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Financial Disclosure
Russell H. Greenfield, MD (executive editor), David Kiefer, MD (peer reviewer), Leslie Coplin (AHC Media executive editor), and Neill Kimball (managing editor) have no financial relationships relevant to this field of study.

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Supplements for Sleeplessness

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INSOMNIA IS RELATIVELY COMMON AND EXPERIENCED AROUND THE world. Estimates have identified prevalence rates ranging from 5-50%.[1] This variation is likely due to cultural differences and varying methodologies used in surveys. Incidences ranging from 20-38% are most commonly reported.[2] A recent survey of U.S. workers found that 23.2% of employees experienced insomnia, contributing to 11 days of lost work annually per person impacted, at an extrapolated cost of $63 billion.[3] Another well-designed survey found that 29.9% of Canadian adults experienced insomnia regularly, with 9.5% meeting the criteria for insomnia syndrome.[1] This survey found that 13% of all respondents consulted a health care professional about insomnia, primarily family physicians.

Interest in complementary and alternative therapies for sleep disorders has been growing over the past two decades.[4] The Canadian survey found that 9% of the sample used natural remedies for their insomnia, with more than half of the people taking these remedies at least 3 nights a week.[1] However, the amount and quality of the research evidence available to guide users of herbs and supplements for insomnia remains low.[4] Given the relatively high prevalence of insomnia, and the regular use of natural remedies for self-treatment, health care professionals should be aware of the most commonly used "natural" sleep remedies and the evidence for their effectiveness and side effects.

Valerian

By far the most-researched herb for insomnia is valerian. Remedies made from *Valeriana officinalis* have been used for sleeping difficulties since ancient Greek and Roman times.[5] Numerous controlled trials of valerian have been conducted and these have been systematically reviewed in recent years. The latest meta-analysis of valerian vs placebo for insomnia identified 18 randomized controlled trials (RCTs).[6] Studies involving valerian in combination

with other herbs were excluded. The reviewers carried out three separate meta-analyses based on how outcomes were measured. In six studies, sleep quality was measured dichotomously (asking participants if sleep improved or not), and valerian was found to provide significant benefit. The relative risk (RR) was 1.37 (95% confidence interval [CI], 1.05–1.78). In other words, those taking valerian were 1.37 times more likely to have improved sleep quality compared to those taking placebo.

However, outcome measurement with insomnia is challenging, especially when considering subjective measurements tools like questionnaires. Only two of these four studies used validated methods. Quantitative outcome measures are preferred, such as visual analogue scales (VAS) of sleep quality or latency time (LT) to get to sleep. Ten studies measured outcomes using LT in minutes and meta-analysis found no significant benefit from valerian (mean difference of 0.70 min; 95% CI, -3.44–4.83). Seven studies used VAS and likewise found no significant benefit from valerian (mean difference of -0.02; 95% CI, -0.35–0.31).

These results are similar to an earlier meta-analysis that identified 16 RCTs of valerian, either with or without other herbs.[7] The most commonly reported outcome measurement method was the dichotomous question asking whether sleep improved or not. This showed significant benefit for valerian (RR 1.8; 95% CI, 1.2–2.9). The reviewers did not carry out a meta-analysis with the other studies because many different outcome measures were used and little statistical data was presented. Overall, they concluded that the quality of the studies was poor, but there was some evidence that valerian may improve sleep quality.

Another systematic review identified 37 studies.[8] The authors included more studies in this analysis because they did not exclude studies using valerian along with other herbs (hops, lemon balm, or passion flower) or studies that were not double-blinded (i.e., open-label trials). They did not conduct a meta-analysis because the methodology of the trials varied widely and was generally of poor quality. They noted that most studies did not find significant differences between valerian and placebo either in healthy adults or in those with sleep disturbances or insomnia.

Overall, the evidence from larger and higher quality studies does not support the use of valerian for insomnia. While some studies have found beneficial results, the quality of these studies is low. Several studies also have examined its safety and found that adverse effects are rare and mild.[8] A few cases of hepatotoxicity have been reported, but it is possible that the adverse effects were due to contaminants. A review by the National Toxicology Program found that valerian could not be shown to be the cause of the liver damage.[9] The most common side effects were dizziness or headache and mild gastrointestinal effects. Valerian is thought to have sedative-hypnotic effects, and therefore may have additive effects with other sleeping agents.

German Chamomile

Chamomile is used for many purposes, including as a natural sleep aid. Many different species are called chamomile, with German, or genuine, chamomile (*Matricaria recutita*) most commonly used medicinally. Roman, or English, chamomile is an unrelated plant. German chamomile leaves and flowers can be brewed as a tea or placed under the pillow to aid sleep. One recent survey in Canada found that German chamomile was the most popular herbal sleeping aid.[10] Prior to September 2011, the only reported study of chamomile for insomnia was published in 1973 in which 12 hospitalized heart patients were given a strong cup of chamomile tea (strength not defined).[11] Ten of the patients immediately fell into a deep sleep that lasted 90 minutes. A pilot RCT was recently published involving 34 patients with primary insomnia for at least 6 months.[12] Subjects were randomized to placebo or 270 mg chamomile twice daily for 28 days. No significant differences were found for sleep outcomes as reported in sleep diaries. Secondary outcomes related to daytime functioning also were measured. These favored chamomile, but were not statistically different. Adverse effects did not differ between chamomile and placebo and all were mild and transient. The cause of any sedative effects is unknown, with studies having contradictory

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin
MANAGING EDITOR: Neill Kimball
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Alternative Medicine Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

results. While chamomile is commonly used, evidence to guide patients is minimal, but at least side effects are minimal.

