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Cognitive Behavior Therapy (CBT) vs Zopiclone for Treatment of Chronic Primary Insomnia in Older Adults

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta

Dr. Berga is a consultant for Pfizer, Organon, and is involved in research for Berlex and Health Decisions, Inc.

Synopsis: *Short-term and long-term measures of sleep improved more in those treated with CBT than with pharmacotherapy with a commonly prescribed hypnotic sleep medication unrelated to benzodiazepines or barbiturates.*

Source: Sivertsen B et al. Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults: a randomized controlled trial. *JAMA*. 2006;295:2851-2858.

PRIMARY INSOMNIA UNRELATED TO DEPRESSION IS A COMMON and debilitating condition that heightens the risk for accidents, cardiovascular disease, and other long-term health conditions. About 10-25% of adults older than age 54 years report insomnia defined as subjective complaints of poor sleep accompanied by impairment in daytime functioning. Insomnia encompasses complaints of insufficient sleep, difficulty initiating sleep, interrupted sleep, and poor-quality or nonrestorative sleep. Most individuals with chronic insomnia remain untreated and optimal treatment for those who seek help is controversial. Most primary care physicians prescribe pharmacotherapy despite the recognition that long-term use involves risks of dependency and tolerance. Further, next-day sleepiness due to pharmacotherapy has been linked to an increase in traffic accidents. No studies have compared newer nonbenzodiazepine sleep medications with nonpharmacological treatments and none have documented the impact of pharmacotherapy upon slow-wave sleep, which is felt to be the most restorative component. Indeed, most trials comparing sleep medications have

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relied on subjective rather than state-of-the-art objective measures. This randomized, controlled trial compared the impact of cognitive behavior therapy (CBT) with placebo and zopiclone, a commonly prescribed hypnotic unrelated to benzodiazepines or barbiturates. Both subjective (sleep diaries) and objective (polysomnography) measures of sleep were collected at 3 time points: before, 6 weeks, and 6 months. Active treatment lasted 6 weeks. Rigorous inclusion and exclusion criteria were used, including exclusion of those with depression and sleep apnea. Ninety two subjects were screened to enroll 48 participants: the mean age was about 61 years and roughly half were women. CBT included sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques.

At 6 weeks, total sleep time did not increase in any group but the amount of PSG-recorded slow-wave sleep (stages 3 and 4) improved significantly over time in the CBT group as compared with placebo and zopiclone groups. The zopiclone group had significantly less slow-wave sleep after treatment as compared with before. Subjective measures did not show any between-group differences. At 6 months, total sleep time increased significantly in the CBT group as compared with 6 weeks. There was no change at 6 months as compared with 6 weeks in the zopiclone group. Comparing the 2 active treatment conditions at 6 months, total wake-time, sleep efficiency, and slow-wave sleep were all significantly better in the CBT group than in the zopiclone group. In the CBT group, 72% had a sleep efficiency of at least 85% at 6 weeks while 78% fulfilled this criterion at 6 months. In contrast, only 47% of the participants in the zopiclone group had a sleep efficiency of at least 85% at 6 weeks and 40% at 6 months. The group differences were statistically significant at both 6 weeks and 6 months. In summary, CBT was more effective immediately and in the long term than both pharmacotherapy and placebo in older adults with chronic primary insomnia.

COMMENTARY

Insomnia increases with age and is a common office complaint. I suspect that most of us do not feel comfortable with this topic, which is one reason to bring this study and its results to your attention. The other main reason for highlighting this study is that it demonstrates the enduring impact of cognitive behavior therapy versus pharmacotherapy in the treatment of nonpsychiatric conditions which compromise quality of life and increase health burden. So what is CBT really? In the most simplistic terms, CBT is a form of "psychoeducation" in which an individual learns to harness the power of the mind to address a targeted symptom with the objective of gaining a tangible health benefit. The instructor can be a psychologist, social worker, or physician; it can be, but does not have to be, conducted by psychiatrist. It is common to use structured forms of CBT in which there is a manualized learning plan with specific modules that cover critical topics. Typically the modules are tailored to the condition being treated. Common uses of CBT include the treatment of stress, anxiety, depression, hypertension, back pain, head ache, premenstrual syndrome, and stress-related amenorrhea and infertility. The most impressive aspect of CBT is that its treatment effects typically not only endure but grow with time. CBT is sometimes coupled with pharmacotherapy for more serious conditions such as major depression or anorexia nervosa.

