyning et al, 2005). The "traditional" treatment regiments are cited as between 58% (Minor et al, 2004) and 80% (Van de Heyning et al, 2005) successful in controlling vertigo. The figure 70% improvement is frequently cited.

Given the similarity between the effectiveness of traditional treatment and the improvement expected from a debonafide effect, it is reasonable to assume that at least

some portion of the treatment effectiveness can be attributed to the support provided by the clinician. As with tinnitus, reassurance that Ménière's is not the result of intracranial tumors can reduce stress to beneficial effect (Brookes, 1997). Since this reassurance often is coupled with the prescription of one or more of the standard pharmacological treatments, it is frequently not clear the role of the pharmacological agent versus the neurophysiologic effect on the cholinergic system that stress reduction alone produces.

In general, when subjected to rigorous testing, treatments considered traditional and effective do not withstand the scrutiny. The reader is referred to Gate's article in this issue for a review of the effectiveness of medical treatment. The literature reviews of Minor et al (2004), Brookes (1997), and Thai-van et al (2001) also serve as references.

The importance of placebo-controlled experimentation is evident in reviewing the history of the use of steroids in the treatment of Ménière's. Steroid prescription is based on the theory that Ménière's is an autoimmune response (Silverstein et al, 1998; Minor et al, 2004). Oral steroid use has potent side effects: hypertension, hip necrosis, and insulin resistance. Therefore transtympanic administration by injection, by microcatheter, or by Merocel wick is favored (Doyle et al, 2004). Complications can include pain, otitis media, and posttreatment TM perforation, which may be slow to heal (Doyle et al, 2004). Retrospective studies varied in their reported efficacy. Dodson et al (2004) reported 54% achieved vertigo relief, and reviewed literature citing relief rates anywhere from 32% to 90%. While approximately half of clinical patients responded to steroid treatment, Silverstein et al (1998) failed to find evidence for superiority of transtympanic desamethasone over placebo. Neither the treatment nor placebo group had significant improvement in tinnitus, aural fullness, or ENG results. Thus, a treatment once considered effective has fallen from favor and illustrates that a clinical treatment for Ménière's disease can have the same debonafide/remission response rate as reported in literature for other physiologically based diseases.

Steroid treatment is not an isolated example. Many of the traditional, relatively conservative pharmacological Ménière's disease treatments have not been tested in controlled trials, and some conservative, traditional medical treatments that have been studied have been found to be no better than placebo. Yet the literature indicates that 70% of patients respond to these forms of clinical treatment. Is the treatment largely a debonafide effect? Is stress reduction a key component to successful treatment? Perhaps the failure of treatments to withstand the rigors of controlled clinical trials is a result of the experimental irritation they may invoke—the fact that the clinical trials reduce the expectation of benefit and therefore the stress-relieving effects that accompany medical intervention. Alternatively, the report of 70% clinical effectiveness in retrospective clinical studies of pharmacological agents may reflect some level of obliging patient report, or remission of the disease.

Tympanostomy Tubes and the Meniett Device

Most Ménière's disease treatment review articles advocate a progressive medical management approach. Those who are not successfully managed with conventional treatment receive a more aggressive treatment, which may be the use of the Meniett device.

As described by Gates in this issue, use of the Meniett device requires insertion of tympanostomy tubes. Previously, insertion of tympanostomy tubes alone was considered a treatment for Ménière's disease, although there is no underlying rationale for its efficacy (Thai-van et al, 2001): Eustachian tube dysfunction has not been associated with Ménière's disease. However, placement of tubes is a precursor to the use of the Meniett device, which does have rational theoretical construct. The Meniett device delivers +120 daPa pulses of air pressure to the ear. It is hypothesized that these pulses change the pressure in the inner ear and may distend the endolymphatic sac since pressure relief is not available through other means. Densert et al (1995) showed reduction in the summating potential/action potential ratio following pressure treatment, supporting physiologic improvement.

