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INSIDE

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Bariatric Surgery Reduces the Risk of Type 2 Diabetes

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen is a consultant for Agile Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Merck; is a speaker for Bayer Healthcare and Merck; and receives research support from Agile Pharmaceuticals, Abbott Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Medicines360.

This article originally appeared in the November 2012 issue of OB/GYN Clinical Alert.

Synopsis: *In a prospectively followed cohort of obese, non-diabetic men and women from Sweden, individuals who underwent bariatric surgery had an 83% reduction in the risk of developing type 2 diabetes over 15 years of follow-up.*

Source: Carlsson LM, et al. Bariatric surgery and prevention of type 2 diabetes in Swedish obese subjects. *N Engl J Med* 2012;367:695-704.

BETWEEN SEPTEMBER 1, 1987, AND JANUARY 31, 2001, A TOTAL OF 4047 obese persons were enrolled in the Swedish Obesity Study (SOS) intervention trial. The SOS evaluated 2010 participants who had chosen to undergo surgery (bariatric surgery group) and a non-surgical control group of 2037 subjects matched with the bariatric surgery group on the basis of 18 variables. The authors previously had reported that the matching process had unexpectedly resulted in adverse selection for the bariatric surgery group, as evidenced by a higher mean body weight and more severe risk factors than the control group. To evaluate the effect of bariatric surgery on incident type 2 diabetes, the current analysis was restricted to 1658 bariatric surgery and 1771 control subjects who did not have diabetes at baseline. Although the study groups had identical inclusion and exclusion criteria, the requirement that none of the patients have diabetes at baseline further exaggerated the adverse selection in the surgical cohort. The inclusion criteria for both the surgical and control cohorts were an age of 37-60 years and a body mass index (BMI) of ≥ 34 in men and ≥ 38 in women, and all subjects needed to have

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no contraindications to surgery. All subjects entered this study with the intention of losing weight; 73% of both cohorts were women. In the bariatric surgery group, 19% underwent banding, 69% vertical-banded gastroplasty, and 12% gastric bypass. Subjects in the control group received the customary treatment for obesity at their primary health care centers (e.g., lifestyle modification, including recommendations regarding eating behavior, food selection, energy intake, and physical activity). After adjustment for follow-up of < 15 years and for death, the 15-year participation rate was 53.5%. During the follow-up period, type 2 diabetes developed in 392 participants in the control group (28.4/1000 person-years) and in 110 (6.8/1000 person-years) in the bariatric surgery group (adjusted hazard ratio with bariatric surgery, 0.17; 95% confidence interval, 0.13-0.21). The effect of bariatric surgery was influenced by the presence or absence of impaired fasting glucose (P = 0.002 for the interaction) but not by BMI (P = 0.54). Sensitivity analyses, including endpoint imputations (done to adjust for the poor long-term follow-up), did not change the overall conclusions. Surgical complications included a postoperative mortality of 0.2%, and 2.8% of bariatric surgery subjects required reoperation within 90 days owing to complications. The authors concluded that bariatric surgery is markedly more efficient than usual care in the prevention of type 2 diabetes in obese persons.

■ COMMENTARY

As I write this, I am sitting outside noting the cooling temperatures of fall. For most of human history, the challenge in late summer was to consume as many calories as possible to store energy in the form of fat to survive the lean time of winter. Some groups evolved to be extremely efficient in converting energy to fat, and the economy of this trait varies widely in the population. Unfortunately, for modern humans eating a western diet, the challenge has changed. Winter and reduced activity arrives as it has for millennia, but now is unaccompanied by a reduction in the availability of food. In fact, the long nights of winter frequently bring feasts and more alcohol consumption. Women spend more time around food preparation than men, and this contributes to high rates of obesity. Much has been written about the obesity epidemic in the United States, and there is no indication that the trend is slowing.

Combating obesity will require a dedicated public health effort. Taxing high-calorie/low-nutrition foods, reducing subsidies for high fructose corn syrup, and promoting physical education in schools are interesting ideas to combat child obesity. But we all know that weight loss through diet is extremely difficult for adults, and that even when weight loss does occur, most fail to maintain a normal body weight. Among the many complications of obesity, type 2 diabetes is one of the principle drivers of high health care costs. Therefore, strategies that could reduce the chance that an obese individual will develop diabetes should not only improve the health of that individual, but also help stabilize health care spending.