If CBT is so good, why not use it more commonly to treat a host of common conditions? Cost is low, but reimbursement may be denied. Patients and physicians are often skeptical. It does require an investment of time by both the patient and the healer. Perhaps the most common barrier, however, is unfamiliarity. Assuming that the patient does have a functional rather than an organic etiology for the symptom or complaint, CBT ought to be the first line of treatment for many common psychosomatic conditions. ■

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Black Cohosh and Menopausal Hot Flushes

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Black cohosh, when studied in appropriate randomized trials, is no different than placebo treatment in affecting hot flushing.*

Source: Pockaj BA, et al. Phase III double-blind, randomized, placebo-controlled crossover trial of black cohosh in the management of hot flashes: NCCTG Trial NO1CC1. *J Clin Oncol*. 2006;24:2836-2841.

POCKAJ AND COLLEAGUES FROM THE MAYO CLINIC reported the results of a double-blind, randomized, cross-over clinical trial to study the efficacy of black cohosh for the treatment of menopausal hot flushes.[1] The studied dose was 20 mg b.i.d. of *Cimicifuga racemosa* (the dose of the most commonly marketed black cohosh product in the United States, Remifemin). The similarity of the studied product with Remifemin was confirmed by high performance liquid chromatography and proton nuclear magnetic resonance analysis. 132 patients were treated for two 4-week crossover periods. Black cohosh reduced hot flushing scores by 20% in the fourth treatment week compared with 27% in the placebo group; and frequency was reduced 17% on black cohosh and 26% on placebo. The authors concluded that black cohosh had no effect on hot flushing beyond that of a placebo response.

COMMENTARY

Black cohosh is also called black snakeroot and bugbane. It has been heavily promoted, especially by German clinicians, for the treatment of menopausal hot flushes. We have learned that the study of hot flushing requires randomization to placebo treatment because placebo treatment is associated with an average 51% reduction in hot flush frequency.[2] Unfortunately, most of the reports supporting the efficacy of black cohosh were case series or studies without placebo control groups or the studies did not directly and quantitatively measure hot flushing.

"Remifemin" is commercially available, as an alcoholic extract of the root. Black cohosh has been reported to contain formononetin, a methylated precursor that is metabolized to the two primary phytoestrogens, genistein and daidzein. More sophisticated analysis, however, using liquid chromatography methods, has failed to detect the presence of formononetin in various black cohosh preparations, nor in black cohosh roots and rhizomes.[3]

An older clinical trial was noteworthy and alone in finding a similar impact on hot flushing with black cohosh and placebo treatment.[4] Finally, recent trials are confirming that early study and providing us with a uniform story. The Herbal Alternatives for Menopause (HALT) Study is centered in Seattle, Washington. This double-blind trial randomized 351 women to placebo or one of 4 treatment groups: (1) black cohosh 160 mg daily (note the higher dose); (2) a multibotanical treatment containing 50 mg black cohosh, alfalfa, chaste tree, dong quae, false unicorn, licorice, oats, pomegranate, and Siberian ginseng, 4 capsules daily; (3) the multibotanical plus counseling to increase dietary soy intake; (4) conjugated estrogens 0.625 mg with or without 2.5 mg medroxyprogesterone acetate.[5] After one year, no differences were observed in hot flushing comparing any of the 3 herbal treatment groups to placebo.[6] The herbal remedies also had no effect on sleep quality as reported after 3 months.[7]

How can I say it any stronger than this: black cohosh is not estrogenic, and black cohosh has no effect on menopausal symptoms. Thus far, all phytoestrogen products (this includes soy and red clover extracts) are proving to be no different than placebo for treating hot flushes. Estrogen products continue to be the most efficacious for this purpose. The serotonin uptake inhibitor class of antidepressants is next most effective. There has not been a head-to-head comparison study of estrogen and SSRIs, but it is reasonable to estimate that an SSRI will reduce hot flushing by about 60% compared to 90% suppression with estrogen. ■

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Initial Experiences with Bevacizumab in Recurrent Ovarian Cancer: Ouch!

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *Combination bevacizumab therapy demonstrated activity in heavily pretreated women with ovarian cancer. Gastrointestinal perforations were identified in 9%. Despite the toxicity of the regimen, prospective studies, particularly in less heavily pretreated patients, are warranted.*

Source: Wright JD, et al. Bevacizumab combination therapy in recurrent, platinum-refractory, epithelial ovarian carcinoma: a retrospective analysis. *Cancer*. 2006;107:83-89.