Barbara et al (2001) evaluated the treatment of 20 patients with tympanostomy tubes and the Meniett device in an unblinded study. All patients had been unsuccessful with a traditional management approach and were awaiting vestibular nerve sectioning. Successful relief from vertigo was achieved

by 18 patients with tympanostomy tube insertion only. Hearing did not change. Subsequent use of the Meniett device did not create a significant improvement, nor improvement in hearing. In this study, it appears that the patients considered the tube placement as a part of the treatment. This minor surgical procedure would qualify as an "elaborate ritual" and could invoke a strong debonafide response. Because these patients had Ménière's for one to twenty years and were awaiting surgical treatment, spontaneous remission of symptoms or change in the natural course of the disease, while possible, is not likely the primary cause of the improvement.

In sharp contrast, controlled studies of the Meniett device have not shown tympanostomy tube placement alone to be efficacious (Odkvist et al, 2000; Gates et al, 2004). These studies contrasted the effect of the active Meniett device to the inactivated device, which produced a clicking sound similar to the working device. No improvement in symptoms was seen for either the treatment or control group after placement of the tubes. Only the active Meniett device elicited a positive effect on vertigo. Gates (e-mail to author, January 28, 2005) confirmed that the placement of tympanostomy tubes was considered preparatory to the experiment. His subjects were so informed; therefore, a debonafide effect from tube placement would not be anticipated.

This raises several possibilities. Perhaps patients can be treated as effectively with an experimentally ineffective treatment such as tympanostomy tubes, if the practitioner conveys belief in the approach. Perhaps some portion of the symptom improvement found by Barbara et al (2001) was the result of obliging patient report, or from experimental error in this study of 20 patients. If the subjects in the Gates et al and Odkvist et al studies were informed that the tube placement would have no effect, experimenter subordination may entice them to obligingly report no improvement. Perhaps the subjects in these two controlled studies were not truly blinded, and thus, subjects were still susceptible to a placebo effect if in the treatment group, and immune from one if in the in the control group. That unblinding could occur if the experimenters or their staff inadvertently provided too much information about the specifics of the pressure sensation that would occur with an active device. Patients may have obtained this information from their own research on the device. Gates et al (2004) reported that many patients did not report feeling the +120 daPa pulses; they conclude that the blinding was effective.

At this time, it is difficult to reconcile the finding of Barbara et al (2001), which showed tube placement alone to be highly effective, with the controlled studies of the Meniett device, which typically did not show tube placement to be effective. Thomsen et al (2005) monitored patients for two months after tympanostomy tube placement, prior to enrolling them in a controlled study of the Meniett device, and excluded patients whose vertigo improved; thus, there is some suggestion that tube placement has an effect on Ménière's. Densert and Sass (2001, p. 620) note that tympanostomy tube placement "primarily failed" to relieve vertigo in their patients. These two studies suggest tube placement may create an effect (actual or placebo). The Barbara et al study cautions us that reports of 90% treatment effectiveness can be obtained from "ineffective" treatments, such as tympanostomy tube placement.

Double-blind clinical trials of the Meniett device generally show some improvement in the placebo group, although an improvement inferior to the active Meniett device. The Odkvist et al (2000) study of outcomes two weeks posttreatment is the exception; no improvement was seen for the placebo group. Studies with longer term evaluation (eight weeks for Thomsen et al [2005] and four months in the Gates et al [2004] study) did show improvement for those in the control group. The degree to which the placebo group improvement is due to vertigo remission versus a nonspecific effect is unclear.

Gentamicin Oblation

The Meniett device may provide relief for many, but for some, the treatment may not be sufficient (Van de Heyning et al, 2005), and some form of vestibular function ablation may be required (Gates, 2004; Van de Hening et al, 2005). Long-term studies of the appropriateness of oblation are warranted. Brookes (1997) reminds us that Silverstein et al (1989) found 59% of patients who decided against ablative surgery had complete control of their vertigo two years later; this figure rose to 70% by eight years.

Gentamicin treatment is often used when the Meniett device is not effective for a patient (Odkvist, 2001). Gentamicin is more vestibulotoxic than ototoxic and destroys endolymph-producing cells in the stria vascularis and cupulas (Van de Heyning et al, 2005). Transtympanic administration is typically used. While often considered low risk, studies differ in their reports of hearing loss. Chia et al's (2004) meta-analysis reported an overall 25% incidence of hearing loss from gentamicin treatment, while the Cohen-Kerem et al's (2004) meta-analysis reported insignificant hearing threshold shift. Gates (this issue) cites a 30% risk of hearing deterioration. Ghossaini and Wazen (this issue) cite studies showing hearing loss in 0% to 81% of patients. No double-blinded effectiveness studies have been conducted (Cohen-Kerem et al, 2004).

