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INSIDE

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Constipation, Cardiovascular Disease, and the Connection

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

Dr. Gupta reports no financial relationship relevant to this field of study.

Synopsis: *In postmenopausal women, constipation is associated with having major risk factors for cardiovascular disease and increased cardiovascular risk.*

Source: Salmoirago-Blotcher E, et al. Constipation and risk of cardiovascular disease among postmenopausal women. *Am J Med* 2011;124:714-723.

CONSTIPATION IS ONE OF THE MOST COMMON PRESENTING COMPLAINTS in a primary care practice. Estimates of population-based studies conducted in North America reveal that up to 27% of individuals may experience constipation, with most estimates ranging from 12% to 19%.[1] Managing constipation is often frustrating and associated with substantial economic costs to the health care system.[2] Constipation is often treated on the basis of a patient's impression that there is a disturbance in bowel function. However, I must admit that I have often enjoyed having medical students and residents struggle with attempting to define something as simple as constipation. This is because constipation often has wide-ranging interpretations for most people. In clinical practice, constipation is generally defined as fewer than three bowel movements per week. While the rates for constipation are on the rise, especially in women and the elderly, very little is understood about the pathophysiology of this common clinical disorder.[3] Many of the risk factors associated with constipation, such as diabetes mellitus, hormonal abnormalities, and neurologic diseases, also contribute to cardiovascular disease. Therefore, it is reasonable to explore whether there may be a direct link between constipation and car-

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diovascular disease in the adult population.

In their study, Salmoirago-Blotcher et al conducted an analysis in 93,676 women enrolled in the observational arm of the Women's Health Initiative. The duration of follow-up in this group of postmenopausal women was between 6 and 10 years and information about constipation was collected by means of a self-administered questionnaire. For this study, the authors defined constipation as "difficulty having bowel movements" over the previous 4 weeks, and this was rated using a scale ranging from none (symptom did not occur), mild (symptom did not interfere with usual activities), moderate (symptom interfered somewhat with usual activities), to severe (symptom was so bothersome that usual activities could not be performed). The study outcomes, identified by self-report, were coronary heart disease, stroke, breast and colorectal cancer, osteoporotic fractures, diabetes, and total mortality.

Due to exclusions, the final analysis included 73,047 women. Researchers found that women with moderate and severe constipation experienced more cardiovascular events (14.2 and 19.1 events/1000 person-years, respectively) compared with women with no constipation (9.6/1000 person-years). Researchers also found that constipation was associated with the following factors: increased age, African American and Hispanic descent, smoking, diabetes, high cholesterol, family history of myocardial infarction, hypertension, obesity, lower physical activity levels, lower fiber intake, and depression. However, after adjusting for these factors, constipation was no longer associated with an increased risk of cardiovascular events, except for the severe constipation group, which had a 23% higher risk of cardiovascular events.

The authors conclude that in postmenopausal women, while evidence for an independent association or for a causal association between constipation and cardiovascular disease was not found, constipation is a marker for the major risk factors for cardiovascular disease and increased cardiovascular risk. Thus, they state that because constipation is easily evaluated in a primary care setting, it may be a helpful tool to identify postmenopausal women who may be at increased cardiovascular risk.

■ COMMENTARY

We know that although constipation is a common condition, only a proportion of the affected individuals will seek health care for their symptoms. However, this does not stop people from utilizing health care resources to attempt to self-treat the condition. On the other hand, cardiovascular disease remains one of the leading causes of morbidity and mortality in women in the United States. Women fare less well than men after a myocardial infarction or cardiac interventions. Their short- and long-term prognosis is worse and the likelihood for adverse events is higher than in men. The postmenopausal state itself renders a woman at higher likelihood for cardiovascular disease.

While the results of this study are not conclusive enough to warrant definitive recommendations, they may provide valuable information regarding health and lifestyle choices of the patients being seen. Along with recommending diet and lifestyle changes, physicians can potentially use constipation in postmenopausal women as another opportunity to discuss cardiovascular risks with the patients as well as to conduct an evaluation for factors such as hypertension, hyperlipidemia, obesity, and smoking status. ■

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We Can Help our Seniors Sleep Better Without Dangerous Pills

ABSTRACT & COMMENTARY

By Joseph E. Scherger, MD, MPH

Vice President, Primary Care, Eisenhower Medical Center, Clinical Professor, Keck School of Medicine, University of Southern California

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

Synopsis: *A brief amount of face-to-face and telephone counseling helps seniors sleep better without prescription medications. Direct counseling is superior to giving reading materials.*

Source: Buysse DJ, et al. Efficacy of brief behavioral treatment for chronic insomnia in older adults. *Arch Intern Med* 2011;171:887-895.