Bevacizumab is a fully humanized, monoclonal antibody targeting the proangiogenic factor, vascular endothelial growth factor or VEGF. Animal models documented this agent's efficacy in several solid tumors including ovarian cancer and phase III clinical investigation has confirmed its activity in some solid tumors. Given the relationship of angiogenesis and ovarian cancer, there has been great interest in the use of bevacizumab for ovarian cancer therapy. The authors of the current study reviewed their experience of bevacizumab, administered in combination with cytotoxic(s), to women with recurrent ovarian cancer. In this retrospective analysis, 23 patients were identified with at least assessable disease. The median number of prior regimens was 7, including a median 3 prior platinum regimens.

Overall, 8 patients achieved a response (all partial) for a response rate of 35%. Stable disease was observed in another 10. The median time to progression for responders was over 5 months and for those with stable disease over 2 months. Severe or life-threatening toxicity was observed in 4 (17%) patients including 2 patients with gastrointestinal perforation. In addition, 2 responding patients were found with chylous ascites, a rare complication in gynecologic malignancies. One patient also experienced a hypertensive encephalopathy. Despite these observed and unusual toxicities, the authors suggest the agent should be studied further in larger prospective trials of less heavily pretreated patients.

COMMENTARY

Clearly one of the most promising recent developments in solid tumors cancer management has been the discovery of agents targeting cell signaling and the tumor microenvironment. In a previous issue of *OB/GYN Clinical Alert (June 2006),* I reviewed the emerging strategy of angiogenesis targeting, which in tumors arising in the colon, kidney, breast and lung have been positively confirmed through the use of agents targeting the proangiogenic factor, VEGF. The agent furthest along in clinical development in this regard is bevacizumab, which has just begun phase III study in front-line ovarian cancer and, in the near future, recurrent ovarian cancer. As is frequently the case with many new therapeutics, initial experience is reported across a variety of tumors and clinical scenarios outside of the clinical study setting. While inference from these types of retrospective studies is limited, early warning signs of potential problems can emerge. The current study joins now 3 other completed trials in the literature—all in patients with heavily pretreated ovarian cancer.[1-3] With the exception of the Gynecologic Oncology Group (GOG) study, each has reported significant and/or life-threatening toxicity, particularly gastrointestinal toxicity in a sizeable proportion of treated patients. The GOG study, reported at the American Society of Clinical Oncology annual meeting in 2005, included patients with one or two prior regimens, and by design, were less heavily pretreated. The authors report just the second trial where bevacizumab has been administered in combination with a cytotoxic regimen. The response rates in their cohort are impressive, particularly given the amount of pretreatment their patients had endured. In the laboratory setting, synergistic effects of combination anti-angiogenic and cytotoxic therapy can be clearly confirmed in ovarian cancer models. It is unfortunately unknown to what degree toxicity will be similarly affected. The current environment reminds one of the early experience with paclitaxel, where unexpected bowel necrosis was

observed. It is likely future work with help to identify risk factors and situations (like bowel impending bowel obstruction) where the agent should be avoided. Currently we are very much in a "two steps forward, one step back" milieu, hopefully to be solidified with current and planned clinical investigation. ■

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Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided.*

Source: Cooper WO, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443-2451.

A POPULAR FAMILY OF ANTI-HYPERTENSIVE MEDICATIONS act by inhibiting angiotensin II converting enzyme. These ACE inhibitors have been implicated as adversely affecting fetal renal function but have generally been ignored as first trimester teratogens.

A report appeared in the June 8 issue of the *New England Journal of Medicine* in which the author searched a Tennessee Medicaid database for infants born between 1985 and 2000 who were exposed to antihypertensives during their mothers first trimesters. Through birth certificates, pharmacy records, etc, and after applying exclusion criteria such as diabetes and exposure to known teratogens, the authors came up with 411 infants who were exposed to antihypertensives in the first trimester and 29,096 infants who were not. In about half (209) the medication used was an ACE inhibitor and in the other half (202) other antihypertensive medications were used.

The results were fascinating. Those on antihypertensives tended to be older, showed up for care earlier, and, generally, had a higher level of education. The percentage of smokers was the same in all categories (29 to 30 % which seemed high). Most importantly, there was a 7.1 % incidence of congenital anomalies in the ACE inhibitor group, compared with 1.73 % in the group of infants exposed to other antihypertensives. The incidence of anomalies in the unexposed 29,096 control infants, was 2.63 %.