Melatonin

Melatonin is another highly popular supplement for sleeping problems. It became something of a "wonder drug" because of its ready availability as a dietary supplement for the relief of sleep disturbances due to jet lag and shift-work.[13] At the same time, extensive research was being conducted into its role as an endogenous hormone involved in sleep regulation. This led to the identification of melatonin receptors in humans involved in synchronizing circadian rhythms.[14] Although much remains unknown about melatonin's mechanism of action, it is not a hypnotic like benzodiazepines and thus does not have their adverse effects.

Clinical trials of melatonin to induce sleep have had mixed results. A 2006 systematic review identified 12 RCTs of melatonin for people with sleep disorders and another 13 trials involving sleep restriction, such as occurs with jet lag.[15] Most trials were very small and the reviewers concluded there was no evidence of effectiveness in either group. The evidence also showed that melatonin was safe with short-term use.

However, the design of these trials has been questioned as more has become known about how melatonin works. Healthy volunteers taking melatonin at night, when endogenous levels are already highest may not benefit as their receptors may be saturated. Thus, in another trial when melatonin was given in the afternoon, it improved total sleep time before midnight by 2 hours compared to a control group.[16]

One meta-analysis included only studies using objective measures of sleep quality and involving people with insomnia who were otherwise healthy.[17] This found that melatonin significantly decreased sleep latency by 3.9 min (95% CI, 2.5–5.4), increased sleep efficiency by 3.1% (95% CI, 0.7–5.5), and increased sleep duration by 13.7 min (95% CI, 3.1–24.3). Doses varied widely between 0.3 and 5 mg daily. Although a subgroup analysis by age was not reported, the reviewers concluded that studies with participants older than 55 years had more beneficial outcomes. Melatonin levels naturally decrease with age.

Melatonin has a very short half-life (about 30 min), leading to research into prolonged-release (PR) formulations. These appear to show more benefit than melatonin, although a systematic review of PR formulations has not yet been published.[18] The 2010 Consensus Statement of the British Association for Psychopharmacology concluded that PR melatonin improves sleeps quality in the elderly when given for 3 weeks.[18] A 6-month RCT of 2 mg PR melatonin found significantly reduced sleep latency compared to placebo in subjects over 65 years with primary insomnia (19.1 vs 1.7 min; $P = 0.002$).[19] Benefits were apparent at 3 weeks and continued for 6 months. Adverse events were similar between groups, with no serious or prolonged side effects. Most of the research on PR melatonin has been conducted on Circadin®, a registered pharmaceutical in Europe and other countries.[19] In the United States, other PR products are available as dietary supplements. In addition, research is being conducted to find more effective melatonin receptor agonists such as agomelatine, tasimelteon, and ramelteon.[14] These are being developed as conventional pharmaceuticals.

Lavender

Lavender oil is another natural remedy traditionally used to promote sleep. The volatile oil is typically inhaled as a fine mist that is diffused throughout a room via an atomizer and has become popular within aromatherapy.[2] Animal studies support the calming effects of lavender. An early report found that when four older patients on various hypnotic drugs were taken off their medications, their sleep duration decreased.[20] When lavender aroma was introduced into their ward, sleep duration increased significantly ($P < 0.05$). A pilot study recruited 10 people with insomnia into a single-blind, crossover trial.[21] Subjects were randomized to use a vaporizer with lavender oil and then sweet almond oil, or vice versa. Each oil was used for 1 week with a 1-week washout period in between. Using the Pittsburgh Sleep Quality Index (PSQI, scoring 0 to 21), the average score decreased by 2.5 when subjects inhaled lavender, and didn't change when sweet almond oil was used.

Another small trial involved 31 healthy adults aged 18 to 30 years.[22] They spent 3 consecutive nights in a sleep laboratory for adaptation, intervention, and control. Subjects laid in bed holding a vial on their chest for 2 minutes every 10 minutes for a total of 30 minutes. On the second night, half the group had lavender in their vials and the other had distilled water. For the third night, they crossed over. Over the whole night, lavender significantly increased deep sleep time ($P < 0.005$) using polysomnography. With questionnaires, the only significant difference noted was greater vigor upon waking for the lavender group ($P < 0.05$). Sleepiness before bedtime was not impacted.

The most recent trial involved 67 Taiwanese women who were randomly assigned to receive either lavender aromatherapy for 20 minutes twice weekly for 12 weeks or a sleep hygiene education program as control.[23] Sleep quality was measured with the Chinese PSQI. Over the 12 weeks, those receiving lavender had significantly improved CPSQI scores ($P < 0.001$), while the control group showed no change.