Any primary care physician treating seniors has patients asking for various pills for sleep. Most of these are sedatives or hypnotics that are on the danger list for seniors due to increased falls and mental health complications. Seniors are often insistent to get these prescriptions in order to get a good night's sleep. We make other suggestions for better sleep but usually these fall on deaf ears.

In this encouraging study, 79 seniors with chronic insomnia were recruited from one primary care clinic and the community to participate in a randomized trial of brief behavior therapy or receiving reading materials to improve their sleep. The seniors were willing to keep a sleep diary and have in-home polysomnography. They were randomly assigned to receive two brief sessions with a nurse practitioner with no special training in cognitive behavior therapy to discuss methods for better sleep, and received two follow-up phone calls. The other group received reading materials that discussed better sleep methods and received one follow-up phone call.

After 4 weeks, 55% of the brief therapy group reported "no insomnia" compared with 13% of the reading group. Sixty-seven percent of the brief therapy group had a positive response to the treatment compared with 25% of the reading group. There was no change in the polysomnography. These improvements were maintained after 6 months.

■ COMMENTARY

This study group is part of the Sleep Medicine Institute in the Department of Psychiatry at the University of Pittsburgh. The authors believe that the face-to-face intervention made the difference in treatment, giving patients time and instruction. No special therapy was required for the results. Obviously, a major limitation of the study was that the patients were motivated to enroll in such a study. The study did not focus on any change in use of medications, and there was no difference between the two study groups on medication use.

Getting seniors off sleeping pills — and avoiding them in the first place — takes special effort and I work on it diligently with some success. We teach children how to go to sleep, a challenge of early parenting, but it seems that adults and seniors often forget how to fall asleep effectively. They have trouble disconnecting their current troubles from their mind and going to a place that is hypnotic. Declining melatonin levels with age may also play a role in decreased sleep for many seniors.

Behavioral treatment for chronic insomnia has a long research history.[1] This study shows that a modest amount of effort is effective in helping seniors overcome insomnia and sleep better. No special training is required — attention, good advice, and follow-up is all that's needed. Personally, I am fairly liberal with the use of melatonin as an optional sleep aid to go along with this counseling. I explain to seniors about the pineal gland that secretes melatonin and how it often calcifies with age with decreased melatonin levels. Melatonin is not a "knock-out" pill, but if taken 30 minutes or more before sleep in an effective dose (usually 5-6 mg), it helps the senior struggling to sleep to do so more effectively, for 6 hours or longer.

Sleep is important for cognitive function, cardiac health, and patient safety, just to mention a few of its many benefits. I've heard sleep described as the "third pillar" of a healthy lifestyle along with nutrition and physical activity. Focusing effectively on healthy sleep for our patients is of major importance to primary care, and this study provides a good way for us to do that. ■

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Why You Should Outsource Your Weight Loss Treatment

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips serves on the speakers bureaus for Cephalon, Resmed, and Respironics.

Synopsis: *Participation in Weight Watchers resulted in a greater weight loss over a year than did clinical intervention in a primary care office.*

Source: Jebb SA, et al. Primary care referral to a commercial provider for weight loss treatment versus standard care: A randomised controlled trial. *Lancet* 2011; doi:10.1016/S0140-6736(11)61344-5.

THIS STUDY (WHICH WAS FUNDED BY WEIGHT WATCHERS) was a multicenter, randomized, controlled trial involving patients recruited from primary care practices in Germany, Australia, and the UK. To be included, patients had to have body mass index (BMI) of 27-35 kg/m^2 and at least one additional risk factor for obesity-related disease, including central adiposity, type 2 diabetes without insulin treatment, family history of diabetes, previous gestational diabetes, impaired glucose tolerance, dyslipidemia, hypertension, polycystic ovarian syndrome, lower-limb osteoarthritis, or abdominal hernia. People were excluded for a variety of reasons, including having had a weight loss of 5 kg or more in the previous 3 months, eating disorders, limitations to regular physical activity, untreated thyroid disease, ongoing or past surgical treatment for weight or appetite, and insulin-treated diabetes. Participants were randomized to receive 12 months of free access to a Weight Watchers program or 12 months of standard care, as defined by national treatment guidelines in the three participating countries.[1-3] A total of 772 people were recruited, screened, and randomized, and were assessed at 2, 4, 6, 9, and 12 months with measurements of weight, fat mass, waist circumference, blood pressure, and biomarkers of cardiovascular risk, as well as self-reported data about food intake and physical activity. The Weight Watchers program was more intensive; participants attending assessment visits for standard care reported a mean of one appointment per month with their health care provider, but those assigned to the Weight Watchers group attended a mean of three meetings per month in the UK and Australia and two meetings per month in Germany.