Several important lessons emerge from the SOS. First, the risk of developing type 2 diabetes is substantially reduced by bariatric surgery. This finding was robust, as the surgical cohort was actually less healthy than the control group at baseline. The authors conducted a sensitivity analysis to compensate for the large study dropout (not surprising in a 15-year study) with no change to the overall conclusion that bariatric surgery reduces the chance of developing diabetes.

Next, bariatric surgery is far more effective than usual care in promoting weight loss. Subjects in the bariatric surgery group had an average maximal weight loss of 31 kg after 1 year. Although partial weight regain then occurred, the average weight loss from baseline values at 10 years and 15 years was approximately 20 kg. Compare this to the control group where mean weight changes never exceeded 3 kg in weight gain or weight loss. Even among those control subjects who sought additional professional help (54%), the mean weight change at year 2 was only a loss of 0.6 kg. Those who did not receive this help gained 1.4 kg! It is important to note that the magnitude of obesity was not associated with the reduction in risk; the incidence of type 2 diabetes and the preventive effect of bariatric surgery were similar among participants with a BMI at or below the median of 40.8 and those with

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a BMI above the median. In contrast, patients with an elevated fasting blood sugar at baseline appeared to benefit the most.

Finally, in a system of socialized medicine, the Swedes feel it is cost effective to provide surgical treatment for obesity. A recent review by Picot et al found that the incremental increased cost of bariatric surgery in the U.K. health system was negligible at 5 years and offset by savings over 20 years in patients with type 2 diabetes and class 2 obesity.[1] Although the SOS authors did not conduct a cost analysis, the new results from SOS suggest that cost savings also may occur in obese individuals with elevated fasting glucose, regardless of BMI.

So our role is to advise our patients. Find the trusted resources in your area (or a nearby city) for referral to a bariatric surgery specialist in a comprehensive weight loss practice. When your next obese patient presents (should be tomorrow since one-third to one-half of your patients are obese), consider taking a moment to discuss their past experience with weight loss programs and the long-term success and potential benefits of bariatric surgery (particularly if their fasting glucose is elevated). As a trusted health care provider, your input just might open the conversation and help save their life. ■

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Cognitive Function in Breast Cancer Survivors

ABSTRACT & COMMENTARY

By William B. Ershler, MD

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ershler reports no financial relationships relevant to this field of study.
This article originally appeared in the November 2012 issue of Clinical Oncology Alert.

Synopsis: *There has long been an appreciation of the risk of cognitive decline associated with chemotherapy but questions remain about the magnitude and duration of the observed deficits. In this meta-analysis of studies that included neuropsychological assessments at a minimum of 6 months after completion of breast cancer chemotherapy, definite but small deficits were found for both verbal and visuospatial capabilities. In this analysis, age and educational status were not found to be moderators of acquired deficits.*

Source: Jim HSL, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol* 2012;30:3578-3587.

Whereas there has been substantial research on the cognitive effects of chemotherapy, including prior meta-analyses,[1-4] the issue remains unclear whether such treatment produces long-term deficits, and if so, how much. It remains well-established that moderate-to-severe cognitive impairment occurs in a substantial percent of chemotherapy-treated breast cancer patients (between 15% and 75%[5,6]). Yet, evidence is mixed regarding long-term cognitive deficits in patients treated with chemotherapy. Furthermore, some data now suggest that cognitive deficits may develop after the completion of treatment.[7]

Previous meta-analyses, the latest of which was published in 2006, were not focused specifically on the post-chemotherapy period, and since these publications there have been several reports providing additional information. Thus, Jim and colleagues performed the current meta-analysis, the goal of which was to assess cognitive functioning in breast cancer survivors who were treated with chemotherapy a minimum of 6 months prior to analysis.