The most common anomalies seen in association with the ACE inhibitors involved the heart and CNS, where the odd ratios (OR) were 3.7 (95 % CI = 1.89-7.30) and 4.4 (95% CI = 1.7-14.02), respectively.

COMMENTARY

For some time it has been recommended that ACE inhibitors not be prescribed in pregnancy because of their potential for an adverse effect on the fetal renal system in the second and third trimester. However, little information has been available on their effect in the first trimester, and animal studies have generally yielded unexciting results with regard to teratogenicity.

ACE inhibitors are frequently employed in chronic hypertension because they are well tolerated and they work. Since about half of the pregnancies in the United States are unintended and even those with planned pregnancies may not get to see a provider until organogenesis is complete, a rather high percentage of women on ACE inhibitors will have fetuses that run a 7-fold greater risk of having a major congenital anomaly.

In looking at the data, it is clear, that once cardiac and CNS defects have been ruled out, the risk of other anomalies is no greater than that of the overall population of infants. Therefore, the diagnostic workup in those ACE inhibitors should start between 11 and 14 weeks with a nuchal translucency (NT) assessment (in those who seek care early enough to do this). Since about 50% of fetuses with cardiac anomalies will have an increased NT, these patients can be booked for an echocardiogram later. If early detection is essential for these patients, then a transvaginal fetal cardiac assessment can generally be accomplished prior to 16 weeks. Also, a combination of mater-

nal serum alpha-fetoprotein (MSAFP) and a comprehensive second trimester sonogram should be able to rule out most CNS anomalies. Last, patients should be reassured that they will run about a 93% chance that their fetuses will not have a major abnormality despite being exposed to the ACE inhibitors, and if the above studies are reassuring, the risk drops to almost zero. ■

Additional Reading

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Randomized Trial Comparing Axillary Clearance vs No Axillary Clearance in Older Patients With Breast Cancer

ABSTRACT & COMMENTARY

By Stuart M. Lichtman, MD

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Dr. Lichtman reports no financial relationship to this field of study.

Synopsis: *Avoiding axillary clearance for women 60 years of age and older who have clinically node-negative disease and receive Tam for endocrine-responsive disease yields similar efficacy with better early QoL.*

Source: International Breast Cancer Study Group. Randomized Trial Comparing Axillary Clearance Versus No Axillary Clearance in Older Patients with Breast Cancer: First Results of International Breast Cancer Study Group Trial 10-93. *J Clin Oncol*. 2006;24:337-344.

The incidence of breast cancer increases with age and breast cancer is the most common cancer in women older than 70 years old. In Western countries, approximately 50% of women with breast cancer are older than 65 years old. Given that populations are aging, increasing numbers of breast cancer occurrences can be expected among older women. Comorbid conditions also increase with age. Because these conditions may limit the duration and extent of a surgical procedure, there is a potential advantage to avoiding axillary surgery if it does not compromise tumor control. Avoiding axillary surgery might also reduce postoperative effects on arm pain, mobility, and lymphedema.

Recent data suggest that there is an association between increasing age at diagnosis and the presence of more favorable biologic characteristics of the tumor, such as greater expression of steroid hormone receptors, lower proliferative rates, diploidy, normal p53 expression, and the absence of overexpression of epidermal growth factor receptor and c-erbB-2. This trial investigated whether older patients with clinically node-negative and primarily endocrine-responsive early breast cancer might benefit from a change to the surgical approach that eliminates axillary lymph node dissection. This surgery usually represents the main cause of morbidity after a breast cancer resection, especially because such patients would receive adjuvant treatment with tamoxifen. Their study compares older patients undergoing breast surgery treated with axillary surgery versus patients who received no axillary surgery to determine the effect of axillary surgery on quality of life (QoL), disease-free survival (DFS), and overall survival (OS).

From May 1993 through December 2002, the study randomized 473 postmenopausal patients 60 years or older with clinically node-negative operable breast cancer were randomly assigned preoperatively to receive breast surgery with axillary clearance followed by tamoxifen (20 mg) for 5 years or breast surgery without axillary clearance followed by tamoxifen (20 mg) for 5 years. At the time of random assignment, estrogen receptor (ER) status and pathologic nodal status were unknown. In August 2002, the International Breast Cancer Study Group (IBCSG) Scientific Committee made a recommendation to discontinue tamoxifen for patients with endocrine-nonresponsive tumors. Surgery to remove the primary tumor was either a total mastectomy or breast-conserving surgery. On April 15, 1999, the original protocol was amended to allow institutions to perform sentinel node biopsy (SNB) in patients who had been randomly assigned to surgery, provided they then proceed to axillary clearance. However, only 2 patients used this option. Radiotherapy using 2 tangential fields was recommended after breast-conserving surgery.