The dropout rate was high, with only 61% of those in the Weight Watchers group and 54% of those in the "standard care" program completing the full 12 months of assessment. Notably, the patients from Germany were much less likely to drop out; 75% of them completed the study. Participants who completed the 12-month assessment were significantly older at baseline (mean, 50.2 years) than were those who did not (43.6 years), but there were no significant effects of sex, baseline weight, or diabetes status on whether individuals completed the 12-month assessment. Of those who completed the year of follow-up, those in the Weight Watchers group lost about twice as much weight as those in the usual care group: 5.06 kg (11 lbs) vs 2.25 kg (5 lbs). Those in the Weight Watchers program were also more likely to lose at least 5% or 10% of their weight. Participants randomized to the commercial program also had larger reductions in waist circumference, fat mass, insulin, and ratio of total to HDL cholesterol. There were small reductions in blood pressure in both treatment groups. No adverse events were reported by either group.

■ COMMENTARY

I found the results of this trial dismal, but not surprising. The most discouraging thing was that only slightly more than half of the people (who were motivated enough to enroll and go through screening) completed the trial. It is probably safe to say that those who didn't finish the study probably didn't lose any weight. Also discouraging is that those who *did* complete the most effective protocol only lost about 11 pounds on average. Obesity is a chronic, intractable disease. And dealing with it consumes a great deal of time and emotional energy in almost every aspect of medicine. This report confirms and extends other studies of commercial weight loss programs, including Weight Watchers and Jenny Craig, demonstrating that these types of programs are more effective in addressing the intractable problem of obesity than are interventions in clinicians' offices.[4-8] As a physician who is confronted daily by the implacably obese, I find this to be powerful, time saving-information. Specific referral to a commercial weight loss program may result not only in greater weight loss for my patients, but also in reduced angst, wasted time, and reprimands by customer service personnel for me. ■

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Relationship Between Activity Levels and Cognitive Impairment in Older Adults

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman serves on the speakers bureau for Forest Laboratories.

Synopsis: *Greater daily activity energy expenditure appears to reduce the incidence of cognitive impairment in a dose-response manner.*

Source: Middleton LE, et al. Activity energy expenditure and incident cognitive impairment in older adults. *Arch Intern Med* 2011;171:1251-1257.

Multiple published studies have clearly demonstrated that people who are more physically active in midlife and in late life have lower rates of dementia and cognitive impairment as they reach late life; in other words, physical activity appears to be one of the best preventive strategies against cognitive impairment in the elderly population.[1-5] These studies have all been dependent on self-reporting of physical activity which, of course, may be inaccurate, especially in people with cognitive dysfunction. Self-reported physical activity correlates only moderately with objective measurements[6] and often excludes activity not readily quantifiable by frequency and duration.

Middleton and her colleagues investigated the relationship between activity energy expenditure (AEE), which is an objective measure of total activity, and the incidence of cognitive impairment.[7] Total energy expenditure between two clinic visits approximately 15 days apart was measured by using the doubly labeled water (DLW) method.[8-10] Activity energy expenditure was calculated as 90% of total energy expenditure minus the resting metabolic rate, which was carefully measured. After adjustment for baseline Modified Mini-Mental State Examination scores, self-reported health, and the presence or absence of diabetes mellitus, older adults in the highest sex-specific tertile of AEE were found to have lower odds of having incident cognitive impairment than those individuals in the lowest tertile. There was also a significant dose response between AEE and the incidence of cognitive impairment.