Conclusion

Natural remedies are increasingly popular as sleep aids. However, the evidence for many of the most popular ones remains limited. A large number of other herbs, such as hops, lemon balm, kava, and passionflower are also used, but have even less evidence to guide decision-makers.[2] As noted above, the evidence available for valerian and German chamomile do not support their effectiveness for insomnia, but the herbs are safe and commonly used. The evidence for melatonin is mixed, but as understanding of its underlying mechanism grows, it would appear to be most effective in older people and in people with sleep cycle disturbances. Also, prolonged-released formulations are more beneficial, but long-term safety has yet to be established for these. As with many other drugs originally developed from natural products, it would appear that analogues of melatonin may hold the most potential for the future. Inhalation of lavender oil, while having limited evidence, does consistently produce results that support its effectiveness.

Recommendation

Insomnia can be caused by several health and lifestyle factors, including sleep-disordered breathing and other primary sleep disorders. Careful consideration of these is needed to identify potential contributions to insomnia, including evening food and beverage intake, bedroom TV and lighting, physical activity, etc. Various stress factors should be considered, as well as contributions from other illnesses and side effects from medications. For those with unremitting insomnia, hypnotic drugs remain the most effective intervention. However, given their side effects, especially lingering drowsiness, melatonin or lavender inhalation may warrant a trial period. Older people in particular may benefit from prolonged-release melatonin. The lack of side effects for these natural remedies is particularly attractive. Careful monitoring of sleep quality should be carried out to identify whether the supplements are effective or if conventional medications may be necessary.

Sleep-promoting herbs are thought to act along a spectrum of action, from mild to strong, and from very safe to possibly safe. Herbal experts often recommend a stepwise approach to supplement use for insomnia, based on the severity of a patient's symptoms. ■

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FDA vs HCG Diet Supplements

ABSTRACT AND COMMENTARY

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On December 6, 2011, the Food and Drug Administration (FDA) announced that "HCG products marketed as weight loss aids are unproven and illegal."[1] Seven letters were sent jointly by the FDA and Federal Trade Commission (FTC) to companies involved in selling products for that indication. The press release details their concerns about weight loss products with human chorionic gonadotropin (HCG), which are labeled as "homeopathic" and sold in oral drops, pellets, and sprays, and usually are paired with a very low-calorie diet (500 calories daily) in order to help people lose 20-30 pounds in 40 days.

The FDA's concerns center on the danger of very low-calorie diets and the significant weight loss that occurs in association with them over such short time frames, especially without medical supervision. Furthermore, HCG is an injectable pharmaceutical, approved for medical conditions such as infertility, but not for weight loss; therefore, an over-the-counter (OTC) use of HCG is illegal. Finally, there is an approved list of homeopathic remedies, and HCG is not one of the constituents on that list, again in violation of the law.

Examples of the companies marketing HCG for weight loss are HCG Diet Direct, HCG Platinum, and Nutri Fusion Systems.[2] As of the printing of the article, products from these and other HCG companies were still available for sale through online companies and distributors. Labeling on HCG products includes phrases such as "Appetite Control and Detox," "Weight Loss Protocol Included" (referring to the diet and exercise regimens recommend along with the supplement), and "Weight Loss Formula." Some products contain homeopathic HCG (in strengths of 6X, 10X, 30X, and 60X) combined with homeopathic amino acids, often dosed as 10 drops three times daily. Another has 910 nanograms of a proprietary combination of HCG amino acids isolates in 10 drops and is dosed 10 drops three times daily. There are many other products using various combinations of amino acids, herbal medicines, and other ingredients.

In some cases, the proposed mechanism for HCG on weight loss is mentioned on packaging, but in other cases, manufacturers do not detail the effect. HCG's involvement in physiological changes during pregnancy is theorized to promote mobilization and metabolism of stored fat to produce additional energy, thereby leading to weight loss and a resetting of metabolism.

■ COMMENTARY

In the realm of dietary supplements, the FDA and FTC become involved whenever there is an infraction of laws related to supplement labeling or safety (FDA), or advertising or Internet information (FTC). As described above there were several aspects of HCG supplements and the HCG diet that crossed over the legal line and led to the December 6, 2011, announcement and reprimand.

The FDA press release mentions concerns about safety related to the use of the HCG products specified. It is interesting that most of the concerns discussed had to do with the problems of rapid weight loss (i.e., precipitation of gallstones) that may occur as a result of the HCG weight loss *protocol*, not necessarily the HCG products themselves, which the FDA deems to be ineffective; it is the very low-calorie diet that is presumed responsible for the significant weight loss achieved. The focus on adverse effects of dietary supplements is one of the FDA's mandates. Because of the placement of dietary supplements into the category of food (a result of the 1994 legislation, the Dietary Supplement Health and Education Act), it is a company's responsibility to assure safety prior to release into the marketplace, and the FDA steps in only when concerns about safety surface, essentially postmarketing

surveillance. A quick perusal of Internet sites for some of the companies selling HCG products reveals their approach to the issue of safety, with disclaimers strongly encouraging involvement of health care practitioners, directing consumers to books for more information (thereby avoiding FTC's concerns about the inappropriate dissemination of online medical information), and, in some cases, no use or mechanistic data whatsoever. It may, therefore, be possible for some companies to claim that they are not providing any protocol, per se, only products that consumers will have to figure out how to use by referencing some other source. It will be interesting to see how this aspect of the FDA's concern plays out.

