Tips from Other Journals

Tips from Other Journals are written by the medical editors of *American Family Physician.*

The trade names of drugs listed in Tips from Other Journals are based on what is currently available and not necessarily the brand of drug that was used in the study being discussed.

Does Valproate Prevent Relapse in Patients with Bipolar I Disorder?

Background: Bipolar disorder is a recurrent, chronic illness that is one of the most notable causes of disability in persons 15 to 44 years of age. The traditional maintenance therapy, lithium, has a narrow therapeutic index and significant adverse effects, leading to problems in adherence to therapy. Many alternative therapies have been proposed, particularly anticonvulsant and second-generation antipsychotic agents. Many patients do not respond to monotherapy, leading to the widespread use of combination treatments. The Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation study compared combination therapy of lithium plus valproate (Depacon) with monotherapy using either drug alone to prevent relapse of bipolar disorder.

The Study: Patients with a clinical diagnosis of bipolar I disorder were enrolled at 41 sites in Europe and the United States if the combination of lithium plus valproate was considered reasonable, if there were no contraindications to any of the study medications, and if the patient was judged to be likely to adhere to the assigned therapy. During the four- to eight-week run-in period, participants received therapy with lithium and valproate titrated to a target dosage of 1,250 mg per day of valproate (or the highest dosage tolerated) and serum lithium levels of 0.4 to 1.0 mmol per L. After the run-in period, participants were randomly assigned to one of three treatment groups: lithium monotherapy, valproate monotherapy, or continued combination therapy. In patients assigned to monotherapy, the discontinued drug was withdrawn during a four-week period to reduce the risk of precipitating relapse. Participants were maintained on the assigned therapy for two years or until treatment was proven ineffective. Investigators and participants were aware of treatment allocation, and additional therapies could be continued during the study.

The primary outcome was time to intervention for a new mood episode or hospitalization. Additional outcome measures included global assessment of functioning, quality of life determined by a questionnaire, and adverse effects. Analysis was by intention to treat.

Results: A total of 110 participants were assigned to each of the three treatment groups and were comparable in all important variables. Approximately 22 participants were lost to follow-up in each group. The hazard for the primary outcome was significantly lower for patients in the combination therapy group than for those allocated to valproate monotherapy, but was similar to patients allocated to lithium monotherapy. Similarly, the hazard of the primary outcome was lower for participants treated with lithium than for those receiving valproate. This benefit was most apparent in prevention of manic episodes and was maintained for at least two years. These results persisted after adjustment for relevant factors. Serious adverse events affected five participants during the run-in period and 16 participants after randomization. No suicides occurred during the study. No obstetric complications or congenital abnormalities were noted in the five women who became pregnant during the study.

Conclusion: The authors conclude that lithium and valproate combination therapy is more likely than valproate monotherapy to prevent relapse of bipolar I disorder. Lithium monotherapy also seems more effective than valproate monotherapy. In this study, no significant differences were detected between combination therapy and lithium monotherapy. The study authors acknowledge several limitations and suggest that current guidelines recommending valproate as first-line long-term therapy might be improved by changing that recommendation to combination therapy or lithium monotherapy.

ANNE D. WALLING, MD

Source: Geddes JR, et al.; BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet.* January 30, 2010;375(9712):385-395.

Patient Preference in Treating Depression in Persons with ACS

Background: Persons with acute coronary syndrome (ACS) and depressive symptoms are at higher risk of further coronary events. Few studies of this population have been done, which has impaired the ability to detect whether treatment of depression may improve outcomes in this population. Davidson and colleagues attempted to determine if the Coronary Psychosocial Evaluation Studies (COPES) intervention improved patient satisfaction with depression care.

The Study: The authors of the COPES trial randomized 157 patients with ACS and depressive symptoms to receive usual care or enhanced depression care for six months. Patients in the enhanced care group were allowed to choose whether they would receive medication, problem-solving psychotherapy, or both. In contrast, depression treatment for those in the usual care group was left up to their regular managing physician; the physicians were notified if their patients had elevated depressive symptoms. A separate cohort of 80 nondepressed patients with ACS was also observed during the study. The primary outcome was satisfaction with depression care; the first occurrence of a major adverse cardiac event was recorded as a secondary outcome.