■ COMMENTARY

Many published studies have reported that people who are more physically active have lower risk of developing cognitive impairment in older age.[2-5] The currrent study[7] confirms this conclusion by providing new evidence that objectively measured total daily activity is associated with a significantly reduced incidence of cognitive impairment. Although it is still not clear whether the physical activity has to be moderate or vigorous, or whether even low-intensity physical activity will produce the same degree of cognitive impairment reduction, there appears to be a strong dose-response relationship between the amount of energy expenditure and the resulting cognitive impairment. The mechanism by which the lack of adequate physical activities is related to impairment in late-life cognition is uncertain; however, results of some research studies have suggested that physical activity may improve neuroplasticity by modifying levels of brain-derived neurotrophic factor.[11-13] In addition, increased physical activity appears to be associated with a reduced accumulation of beta-amyloid plaque, which has been demonstrated to be present in individuals with Alzheimer's disease.[14] Finally, regular physical activity is associated with reduced rates and severity of vascular risk factors including hypertension, obesity, and type II diabetes mellitus, each of which is associated with an increased risk of cognitive impairment.

Multiple studies, including the Middleton study,[7] have strongly suggested that increased levels of AEE on a daily basis are associated with a reduced incidence of cognitive impairment in older adults. Hopefully, it will be demonstrated that even low-intensity activities of daily living (which can be performed by virtually all older adults) provide sufficient excercise intensity to prevent progressive cognitive impairment. In summary, physicians should encourage couch potatoes — no matter what their age — to get up and get moving in a motivated and meaningful manner to reduce their chances of developing cognitive impairment. ■

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Pharmacology Update

Crizotinib Capsules (Xalkori®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

A NEW ORALLY EFFECTIVE TARGETED THERAPY FOR THE treatment of non-small cell lung cancer (NSCLC) has been approved by the FDA. Crizotinib is a receptor tyrosine kinase inhibitor including anaplastic lymphoma kinase (ALK). A companion diagnostic test (Vysis ALK Break Apart FISH Probe kit) was also approved to identify the target population. Crizotinib was approved under the agency's accelerated approval program and is marketed by Pfizer as Xalkori.

Indications

Crizotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC who are ALK-positive.[1]

Dosage

The recommended dose is 250 mg taken orally twice daily with or without food.[1] The dose may be interrupted or reduced to 200 mg twice daily or to 250 mg once daily due to individual safety or tolerability.

Crizotinib is available as 250 mg and 200 mg capsules.

Potential Advantages

In patients with advanced ALK-positive NSCLC, the overall response rate ranged from 50-61%.[1,2]

Potential Disadvantages

Common adverse events include vision disorder (62-64%), gastrointestinal-related events (40-57%), edema (28-38%), and fatigue (20-31%).[1] Severe adverse events, including fatal pneumonitis, have been reported with a frequency of 1.6%. Concomitant administration of crizotinib and strong CYP3A inhibitors or inducers should be avoided. Dose reduction may be needed for drugs that are substrates of CYP3A and plasma levels of substrates of p-glycoprotein may be increased. Crizotinib can increase ALT and may prolong QTc interval.

Comments

Crizotinib is a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor. It has been shown to be effective in ALK-translocation-positive patients with NSCLC.[2] The approval of crizotinib was based on two multicenter, single-arm studies in patients with late stage ALK-positive NSCLC (n = 255).[1] The primary endpoint was objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumor (RECIST). ORR was 50% in one study (95% confidence interval [CI], 42%, 59%) and 61% in the second study (95% CI, 52%, 70%). Fifty-five percent (55%) to 79% of responses were achieved within the first 8 weeks of treatment. Median response durations were 41.9 weeks in the first study and 48.1 weeks in the second study. Dose interruptions were required in 36-45% of patients and dose reduction was required in 29% to 44%. Improvement in survival has not been demonstrated.

Clinical Implications

Crizotinib provides effective therapy for a small subset of patients with NSCLC, however, improved survival has yet to be demonstrated. The prevalence of ALK-positive disease is estimated to be 1-7%.[3] Those with ALK-rearrangement tend to be younger, with little or no tobacco exposure, and have adenocarcinoma.[2] ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

CME Questions

1. **In the relationship between constipation and cardiovascular disease in postmenopausal women, which of the following statements is *false*?**
   a. There is a causal association between constipation and cardiovascular disease.
   b. Constipation is associated with having major risk factors for cardiovascular disease.
   c. Constipation is associated with having increased cardiovascular risk.
   d. Both constipation and cardiovascular disease are common in postmenopausal women.