Any unknowns about implied use and adverse effects as discussed above vanish with the other two parts of the FDA/FTC complaint. First, HCG is a pharmaceutical with approved uses, none of which are for weight loss; any other use, therefore, is illegal. Micromedex, the pharmaceutical database, states that chorionic gonadotropin is approved for use in adults to treat cryptorchidism, hypogonadotropic hypogonadism in males, and ovulation induction, whereas a related, recombinant form, chorionic gonadotropin alfa, is used in "assisted reproductive technology" and, again, ovulation induction. There are well-established contraindications and a detailed mechanism of action for the above-mentioned indications that do not seem to overlap the weight loss genre. This seems to be a cut-and-dried case of marketing and distribution of a pharmaceutical beyond its FDA-approved uses, an illegal act and one that will probably be hard for companies to circumvent.

Unless. Yes, there is an "unless." Companies involved with HCG products may be able to make a case that they are not actually using the pharmaceutical form, an injectable solution that, interestingly, is a topic of conversation between pleading, overweight patients and, sometimes, suspect physicians. Using subcutaneous or intramuscular HCG would certainly be an off-label use of this drug. Instead, HCG products on the market are using homeopathic HCG, hence the labels that mention 6X, 10X, et cetera, a reference to the fact that the HCG is diluted and shaken ("percussed") so much that nary an HCG molecule exists in the remaining solution. Homeopathic medical practitioners, and a few research trials, support the efficacy of these "ultra-dilute" preparations; in theory, homeopathic HCG might still be able to exert an HCG effect, obtaining what consumers want from this hormone, and allowing manufacturers to skirt FDA HCG drug regulations. However, here arises the third part of the FDA complaint: It appears that in the official homeopathic compendium, HCG is not mentioned as an allowable homeopathic treatment. The FDA may have had the last laugh, as it targets the illegality of even homeopathic HCG forms.

So, there are legal technicalities that seem to be the origin behind the current press release and seven certified letters. However, what else might be going on behind the scenes of the HCG diet movement, and whether or not there may be any truth to what these products' manufacturers, and many of our patients, claim, is a whole other matter. It takes some detective work to compile general themes from the wide variety of HCG manufacturers, as well as track down the origin of specific claims and possible role of co-ingredients, which is beyond the scope of this commentary. Stay tuned for the full HCG treatise in an upcoming issue. ■

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From Data to Conclusions: How Research is Interpreted

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THIS IS THE FINAL ARTICLE IN A THREE-PART SERIES ABOUT the design and conduct of clinical research. The first installment discussed how research begins with the formulation of research questions, and the second reviewed the strengths and limitations of some common study designs. This article will discuss a few key issues in the analysis and interpretation of research findings.

A basic assumption of the research process is that measuring a characteristic in many people will produce a more stable understanding of nature than will measuring that characteristic in only one person. This presents the problem of how best to report information collected from tens or hundreds or thousands of people. Reporting all individual values is impractical and uninformative, so summary measures are used.

The ability of a single value to stand in for many depends on how the characteristic it represents is conceptualized. Some things are less easily summarized than

others. Opinions and thought processes (e.g. "How does someone choose a chiropractor?" "How do one's spiritual beliefs affect one's health practices?") can be difficult to boil down into one representative answer — or even into a small number of answers. Research involving questions of this sort is commonly described as qualitative, and has its own set of analytical techniques which are beyond the scope of this article. More common in biomedicine are questions that produce counts (e.g. "How many nutritional supplements does the average person take each day?" "On a scale of one to ten, what are patients' pain levels before and after an acupuncture session?" "How many additional pain-free years can a recreational runner with osteoarthritis expect to gain by taking glucosamine?"). Research involving these questions is commonly described as quantitative, and uses numerical techniques and the "language" of statistical testing.

Within quantitative research, there are further distinctions among characteristics in the way they are conceived, analyzed, and reported. Some characteristics fall naturally into categories — gender and race, for instance. Others can be grouped in a way that is analytically useful. For example, in their survey of the prevalence of CAM use and health status, Nguyen and colleagues collect and report participants' health status as Excellent, Very Good, Good, Fair, and Poor. They report age in ranges (18-29, 30-39, 40-49, 50-64, 65+) that are somewhat arbitrary, but which also have some analytical rationale.1 In other cases, these ranges may be determined by the data themselves. A common approach is to arrange the observed values from lowest to highest, and then divide them evenly into fourths (quartiles) or fifths (quintiles). This method may simplify the analytical process, but it can complicate the comparison of a study's results with other published findings. Whatever method is used to create them, these *categorical variables* are usually reported as counts and percents.