Neurectomy/Labyrinthectomy versus Endolymphatic Sac Decompression

Vestibular neurectomy is considered both the most effective and most invasive (and therefore risky) treatment alternative (Van de Heyning et al, 2005), with labryrinthectomy an option if there is no useable hearing in the affected ear (Ghossaini and Wazen, this issue; Thai-van et al, 2001). Even neurectomy surgery is not universally successful. Minor et al (2004) cite a 90% success rate in the treatment of intractable vertigo. They consider facial nerve paralysis or paresis, hearing loss, cerebrospinal fluid leak, and headache as rare side effects. Van de Heyning et al (2005) report the risk of hearing loss with vestibular neurectomy as less than 10%. Huang (2002) argues that such "dangerous surgery" should be a choice of last resort, with the much maligned endolymphatic sac surgery being attempted first.

As Gates (this issue) and Ghossaini and Wazen (this issue) report, endolymphatic sac decompression was found to be no more successful than "sham" surgery—a simple mastoidectomy (Bretlau et al, 1984, 1989). However, it is possible that the anesthesia administration improved patient outcome, or that the mastoid surgery itself created a change in the endolymphatic sac function. Therefore, it is not known whether the control group was influenced solely by the placebo effect. Huang reports that the outcome of decompression surgery is 90% control of vertigo with hearing preservation or improvement and advocates for this more conservative surgery. Huang's (2002) argument in favor of a endolymphatic sac decompression underscores a recurring theme in Ménière's treatment. The least risky treatments should precede those with greater risk, even though the efficacy of treatments used frequently do not withstand placebo-controlled experimentation. The degree to which experimental irritation and deprivation of the debonafide effect influences the poor outcomes in controlled studies is not yet fully understood.

SUMMARY AND DIRECTION FOR FUTURE STUDY

The majority of treatment options for Ménière's have not withstood the rigors of controlled experimental testing. Clinical studies of treatment effectiveness illustrate that progressively aggressive treatments, beginning with lifestyle counseling and medication, and progressing to ones with increasingly more elaborate administration procedures, each has approximately 70% effectiveness. These clinical studies do not typically account for the cyclical remission and the generally time-limited vertigo in Ménière's. When subject to placebo-controlled testing, several studies suggest that the improvement appears to be largely a debonafide effect. The Danish endolymphatic shunt decompression surgery was no better than simple mastoidectomy; both were effective (Bretlau et al, 1984, 1989), and intratympanic steroid injection caused no improvement relative to placebo, with neither group improving (Silverstein et al, 1998).

Comparison of the effect of tympanostomy tube placement in studies on the Meniett device raises intriguing questions. In an uncontrolled, clinical study, patients responded to tympanostomy tube placement alone and had only small and statistically insignificant additional benefit from the use of the device (Barbara et al, 2001). Gates et al (2004) informed their subjects that the tympanostomy tubes were a precursor to treatment, not a form of treatment, and found no effect. Densert and Sass (2001) and Thomsen et al (2005) suggest a possible improvement with tympanostomy tubes alone, for at least some patients. This body of work may suggest that

the magnitude of the debonafide effect is larger than the experimental placebo effect and is generally consistent with studies of pharmacological treatments that appear effective clinically but fail to evidence superiority to placebo in type I research. It is possible that the placebo response was reduced in the randomized controlled studies by unintentional experimental unblinding and a placebo response would have otherwise been observed. A second possibility is that the experimental design deprives patients of a debonafide effect, which is highly effective in producing vertigo reduction. Experimentation that does not lead to the expectation of benefit will not reduce patient anxiety and will not have positive endocrine and neurologic mind-body effects. In that case, the subtractive model is misleading because it discounts clinically effective debonafide effects. Use of the treatment alone (or a placebo alone) may evoke a debonafide effect that could cause symptom improvement. That is, perhaps *either* the debonafide effect of tympanostomy tube placement *or* the Meniett device can treat the same underlying symptoms through different processes.