There were 473 patients who were equally balanced according to randomly assigned treatment arm. The median age was 74 years and 22% of the patients had received prior hormone replacement therapy and 80% of

the patients had primary tumors classified as ER positive. Twenty-eight percent of the patients who had axillary clearance were found to have involved nodes. The median number of examined lymph nodes was 13. Forty-five percent of the patients were treated with mastectomy, 33% had breast-conserving surgery with radiotherapy, and 23% had breast-conserving surgery without radiotherapy. Physicians were asked whether the patient experienced restricted ipsilateral arm movement and whether the patient experienced arm pain. For both end points, we found a statistically significant increase in physician-reported adverse effects in the first postoperative period for patients who had an axillary clearance. However, after the immediate postoperative period, the percentage of patients for whom the physicians reported restricted arm movement approached the preoperative values in both groups. Similar results were observed for physician-reported arm pain. This difference between treatments was no longer statistically significant at later follow-up assessments. The proportion of patients that developed lymphedema, defined as a 5% or greater increase in arm circumference from baseline, was also not significantly different between treatments. Overall, the 2 treatment groups were similar with respect to both DFS and overall survival. Within the ER-positive cohort the 2 treatment groups were similar with respect to both DFS and OS. Similarly, no treatment difference was observed for the ER-negative cohort for DFS and OS without axillary clearance. Sites of first event were similar between the 2 treatment groups. A 2% incidence of axillary recurrence overall (as first event) and no statistically significant difference between the 2 treatment options. One patient, who did not receive an axillary clearance, experienced a subsequent axillary recurrence. All of the patients who had an axillary recurrence received a late axillary clearance after recurrence. Seventeen percent of the patients experienced a breast cancer-related recurrence, whereas 21% experienced a nonbreast second primary cancer or death without recurrence.

COMMENTARY

The morbidity of axillary dissection has led some investigators to question its necessity, whereas others have studied alternatives such as axillary radiation therapy and sentinel node biopsy. This randomized study examined the option of avoiding axillary surgery altogether and shows that in older women with clinically negative axillary examination, this transiently improves QoL apparently without compromising DFS or OS results. The median age of the patients enrolled into IBCSG Trial 10-93 was 74 years, which is substantially older than the median age in most adjuvant therapy trials conducted for postmenopausal patients. QoL measurements by both physician and patient showed significantly inferior arm-related QoL scores after axillary surgery. The authors concluded that axillary clearance does not contribute greatly to DFS or OS. Regional recurrence or reappearance of disease in the axilla was observed for only 2% of the patients overall (3% without axillary clearance and 1% with axillary clearance).

Given the postoperative morbidity and the decrease in QoL associated with axillary surgery, especially for this elderly population, the trial results provide important evidence to support the option of avoiding axillary clearance. A recent randomized study conducted by the Cancer and Leukemia Group B (CALGB)[1] evaluated the role of radiotherapy in older women with clinical stage I (T1, N0, M0) and ER-positive breast carcinoma treated with lumpectomy and tamoxifen for 5 years. In the CALGB trial, the axillary node dissection was allowed but discouraged, confirming our hypothesis that this approach is common in clinical practice in populations of women older than 70 years. In the CALGB trial, only 2 isolated axillary recurrences were found in women treated with lumpectomy and tamoxifen. Conversely, avoiding axillary clearance for older women with ER-negative tumors may not be as safe, as suggested by the overall outcomes reported in the IBCSG study. It may be argued that axillary surgery might still be worthwhile to determine whether to offer chemotherapy to these patients.

Although knowing the axillary nodal status may be necessary to choose the best adjuvant systemic therapy, it is less relevant in an elderly population at low risk and with a potentially shorter life expectancy. Thus, the recent trend to substitute sentinel node biopsy can also be called into question, given that this present results seem to support avoidance of axillary dissection. This line of reasoning is based on the prior supposition that chemotherapy should be used for older patients with node-positive disease, but not for patients with node-negative disease.