Other characteristics are not as easily grouped or are more appropriately analyzed without the imposition of (perhaps artificial) categories. In such cases, it is necessary to find a single value that is representative of the complete possible range. If the values in a population are normally distributed (that is, follow a bell-shaped curve), the mean or average will be the value that is both at the middle of the range and most commonly observed. The standard deviation is usually reported with the mean to give a sense of how closely grouped the other values are around the mean. Variables of this type are often referred to as being continuous. When the assumptions necessary for this approach are not met, categorization (as described above) may be used, or the median, the value at the middle of the range, may be reported instead. For example, in their report of a randomized trial of Echinacea for cold treatment, Barrett and colleagues found considerable skewness (uneven distribution) of cold severity ratings. To address this, they reported and tested median differences by treatment group as well as mean differences.[2]

Continuous and categorical variables each have a number of associated statistical tests that are used in assessing the significance of differences in observed values by categories or levels of some other variable. It is important to note that many tests, especially those used with continuous variables, have underlying assumptions that must be satisfied for the results they produce to be interpreted correctly — these are commonly called parametric tests. Often when one or more of these assumptions cannot be met, alternative tests are available — these are commonly called non-parametric tests. It can be difficult (and at times impossible) for the reader of a journal article to know whether all necessary statistical steps have been done as they should be, so it is all the more important for researchers to have good statistical advice in the design and analysis of their work. It is also important to note that the "best" test for any analytical situation may not be the most powerful or sophisticated one, but rather is the one that fits the available data and the assumptions that can or cannot be made about them. (*See Table.*)

Table

Variable Type	Reporting Format	Common Statistical Techniques
Categorical	Frequencies & percents	Chi-square test
		Fisher's exact test
		Logistic regression
Continuous	Mean & standard deviation	***Parametric***
	Median & range	Student's T-test
		Analysis of variance (ANOVA)
		Linear regression
		Non-Parametric
		Wilcoxon rank-sum test
		Kruskal-Wallis test

Statistical tests of comparisons in study data produce results that are not, by themselves, definitive. To provide the desired yes/no answer as to statistical significance, they must be judged according to a standard that is both uniform and decided upon in advance. Two common ways of doing this are with the use of p-values and confidence intervals.

The interpretation of statistical test results can be seen as the setting up of two opposing propositions:

- The test result we see is due to chance (the default option);
- The test result we see is not due to chance (i.e., the difference we observe in some characteristic across the levels of another characteristic really is as it appears).

Since either of these propositions may be true, our goal is not to show one or the other to be absolutely certain, but simply sufficiently more likely than the other to remove reasonable doubt. The definition of "sufficiently more likely" is straight-forward and mathematical — for example, 1 chance in 1000, or 1 chance in 100, or 1 chance in 20. The last option, expressed as a decimal (0.05) is by far the most common standard of improbability. In much of published science, any test result with a probability of less than 0.05 (i.e., 1 in 20) is deemed to be sufficiently extreme to justify rejecting the default assumption of a chance event in favor of the alternate view that the difference in the associated characteristic is really as observed. This probability estimate is referred to as the *P* value.

A second method begins from the observation that most characteristics can take on a value from a finite number of possibilities. Once that range is defined, it becomes predictive. For example, if we measured the heights of 1000 men, and calculated the minimum and maximum values, we could be fairly certain that the height of any additional man would also fall within that range. For characteristics of interest in research, and also for the results of statistical tests, the range of values — called the confidence interval — can be calculated if we have some basis for estimating the likely variability in the thing being measured. The overlap of confidence intervals, and the presence within them of values defined as indicating "no difference," is interpreted in a way that is parallel to *P* values.

Discussion of statistical significance leads logically to the topic of study power. Since we usually cannot capture an entire population (i.e., every woman with breast cancer or every person who takes garlic supplements), we use a sample. The larger the sample, the greater the chance that we will measure accurately the characteristics of the population is represents. However, practical concerns compel us to keep study samples within limits that are manageable and affordable. Calculations for study power and sample size tell us how large a sample is needed to meet two needs: 1) to ensure that if our study hypothesis is in fact false, we will not mistakenly conclude that it is correct (also called avoidance of "Type I" error), and 2) to ensure that if our study hypothesis is in fact correct, we will show it to be so (also called avoidance of "Type II" error). It is common practice to choose a sample size that allows no more than a 5% chance of a Type I error (this is the origin of near-universal < 0.05 threshold for *P* values), and no more than a 20% chance of a Type II error. The methods and equations associated with estimating power and sample size are sophisticated enough to require expert advice.

Although these details may seem arcane, the underlying points that they support can — and should — be expressed simply. Statistics and statistical tests are based in and flow from the actual data collected in the study. Because they are interpreted in much the same way by everyone, they permit the comparison of findings across studies. Because they play a role in what data will be collected, how those data will be collected, and how the questions that drive a study are answered, analytical and statistical details are important elements of study design from the very beginning.