Further study of the placebo effect in Ménière's disease treatment could evaluate not only the effectiveness of Ménière's treatments but the veracity of the subtractive model for estimating treatment benefit. The following design is proposed for evaluating the Meniett device, to be conducted by researchers with no affiliation with the manufacturer, nor experience with the device, to minimize potential for bias or unintentional unblinding. A group of patients, naïve to the nature of the Meniett device, would be randomized into three groups. The first two groups would be informed that the study sought to compare two treatments shown to be highly effective in at least some clinical trials. In this way, these two groups would have a debonafide effect. Subgroup 1 would receive tympanostomy tubes and an active Meniett device; subgroup 2 the tympanostomy tube treatment and inactive device.[1] Experimenters would be blind to the experimental condition. The third subgroup would participate in a crossover design study, using the active and inactive device, having been informed of the nature of the design. These subjects would know that the device would be inactive for half of the study, which should reduce the placebo response. If the subtractive model is correct, the treatment advantage between subgroups 1 and 2 and that demonstrated in the crossover design will be equal. That is, both groups one and two have a placebo effect, so group 1's superiority indicates the treatment effect, less debonafide effect. The crossover design would permit the typical subtractive estimate of treatment benefit, having controlled for and minimized the placebo effect by the experimental design. If relief from some of the symptoms of Ménière's can be achieved *either* through debonafide effects *or* through treatment effects, then the treatment effect demonstrated by the difference between subgroups 1 and 2 will be smaller than seen in the crossover study.

A study of this nature has not yet been undertaken, to my knowledge. Thus, the question of the relative contribution of the placebo/debonafide effect and spontaneous remission of symptoms remains elusive.

NOTE

1. Although it is true that uncontrolled clinical studies have shown effectiveness of tympanostomy tubes without an active device, the supervising Institutional Review Board would have to approve the patient deception, and ethically, subjects should be offered active treatment at the study termination if in group two.

REFERENCES

Barbara M, Consagra C, Monini S, Nostro G, Harguindey A, Vestri A, Filipo R. (2001) Local pressure protocol, including Meniett, in the treatment of Meniere's disease: short term results during the active stage. *Acta Otolaryngol* 121:939–944.

Blackwell B, Boomfield SS, Buncher CR. (1972) Demonstration to medical students of placebo responses and non-drug factors. *Lancet* 10(7763):1279–1282.

Bretlau P, Thomsen J, Tos M, Johnsen NJ. (1984) Placebo effect in surgery for Meniere's disease: a three year follow-up study of patients in a double-blind placebo-controlled study on endolymphatic sac shunt surgery. *Am J Otol* 5:558–561.

Bretlau P, Thomsen J, Tos M, Johnsen NJ. (1989) Placebo effect in surgery for Meniere's disease: nine year follow-up. *Am J Otol* 10:259–261.

Brookes GB. (1997) Medical management of Meniere's disease. *Ear Nose Throat J* 76(9):634–640.

Chia SH, Gamst AC, Anderson JP, Harris JP. (2004) Intratympanic gentamicin for Meniere's disease: a meta-analysis. *Otol Neurotol* 25:544–552.

Cohen-Kerem R, Kisilevsky V, Einarson TR, Kozer E, Koren G, Ruka JA. (2004) Intratympanic gentamicin

for Meniere's disease: a meta-analysis. *Laryngoscope* 114:2085–2091.

Densert B, Sass K. (2001) Control of symptoms in patients with Meniere's Disease using middle ear pressure applications: two years follow-up. *Acta Otolaryngol* 121: 616–621.

Densert B, Sass K, Arlinger S. (1995). Short term effects of induced middle ear pressure change on the electrocochleogram in Meniere's Disease. *Acta Otolaryngol* (Stockh) 115:732–737.

Dodson KM, Woodson E, Sismanis A. (2004) Intratympanic steroid perfusion for the treatment of Meniere's disease: a retrospective study. *Ear Nose Throat J* 83(6):394–898.