More recently, the endocrine responsiveness of the primary tumor, not the nodal status, is the relevant feature used for guidance in the decision whether to use chemotherapy. Data for the 50- to 69-year age group from the Early Breast Cancer Trialists' Collaborative Group Overview demonstrate that for patients with endocrine-responsive disease, endocrine therapy (specifically tamoxifen) provides the majority of the advantage associated with adjuvant treatments.[2] Thus, because nodal status is less relevant for determining whether chemotherapy is indicated, there

may be no need to perform even SNB procedures for an older woman with endocrine-responsive and clinically node negative disease. For older women who do require axillary dissection either because of clinical node involvement or because of a positive SNB, the results of this study are reassuring, demonstrating that for most of these women, there is little effect from this surgery on their long-term daily functioning or their QoL. IBCSG Trial 10-93 has demonstrated that avoiding axillary clearance for older women with clinically node-negative breast cancer who receive adjuvant tamoxifen seems safe and results in early improved QoL for this older population of patients. These results apply primarily for patients with endocrine-responsive disease in whom the use of tamoxifen is associated with substantial benefit in terms of disease control. For older women with endocrine-nonresponsive disease, the tailored use of adjuvant systemic chemotherapy is being investigated in a ongoing randomized clinical trials. ■

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CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

5. In the present study, sleep measures which improved more with CBT than pharmacotherapy included all on the following *except*:

a. sleep duration.
b. sleep efficiency.
c. slow-wave sleep.
d. self report.

6. The following statements are true regarding black cohosh *except*:

a. black cohosh does not contain a phytoestrogen.
b. the efficacy of black cohosh depends on administration.
c. doses even greater than marketed products have been ineffective.
d. black cohosh does not improve sleep quality.

Answers: 1 (d); 2 (b)

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The Safety of Long-Acting Beta Agonist Inhalers

Do long-acting beta agonist inhalers increase the severity of asthma? Yes, according to the results from a large meta-analysis recently published in the *Annals of Internal Medicine*. Pooled data from 19 trials with nearly 34,000 participants found that the long-acting beta agonists salmeterol, formoterol, and eformoterol were associated with higher rates of asthma exacerbations, requiring hospitalization, (odds ratio 2.6 [95% CI, 1.6-4.3]) and life-threatening exacerbations (odds ratio 1.8 [CI, 1.1-2.9]), compared to placebo. In subgroup analyses, the odds ratio for hospitalizations was 1.7 for salmeterol and 3.2 for formoterol. The risk of hospitalization was especially high in children on long-acting beta agonists (odds ratio 3.5 [CI, 1.3-9.3]). The odds ratio for adults was 2.0 (CI 1.1-3.9). Although the rate of death was low, the odds ratio for asthma-related death was 3.5 (CI, 1.3-9.3).

In the largest of the studies included in the meta-analysis, the Salmeterol Multicenter Asthma Research Trial (SMART), in which 26,000 patients were followed for 6 months on salmeterol or placebo, there was a 2-fold increase in life-threatening asthma exacerbations and a 4-fold increase in asthma related deaths. The authors conclude that long-acting beta agonist use increases the risk of hospitalizations due to asthma, life-threatening asthma exacerbations, and asthma-related deaths. The authors also conclude that inhaled corticosteroids cannot adequately protect against the adverse effects of these drugs (*Ann Int Med*. 2006;144:904-912).

An accompanying editorial suggests that physicians should follow current guidelines which emphasize use of inhaled corticosteroids as the first-line treatment for patients with mild-to-moderate persistent asthma. Only after maximal corticosteroid doses have been reached should long-acting beta agonist be considered (*Ann Int Med*. 2006;144:936-937).

The FDA met one year ago to discuss long-acting beta agonist and required black box warnings on the labeling for these drugs; however, there usage has changed very little in the ensuing year.

Treating Chronic Primary Insomnia

Cognitive behavioral therapy is more effective than zopiclone for the treatment of chronic primary insomnia in older adults, according to a new study from Norway. In a randomized, double-blind, placebo-controlled trial, 46 adults (mean age, 60.8; 22 women) with chronic primary insomnia were randomized to cognitive behavioral therapy, sleep medication with zopiclone 7.5 mg each night, or placebo for 6 weeks. The cognitive behavioral therapy consisted of 6 weekly sessions lasting 50 minutes that covered sleep hygiene education, sleep restriction, stimulus control, cognitive therapy, and progressive relaxation techniques. The main outcome was

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polysomnographic data and sleep diaries, which were used to determine total wake time, total sleep time, sleep efficiency, and slow-wave sleep.