This discussion of quantitative methods is important for an understanding of the later phases of a research project, but it should not distract from the goal it is intended to serve — the production of clinically and scientifically relevant information. Statistical significance should not be confused with clinical significance. It is possible to produce results that are statistically significant but practically irrelevant — this sometimes happens in very large studies. It is equally possible to produce findings that are statistically non-significant but of great clinical importance — this sometimes happens in very small studies.

The object of the interpretation of study findings should always be to bring things full-circle, back to the questions that prompted the research, and then to serve as the basis for the next set of questions, as well as for the improvement of clinical care. ■

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Define and Conquer? IM and GYN Cancer

ABSTRACT& COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *Results from this small pilot trial suggest that clinical hypnosis, massage, and energy work can all be offered to people receiving chemotherapy without interfering with conventional medical care. The findings also suggest little clinical benefit, but there are considerable study limitations, and the findings speak more to feasibility than to therapeutic utility.*

Source: Judson PL, et al. A prospective, randomized trial of integrative medicine for women with ovarian cancer. *Gynecol Oncol* 2011;123:346-350.

In a prospective, randomized controlled pilot trial performed at the University of Minnesota, researchers sought to assess the feasibility of providing integrative medical care (IM) to women receiving treatment for gynecologic malignancy. Women were eligible to participate if they had newly diagnosed ovarian, primary peritoneal, or fallopian tube carcinoma at any stage or histology, and were scheduled to receive at least six cycles of chemotherapy. Those subjects randomized to the control group received standard treatment for nausea and vomiting, and bone marrow support. While not prohibited, they were also encouraged not to seek complementary and alternative medical (CAM) therapies. Women randomized to the IM group received clinical hypnosis, massage therapy, and healing touch at the time of administration of chemotherapy. Participation in support groups was freely permitted.

Clinical hypnosis was performed three times in the presence of a hypnotherapist (chemotherapy cycles 1, 2, and 4). These sessions were recorded and patients were given headsets to listen to them whenever they desired and at chemotherapy cycles 3, 5, and 6. Prior to the first hypnosis session, subjects were given a pamphlet describing the therapy, and subjects were asked to identify their major concerns and ways they thought such concerns might be quelled. The content of the hypnosis sessions were then semi-structured to the individual's needs. The initial session lasted 60 minutes, all others were 30 minutes in duration, and afterwards the subject's experience with hypnosis was evaluated.

Therapeutic massage was administered with each cycle of chemotherapy for 30 minutes, using the same provider, with the patient resting in a chemotherapy recliner. Standard manual massage techniques were individualized and employed over the head, neck, shoulders, back, hands and/or feet.

Healing touch was delivered following massage therapy. Prior to the first session a handout describing healing touch was given to participants in the active group. Treatment was provided by one healing touch practitioner who was certified in the practice. Sessions were tailored to patients' needs and lasted 30 minutes.

At each chemotherapy visit subjects underwent performance assessment and laboratory testing that included immune parameters such as white blood cell count with differential, T and B-cell count, salivary IgA levels, and NK cell count. Quality of life was assessed prior to chemotherapy cycles 1, 3, and 6, as well as 6 months after chemotherapy was completed, using the FACT-O and Mental Health Inventory. Information on delays in chemotherapy protocol, infection rate, re-hospitalization rate, and antiemetic use was collected prospectively. Demographic and disease stage information were also collected.

A total of 43 women with ovarian, primary peritoneal, or fallopian tube cancer were recruited into the study, with 20 randomized to the control arm. The groups were comparable at baseline on the basis of demographics and disease state. One patient withdrew consent prior to receiving any treatment and was removed from analysis.

Multimodality IM was deemed both feasible and acceptable to all the women enrolled in the active arm. Each received the full slate of interventions in their chemotherapy chairs. The IM interventions did not interfere with the delivery of chemotherapy. Average FACT-O and MHI survey scores revealed no statistically significant differences between the groups at any time point. Save for some immune function measurements, no differences were found between the groups for any of the other parameters being followed. WBC counts were no different between groups, but compared to controls, participants receiving multimodal IM had consistently higher CD4, CD8, and NK cell counts at each cycle of chemotherapy. The differences were not statistically significant.

The authors concluded that offering combined IM therapies to women receiving chemotherapy for gynecologic malignancies is feasible and well-tolerated, but may not offer clinically important effects on quality of life as presupposed.

■ **COMMENTARY**

Women being treated for ovarian cancer report high levels of depression and anxiety. Many turn to CAM therapies for relief, and some trials have reported benefits on measures of emotional and physical well-being, and even on measures of immune modulators in some trials. Some consider the addition of CAM therapies to the conventional medical armamentarium equivalent to integrative care. It is not.

There are many ways that integrative medicine can be defined, but perhaps the most accepted definition comes out of the Arizona Center for Integrative Medicine at the University of Arizona: "Healing-oriented medicine that takes account of the whole person (body, mind, and spirit), including all aspects of lifestyle. It emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative." There are other important tenets, including that good medicine is based in good science, is inquiry-driven, and is open to new paradigms. But another central theme is individualization of care, and that's a major concern with this paper.