2. **Which method was shown to be effective in helping seniors overcome insomnia?**
   a. Intensive cognitive behavioral therapy
   b. Reading materials from a quality source instructing better sleep
   c. Brief counseling with follow-up phone calls to help seniors sleep better
   d. Zolpidem titrated to the lowest effective dose

3. **Regarding effects of weight loss strategies:**
   a. commercial programs are more successful than intensive advice.
   b. women are generally more successful at weight loss than are men.
   c. retention in a structured weight management programs is generally high, averaging 75-85%.
   d. individuals who complete 12 months of a structured weight loss program typically lose 20-25 pounds.

4. **Objectively measured activity energy expenditure (AEE) revealed that:**
   a. cognitive impairment is not related to the amount of energy expenditure.
   b. greater activity energy expenditure may be protective against the development of cognitive impairment.
   c. there was no relationship between the incidence of cognitive impairment and the amount of energy that was expended.

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Accuracy of Stated Energy Contents of Restaurant Foods

Source: Urban LE, et al. Accuracy of stated energy contents of restaurant foods. *JAMA* 2011;306:287-293.

Eating out has increased in the general population, and is associated with increased body mass index. Indeed, United States data suggest that more than one-third of all daily calories are provided from restaurants. If clinicians and their patients want to make more healthful choices when eating out, they must rely to some degree on the listed caloric content of these foods, but have little assurance that such listings are accurate.

Urban et al performed bomb calorimetry on 269 food items from 42 different restaurants, and compared calorimetry results with caloric content listed by restaurants.

Nineteen percent of the sampled foods were substantially (more than 100/kcal) above their listed energy content when tested with calorimetry. At the highest decile of discrepancy, foods averaged greater than 250 kcal/portion more than their restaurant listings indicated. It is estimated that eating an extra 100 kcal/d on a chronic basis could result in 5-15 kg of weight gain per year. Encouragingly, the overall food caloric assessments stated in restaurants were reasonably accurate; in the minority of cases where inaccuracies underestimate caloric content, health-conscious consumers may be getting more than they bargained for. ■

The Past and Future Burdens of Violence Against Women

Source: Rees S, et al. Lifetime prevalence of gender-based violence in women and the relationship with mental disorders and psychosocial function. *JAMA* 2011;306:513-521.

More than 20% of adult American women report being victims of rape, intimate partner violence, or stalking. Limitations of previous data sets preclude identifying associations between lifetime experiences of violence and subsequent mental health issues.

Rees et al performed an analysis of data from the second Australian National Mental Health and Well-being Survey, which included 4451 adult women ages 16-85. The overall lifetime prevalence of any mental disorder (as per DSM–IV criteria) was 37.8% including anxiety disorder (24.6%), mood disorder (18.3%), substance use disorder (13.9%), and post-traumatic stress disorder (9.8%). One or more of the above mentioned forms of violence was reported by 27.4% of these same women.

Data analysis found that victims of violence were more likely to also experience mental health disorders; additionally, the severity of these victims' mental health disorders was greater, as was the likelihood that more than one mental health disorder would ensue. The authors suggest that the magnitude of the burden of violence against women and its mental health sequelae merit an enhanced public health focus on the problem. ■

Does Androgen Deprivation Improve Outcomes for Localized Prostate Cancer?

Source: Jones CU, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107-118.

Antiandrogen treatment has been shown to induce tumor cell regression in some androgen-responsive cancers, including some prostate cancers. Unfortunately, the survival benefits seen in clinical trials with long-term antiandrogens have been tempered by increased adverse effects, including erectile dysfunction and myocardial infarction. Jones et al performed a controlled trial of radiotherapy for men with localized prostate cancer (n = 1979), with or without short-term (4 months) androgen-deprivation treatment (goserelin or leuprolide).

Overall 10-year survival in patients receiving androgen-deprivation treatment was statistically significantly greater than in men who only received radiotherapy (62% vs 57%). Prostate cancer-associated mortality was also superior in the group receiving androgen-deprivation treatment (8% vs 4%). Black men enjoyed the same degree of risk reduction as non-blacks.

Hepatotoxicity did occur in a minority of men treated with androgen-deprivation treatment, but was low-grade in more than 95% of cases. Short-term androgen deprivation improves outcomes in men with localized prostate cancer. ■

In Future Issues:

2011 Guideline on the Management of Patients with Extracranial Carotid and Vertebral Artery Disease: Executive Summary