Results: By the end of the study, both antidepressant and psychotherapy use were greater in the enhanced care group (48 and 39 percent, respectively) than in the usual care group (30 and 12 percent, respectively). Significantly more patients in the enhanced care group believed that their depression care was very good compared with patients in the usual care group (54 versus 19 percent). Although depressive symptoms improved in both groups, greater improvement occurred in the enhanced care group than in the usual care group (mean of 5.7-point reduction versus 1.9-point reduction on the Beck Depression Inventory). The major adverse cardiac event rate in the enhanced care group was similar to that in the nondepressed observational cohort (4 versus 6 percent, respectively), and was significantly lower than in the usual care group (13 percent).

Conclusion: The authors conclude that allowing patients with ACS and depressive symptoms to choose the type of depression treatment significantly improves their satisfaction with care. Fewer subsequent cardiovascular events occurred in this group; however, the authors caution that their study was not fully powered to investigate this outcome.

KENNETH T. MOON, MD

Source: Davidson KW, et al. Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. *Arch Intern Med.* April 12, 2010;170(7):600-608.

High Soy Food Intake May Improve Breast Cancer Survival

Background: Estrogen is thought to play a major role in breast cancer growth; therefore, blocking estrogenic exposure or effects is widely used in breast cancer therapy. Soy foods are rich in isoflavones, which have both estrogen-like and antiestrogenic actions. Although American women eat significantly less soy than Chinese women (1 to 6 mg per day of isoflavones compared with 47 mg per day), soy consumption is increasing in the United States and, with it, the concern that soy isoflavones may exert estrogenic effects and promote cancer recurrence. Reports also suggest that soy isoflavones may interact with tamoxifen. To date, ▶

there has not been a comprehensive study evaluating the effect of soy food consumption on breast cancer recurrence and survival. Shu and colleagues analyzed data from the Shanghai Breast Cancer Survival Study, a longitudinal cohort study, to assess the relationship between soy food consumption and breast cancer recurrence.

The Study: Study participants were women identified through the population-based Shanghai Cancer Registry who were 20 to 75 years of age and were diagnosed with primary breast cancer between March 2002 and April 2006. Recruitment occurred approximately six months after diagnosis. The researchers conducted in-person standardized interviews with a validated questionnaire to assess baseline demographic data, including reproductive history, disease history, lifestyle factors, diet, use of complementary medicine, and quality of life. Specific dietary habits were assessed at baseline to review intake for the preceding six months, at 18 months for the preceding 12 months, and at 36 months for the preceding 18 months. The 60-month review is ongoing. The food frequency questionnaire measured consumption of commonly used soy foods, including tofu, soy milk, and fresh soybeans. The primary end points were all-cause mortality and cancer recurrence/metastasis or death related to breast cancer. Cox proportional hazard models were used to evaluate the relationship between soy intake and the study outcomes. Soy protein and soy isoflavones were categorized by quartiles of intake amount.

Results: Of 6,299 women identified through the registry, 5,042 (80 percent) consented to participate. Nine were excluded because they did not have surgical treatment. Follow-up ranged from 0.5 to 6.2 years, with a median of 3.9 years; 444 total deaths and 534 breast cancer recurrences or cancer-related deaths occurred in the cohort. Advanced age or disease stage at diagnosis, negative estrogen or progesterone receptor status, low education level or income, presence of comorbidities, more than three pregnancies, and receiving radiation therapy were inversely associated with survival. Use of tamoxifen and previous use of hormone therapy for menopausal symptoms were directly associated with survival. Women in the highest quartile of soy intake had significantly decreased four-year mortality and recurrence rates compared with those in the lowest quartile (multivariate-adjusted mortality: 7.4 versus 10.3 percent; recurrence: 8.0 versus 11.2 percent). The survival benefit of soy followed a linear dose-response curve until soy protein intake reached 11 g per day (40 mg per day of soy isoflavone). The benefit did not vary with the presence of estrogen receptors or menopausal status. Tamoxifen use in women who were estrogen receptor positive was not adversely affected by soy intake.

Conclusion: The authors conclude that soy food intake is safe and is associated with improved survival in women with breast cancer, but no additional benefit occurs once soy protein intake exceeds 11 g per day.

AMY CRAWFORD-FAUCHER, MD

Source: Shu XO, et al. Soy food intake and breast cancer survival. *JAMA.* December 9, 2009;302(22):2437-2443.