The authors of this well-done trial sought primarily to assess the feasibility of providing a preset combination of CAM therapies (clinical hypnosis, massage therapy, and healing touch/energy work) to patients in and around the time of administration of chemotherapy. They succeeded in showing that such an approach could be offered without interfering with conventional care and in a manner that was acceptable to participants. Keeping in mind the small sample size, the authors' assertion that the study was inadequately powered to determine the clinical impact of their multimodality CAM approach, and the lack of blinding, the conclusion that some will nonetheless glom onto is that little or no clinical benefit is associated with an "integrative oncology" approach. Consider, however, that three separate forms of care were offered at each chemotherapy session, and none (except for the opportunity to listen to hypnosis tapes) in between sessions. Consider that in a truly integrative approach the needs of the individual would determine whether or not hypnosis, massage therapy, and/or healing touch would be recommended at all. Consider that in reality many, if not most, patients receive the majority of CAM treatments before or after the date of chemotherapy administration, or that receiving three separate forms of care together with chemotherapy might be stressful and time-consuming for some. Lastly, consider that diet and lifestyle measures, the centerpiece of integrative care, were not the centerpiece of care.

A combined offering of preset CAM therapies to people on the day they are to receive chemotherapy is unique and potentially beneficial, but in and of itself does not set the standard for integrative oncology, where a given approach is decided upon and utilized based on the individual nature of the patient and her needs.

The study was very well done and shows that clinical hypnosis, massage, and energy work can be offered to patients, combined or separately, in the infusion center without disrupting care. The findings cannot reasonably be used to determine the clinical utility of this combination of therapies due to the shortcomings readily stated by the researchers, nor should it be used to judge integrative oncology as a whole. Grafting a set of CAM therapies onto the conventional medical treatment of cancer is not synonymous with integrative medicine. ■

MOTIVE-ation!

ABSTRACT & COMMENTARY

By Allan J. Wilke, MD

Professor, Department of Introduction to Clinical Medicine, Ross University School of Medicine, Commonwealth of Dominica

Dr. Wilke reports no financial relationships relevant to this field of study.

This article originally appeared in the December 29, 2011, issue of Internal Medicine Alert. At that time, it was peer reviewed by Gerald Roberts, MD, Assistant Clincial Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr Roberts reports no financial relationships relevant to this field of study.

Synopsis: *Behavioral therapy works as well as drug treatment for male overactive bladder.*

Source: Burgio KL, et al. Behavioral versus drug treatment for overactive bladder in men: The Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. *J Am Geriatr Soc* 2011;Nov 7. doi: 10.1111/j.1532-5415.2011.03724.x [Epub ahead of print].

BURGIO AND COLLEAGUES ENROLLED 203 MALE VETERANS (out of 360 assessed for eligibility), attending two VA Medical Centers in Alabama and Georgia, in this randomized, controlled equivalence trial of behavioral therapy (BEH) vs extended-release oxybutynin (OBN) for overactive bladder (OAB). All subjects underwent a clinical evaluation, which included urinalysis, urodynamic testing, post void residual volume (PVR) determination by ultrasound, and kept a voiding diary. They took the alpha-blocker tamsulosin 0.4 mg/d during a 4-week run-in pe-

riod and continued it throughout the study. Inclusion criteria were self-reported urgency, frequent urination, and > 8 voids/day. Exclusion criteria were recent urological surgery, bed-bound, urine flow rate < 5 mL/s at baseline or < 10 mL/s after run-in, PVR > 250 mL at baseline or > 150 mL after run-in, continuous urine leakage, urinary tract infection, hematuria, fecal impaction, diabetes mellitus in poor control, unstable medical condition, dementia, narrow-angle glaucoma, gastric retention, hypersensitivity to the study drugs, new onset diuretic therapy, and sleep apnea.

The subjects in the behavioral arm were seen by nurse practitioners (NPs) for a comprehensive training program. The NPs taught them how to contract and relax their pelvic floor muscles. They were also instructed on the techniques of delayed voiding and urinary urge suppression. Nocturia was specifically addressed. The BEH group was told to restrict their fluid intake after 6 p.m. They were taught that if they awoke with the urge to void, they were to lie in bed and try to suppress the urgency by contracting their pelvic floor muscles.

Subjects in the drug-therapy arm were started on extended-release oxybutynin 10 mg daily. The dose was titrated upward or downward at follow-up visits, depending on patient tolerance of side effects and whether PVR was greater than 150 mL, which would trigger a dose reduction.

The trial lasted 10 weeks. The primary outcome was the average number of voids in a 24-hour period. Secondary outcome measures included patient global ratings, ratings of activity restriction, and measures of how disturbing the symptoms and side effects of the treatment were. The subjects were also asked whether they wanted to continue their present therapy or receive another form of treatment.