Cognitive behavioral therapy (CBT) resulted in improved short-term and long-term outcomes compared with zopiclone on 3 of 4 outcome measures. CBT improved sleep efficiency from 81.4% to 90.1% at 6-month follow-up compared to a decrease from 82.3% to 81.9% with zopiclone. CBT resulted in better sleep architecture and less time awake during the night. Total sleep time was similar in all 3 treatment groups but, at 6 months, patients receiving CBT had better sleep efficiency than those taking zopiclone. The authors conclude that cognitive behavioral therapy is superior to zopiclone for management of insomnia, both in the short term and long-term. For most outcomes, zopiclone did not differ from placebo (*JAMA*. 2006;295:2851-2858).

Zopiclone is a new generation sleep medication available in Europe. The active isomer of zopiclone has been available in the United States since April 2005 (eszopiclone - Lunesta).

New Breakthrough in Smoking Cessation?

Varenicline, Pfizer's new smoking cessation drug, is the subject of 3 articles in the July 5 issue of *JAMA*. The drug, which is a partial agonist of the 4 2 nicotinic receptor, blocks the action of nicotine but provides a lower level of stimulation of dopamine release to reduce craving and withdrawal symptoms. Two of the 3 articles compared varenicline to bupropion and placebo in combination with behavioral counseling over 12 weeks of treatment. In both studies, varenicline was significantly more effective than placebo or bupropion (*JAMA*. 2006;296:47-55, 56-63). In the third study, 12 more weeks of varenicline was found to be significantly more effective than placebo in maintaining abstinence. This study also found that after 24 weeks of treatment, the benefit of the drug was maintained up to one year (*JAMA*. 2006;296:64-71). An accompanying editorial points out that while the studies of varenicline are promising and the drug represents a new agent with a different mechanism of action, it is not a panacea for smoking cessation, with quit rates still under 50% in these studies (*JAMA*. 2006;296:94-95). These studies could not come at a better time for Pfizer, as the company plans to market the drug within the next few months under the trade name Chantix.

FDA Actions

The FDA has given Biogen-Idec approval to resume marketing natalizumab (Tysabri) for the treatment of relapsing forms of multiple sclerosis. The monoclonal antibody was initially marketed in November 2004, but was withdrawn four months later, after three patients developed progressive multifocal leukoencephalopathy (PML) in clinical trials. Subsequent trials have not shown any additional cases of PML, but the drug is limited to use in patients who have failed or have not tolerated alternative therapies for multiple sclerosis. The re-approval is a restricted distribution program which includes registration of patients, prescribers, infusion centers, and pharmacies and includes patient education materials. Patients are also required to have a brain MRI prior to initiation of therapy. More information is available at: www.fda.gov/cder/drug/infopage/natalizumab/default.htm.

Duramed Pharmaceuticals have received approval to market a new 91 day birth control regimen consisting of 84 days of levonorgestrel 0.15 mg with ethinyl estradiol 0.03 mg, and seven days of ethinyl estradiol 0.01 mg (Seasonique). This product differs from the company's other 91 day birth control regimen (Seasonale) in that it incorporates estradiol rather than placebo for the last seven days in order to reduce bloating and breakthrough bleeding. Both products result in four menstrual periods per year.

The FDA has approved Genentech's ranibizumab (Lucentis) for the treatment of neovascular (wet) age-related macular degeneration (AMD). The drug, which is injected intraocularly, inhibits vascular endothelial growth factor A which is thought to contribute to proliferation, vascular leakage, and angiogenesis. Many ophthalmologists have been using Genentech's other anti-angiogenesis drug bevacizumab (Avastin) for the treatment of AMD, although it is not approved for this indication. Compounded bevacizumab injected intraocularly is approximately $17 per dose. Ranibizumab marketed as Lucentis is projected to cost approximately $2000 per dose.

Two former blockbuster drugs are making the switch to generics. Sertraline (Zoloft- Pfizer) will be available later this year in both generic pill and liquid form. In 2005, Zoloft was the most popular antidepressant in the US. The FDA has also approved a generic form of simvastatin (Zocor) Merck & Co.'s enormously popular statin for the treatment of hypercholesterolemia. Generic simvastatin is currently available 5, 10, 20, 40, and 80 mg strengths. ■