Donnelly G. (2004) The placebo effect and holistic interventions. *Holist Nurs Pract* 18:239–241.

Doyle KJ, Bauch C, Battista R, Beatty C, Hughes GB, Mason J, Maw J, Musiek FJ. (2004) Intratympanic steroid treatment: a review. *Otol Neurotol* 25:1034–1039.

Gates GA. (2004) Meniere's in 2004. *Hear Health* (Spring):17–21.

Gates GA, Green D Jr, Tucci DL, Telian SA. (2004) The effects of transtympanic micropressure treatment in people with unilateral Meniere's disease. *Arch Otolaryngol Head Neck Surg* 130:718–725.

Hahn RA. (1997) The nocebo phenomenon: concept, evidence, and implications for public health. *Prev Med* 26(5, Pt.1):607–611.

Huang TS. (2002) Endolymphatic sac surgery for Meniere's disease: experience with over 3000 cases. *Otolaryngol Clin N Am* 35:591–606.

Johnson CE, Danhauer JL. (2002) *Handbook of Outcomes Measurement in Audiology*. Clifton Park, NY: Thomson Delmar Learning.

Kaptchuk TJ, Goldman P, Stone DA, Stason WB. (2000) *J Clin Epidemiol* 53:786–792.

Kiene H. (1996a) A critique of the double-blind clinical trial. Part I. *Altern Ther Health Med* 2(1):74–80.

Kiene H. (1996b) A critique of the double-blind clinical trial. Part II. *Altern Ther Health Med* 2(2):59–64.

Kienle GS, Kiene H. (1996) Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Altern Ther Health Med* 2(6):39–54.

Minor LB, Schessel DA, Carey JP. (2004) Meniere's disease. *Curr Opin Neurol* 17(1):9–16.

Moertel CG, Taylor WF, Roth A, Tyce FA. (1976) Who responds to a sugar pill? *Mayo Clin Proc* 51:96–100.

Odkvist L. (2001) Pressure treatment versus gentamincin for Meniere's disease. *Acta Otolaryngologica* 121:266–268.

Odkvist LM, Arlinger S, Billermark E, Densert B, Lindholm S, Wallqvist J. (2000) Effects of middle ear pressure changes on clinical symptoms in patients with Meniere's disease—a clinical multicenter placebo-controlled study. *Acta Otolaryngol Suppl* 543:99–101.

Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. (1999) An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental design. *Pain* 83:147–156.

Roberts AH, Kewman DG, Mercier L, Hovell M. (1993) The power of non-specific effects in healing: implications for psychosocial and biological treatments. *Clin Psychol Rev* 13:375–391.

Sherman D, Massoud EAS. (2001) Treatment outcomes of benign paroxysmal positional vertigo. *J Otolaryngol* 30:295–299.

Silverstein H, Isaacson JE, Olds MJ, Rowan T, Rosenberg S. (1998) Dexamethasone inner ear perfusion for the treatment of Meniere's disease: a prospective, randomized, double-blind crossover trial. *Am J Otol* 19:196–201.

Silverstein H, Smouha E, Jones R. (1989) Natural history versus surgery for Meniere's disease. *Otolaryngol Head Neck Surg* 100:6–16.

ter Riet G, de Cren AJM, de Boer A, Kessels AGH. (1998) Is placebo analgesia mediated by endogenous opiods? A systematic review. *Pain* 76:273–275.

Thai-van H, Bounaix M-J, Fraysse B. (2001) Menière's disease: pathophysiology and treatment. *Drugs* 61(8):1089–1102.

Thomsen J, Sass K, Odkvist L, Arlinger S. (2005). Local overpressure treatment reduces vestibular symptoms in patients with Meniere's disease: a clinical, randomized, multicenter, double-blind, placebo-controlled study. *Otol Neurotol* 26:68–73.

Van de Heyning PH, Wuyts F, Boudewyns A. (2005) Surgical treatment of Meniere's disease. *Curr Opin Neurol* 18(1):23–28.

Vase L, Robinson ME, Verne GN, Price DD. (2003) The contribution of suggestion, desire and expectation to the placebo effects in irritable bowel syndrome patients. *Pain* 105:17–25.