After the alpha-blocker run-in, 143 of the 203 men who were enrolled continued to have OAB symptoms, 73 randomized to BEH and 70 to OBN. Nineteen subjects dropped out, 9 from BEH and 10 from OBN. The average age of the participants was 64 years (range 42-88), 64% were white, 35% black, and 1% Hispanic. Subjects in BEH reduced their daily voids from an average of 11.3 at baseline to 9.1 at the end of the trial (normal ≤ 8.) Similarly, subjects in the oxybutynin arm reduced their voids from 11.5 to 9.5. Both of these results were statistically significant. Before treatment, subjects in the behavioral arm averaged 2.2 episodes of nocturia per night vs 2.3 for subjects in OBN. Subjects in the behavioral arm had greater reduction in the number of nocturia episodes compared to the drug group (0.7 vs 0.32); this was statistically significant. When the investigators looked at mean urgency scores, OBN subjects had a statistically significant reduction compared to BEH. There was greater patient satisfaction among men in BEH, but this did not reach statistical significance. There were fewer men who complained of bothersome side effects in the behavioral group than the drug therapy group (12.6% vs 28.8%) and fewer wanted to change therapy (29.0% vs 50.0%). Both of these were statistically significant.

■ COMMENTARY

As these investigators define it, OAB is urinary urgency, urge incontinence, frequency, and nocturia. Nocturia, which is often associated with urinary frequency, is defined as an urge to urinate that awakens the person during the night. OAB is usually thought of as a syndrome that afflicts females. However, 17% of males older than 60 years in the United States suffer from it.[1]

Although alpha-blockers commonly are associated with relaxation of the prostatic and bladder neck smooth muscles, they also relax the bladder dome smooth muscle, which accounts for their efficacy in OAB. Antimuscarinic drugs inhibit the muscarinic receptors that mediate normal bladder contractions.[2] The oxybutynin-tamsulosin combination previously has been shown to be more effective than tamsulosin by itself,[3] although, as was shown in the run-in period of this study, tamsulosin by itself was effective for 60 men (30% of those enrolled). Like other antimuscarinic drugs, oxybutynin can cause serious reactions, such as heat stroke and psychosis. However, there are many common reactions (dry mouth, dizziness, constipation, etc.) that are bothersome enough for patients to abandon therapy. Ironically, one of the most common reactions is urinary retention, which is why these investigators were using PVR for monitoring the subjects who were using drug therapy. Normal PVR is less than 100 mL.

Pelvic floor muscle strengthening (also known as Kegel exercises) works on the pubococcygeal muscle and other pelvic diaphragm muscles. Although primarily known as treatment for female stress incontinence, Kegel exercises also have been used in men for incontinence following prostate surgery[4] and for premature ejaculation.[5] To my knowledge, there are no adverse effects of performing Kegel exercises. The main problem in prescribing this therapy likely will be convincing the patient to allow a NP to place a finger into his anus, which is how the NP will teach him to recognize which muscles to contract.

This study raises some questions. It was of brief duration. How long-lasting will the results be? The main limitation of this study was that it was conducted on men who were already taking an alpha-blocker, tamsulosin. Would a different alpha-blocker (terazosin, doxazosin, etc.) work as well? Would the results of the study have been the same if the subjects had not been taking an alpha-blocker? The investigators used extended-release oxybutynin with the patients in the drug-therapy arm. Would much cheaper, short-acting oxybutynin have been as effective? What about other antimuscarinic drugs? Extended-release tolterodine in combination with tamsulosin has also been

shown to be effective.[6]

The bottom line is this: Medication works for OAB, but behavioral therapy was as good as, if not better than, drug therapy for all outcome measures except urgency. The side effects of BEH are minimal, if not nonexistent. Antimuscarinic drugs have nontrivial side effects. Consider BEH and an alpha-blocker, unless urgency is the patient's overriding concern and he is willing to put up with the expense and side effects of oxybutynin. ■

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c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

1. Melatonin differs from the other supplements reviewed here because it:
a. does not occur naturally.
b. is an endogenous hormone in humans.
c. has serious adverse effects.
d. All of the above

2. The most commonly occurring adverse effects with the four sleep supplements reviewed here are:
a. serious allergic reactions.
b. cardiac complications.
c. heavy sedation.
d. mild and transient side effects.

3. The sleep supplements reviewed here with the best evidence to support some patients trying them for insomnia are:
a. valerian and chamomile.
b. melatonin and valerian.
c. lavender and melatonin.
d. chamomile and lavender.

4. Standard drug therapy for the treatment of over-active bladder, including alpha-blockers and oxybutynin, has been shown far superior to behavioral approaches.
a. True
b. False

5. Which of the following statements is *FALSE*?
a. Under the DSHEA guidelines, a supplement manufacturer is responsible for assuring the safety of a supplement prior to its being sold.
b. Use of HCG for weight loss is commonly recommended in association with a high-calorie diet.
c. Accepted indications for the use of HCG include cryptorchidism and the induction of ovulation.
d. HCG is generally accepted to be a pharmaceutical agent.

6. What is a Type I error?
a. Concluding that the study hypothesis is incorrect when it is, in fact, true
b. Concluding that the study hypothesis is correct when it is, in fact, false

In Future Issues:

Probiotics for Genitourinary Infections

Cholesterol-lowering Foods and Hyperlipidemia

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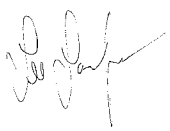

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