EDITOR'S NOTE: An accompanying editorial by Ballard-Barbash and Neuhouser reminds us that, although these results show a positive benefit to soy intake and should be reassuring to survivors of and patients with breast cancer in the United States, more study is needed. Significant differences may exist between the Chinese and U.S. populations that could limit generalizability. Different rates of breast cancer screening could skew the proportion of ductal carcinoma in situ (DCIS) to invasive breast cancer cases, and subsequent survival rates. There were relatively few patients with DCIS in the Chinese study, whereas up to 20 percent of U.S. women with breast cancer have DCIS.[1] The four-year median follow-up is also relatively short, which may not reflect true long-term effects.

Because outcomes were based on disease-free and survival times, accurate staging at study intake is vital; the authors note that disparities in medical record keeping and abstraction between China and the United States could limit comparison between stage- and treatment-specific results. Additionally, larger cohorts are needed to better describe the effects of soy on clinically relevant subgroups, including estrogen receptor status ▶

and tamoxifen use. Finally, not only is soy consumed in much lower quantities in the United States, but soy supplements are used more often; this study does not address the safety or effectiveness of soy components. Despite these limitations, the authors agree that women who have breast cancer and those who have survived the disease should feel comfortable eating soy foods.—A.C.F.

REFERENCE

1. Ballard-Barbash R, Neuhouser ML. Challenges in design and interpretation of observational research on health behaviors and cancer survival [Editorial]. *JAMA.* 2009;302(22):2483-2484.

Long-Term Antibiotic Use Benefits Patients with Crohn Disease

Background: Studies have shown that the underlying pathogenesis of Crohn disease may involve microbial penetration of the bowel mucosal barrier; therefore, antibiotic therapy should be beneficial. Nevertheless, current guidelines recommend antibiotic therapy only for sepsis, bacterial overgrowth syndromes, or perianal disease. Feller and colleagues conducted a meta-analysis of all reported clinical trials of long-term antimicrobial therapy for Crohn disease.

The Study: The authors searched Medline, EMBASE, and the Cochrane Central Register of Controlled Trials to identify eligible studies. The references of all identified articles were also checked for additional studies. Eligible trials randomly allocated participants to treatment and placebo groups and lasted at least three months. Studies restricted to perianal disease were excluded from the meta-analysis.

Data about the study conduct and outcomes were independently extracted by two researchers. Drugs from the same class were analyzed together (e.g., the antituberculosis agents rifampicin [available as rifampin in the Unites States], isoniazid, and ethambutol).

Results: Of the 43 identified studies, 16 trials involving more than 800 patients met eligibility criteria. The quality of reporting study methods was low, with only four studies adequately describing allocation concealment. Eleven studies involved patients with active disease, and three studies concerned patients with inactive disease. Four studies did not report diagnostic criteria for Crohn disease.

The 13 different treatment regimens studied ranged from single agents to combinations of four different drugs. Antituberculosis drugs and nitroimidazoles were each used in three studies; clarithromycin (Biaxin) and clofazimine were each used in four studies. Three studies incorporated steroid therapy, seven studies allowed steroids if clinically indicated, and four studies excluded steroid use. The median duration of treatment was six months.

The principal outcome was remission or recurrence of symptoms. The Crohn's Disease Activity Index was used to assess outcomes in 11 studies, and another disease activity index was used in an additional four studies.

The combined odds ratio (OR) from the three studies of 107 patients treated with antituberculosis drugs was 0.58, indicating no benefit. The three studies involving 206 patients treated with nitroimidazoles reported a combined OR of 3.54, indicating benefit.

Similarly, benefit was demonstrated in the four studies involving 322 patients treated with clofazimine (OR = 2.86) and one trial using ciprofloxacin (Cipro; OR = 11.3). Little evidence of benefit was found in a trial of rifaximin (Xifaxan) or a trial of sulfadoxine/pyrimethamine. Results from the four studies using clarithromycin (287 patients) were heterogeneous and were excluded from the meta-analysis. The estimated number needed to treat to keep one additional patient in remission was 3.4 for nitroimidazoles and 4.2 for clofazimine.

Conclusion: The authors conclude that patients with Crohn disease receive substantial benefit from three or more months of therapy with nitroimidazoles and clofazimine. The authors found one trial that supported ciprofloxacin use. Little evidence of benefit was found for clarithromycin or classic antituberculosis drugs.

ANNE D. WALLING, MD

Source: Feller M, et al. Long-term antibiotic treatment for Crohn's disease: systematic review and meta-analysis of placebo-controlled trials. *Clin Infect Dis.* February 15, 2010;50(4):473-480. ■