The investigators, by searching PubMed and other major databases, found 2751 abstracts, and from these they found 17 studies that met stringent criteria for inclusion in this analysis. The 17 studies included 807 patients previously treated with standard-dose chemotherapy for breast cancer and on whom cognitive studies were performed 6 months or more after completion of chemotherapy. Neuropsychological tests were categorized according to eight cognitive domains: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability.

Deficits in cognitive functioning were observed in patients treated with chemotherapy relative to controls or prechemotherapy baseline in the domains of verbal ability ($g = -0.19$; $P < 0.01$) and visuospatial ability ($g = -0.27$; $P < 0.01$). Patients treated with chemotherapy performed worse than non-cancer controls in verbal ability and worse than patients treated without chemotherapy in visuospatial ability (both $P < 0.01$). Age, education, time since treatment, and endocrine therapy did not moderate observed cognitive deficits in verbal ability or visuospatial ability (all $P \geq 0.51$).

■ COMMENTARY

Results indicate that, on average, observed cognitive deficits in patients with breast cancer previously treated with chemotherapy are small in magnitude and limited to the domains of verbal ability and visuospatial ability. That

the magnitude of observed deficits is small is reassuring, particularly when considering some of the fairly dramatic changes that have been reported for breast cancer patients actively receiving therapy. However, persistence of deficits 6 months and beyond raises concerns that such deficits might be long lasting, if not permanent.

One unexpected finding was that age and education status were not shown to moderate the effects of chemotherapy-induced cognitive change. However, the strength of this and other conclusions based on meta-analysis is only as robust as the studies examined in the analysis, and the authors acknowledged that there might not have been sufficient numbers of older or less-educated patients to demonstrate significant associations. In contrast, in one recent report,[8] age and "cognitive reserve" (an attribute comprised of such factors as education, employment, and cognitive stimulation) were shown to be important factors predicting chemotherapy-associated decline. Thus, older patients with low levels of pretreatment cognitive reserve were found to be most vulnerable to post-treatment cognitive decline.

Another concern is that this, as with many of the reports of chemotherapy-associated brain deficits, focused on breast cancer patients only. Such patients often receive additional and somewhat complex treatment regimens that include surgery, radiation, and hormonal treatments, all of which may confound interpretation of observed findings. Thus, it would be premature to generalize these findings to chemotherapy treatment in general. Further, most of the primary studies on this topic exclude patients who might be at highest risk for cognitive decline, such as those with significant comorbidities, depression, or neurologic disorders. Thus, as highlighted by the accompanying editorial,[9] the findings from this meta-analysis might significantly under represent the magnitude of the cognitive impact of cancer treatments. ■

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Controlling Diabetic Neuropathic Pain

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College, New York, NY

Dr. Rubin reports no financial relationships relevant to this field of study. This article originally appeared in the November 2012 issue of Neurology Alert.

Synopsis: *Three common medications — amitriptyline, duloxetine, and pregabalin — all appear equally efficacious in treating neuropathic pain from diabetic neuropathy.*

Source: Boyle J, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain. *Diabetes Care* 2012; Sept 18 [Epub ahead of print. http://www.ncbi.nlm.nih.gov/pubmed/22991449].

Among the 246 million diabetics worldwide, approximately 20-30 million are at risk for polyneuropathy. More than 80% of patients with diabetic polyneuropathy have the distal, symmetric form, which is painful in 16%, unreported in 12.5%, and untreated in 39%. Relief is desperately sought. Which agent works best?

Type 1 and type 2 diabetics who were ≥ 18 years of age and had neuropathic pain manifested by lower extremity allodynia, dysesthesiae, hyperalgesia, and burning or lancinating pain were recruited to participate in a

double-blind, randomized, placebo-controlled, parallel group trial of low-dose, followed by higher-dose, pregabalin, amitriptyline, and duloxetine. Low doses comprised amitriptyline 25 mg bid, duloxetine 60 mg qd, and pregabalin 150 mg bid, whereas high doses comprised amitriptyline 25 mg qAM and 50 mg qhs, duloxetine 60 mg bid, and pregabalin 300 mg bid. Diagnosis of painful neuropathy was confirmed with a score of > 12 on the Leeds Assessment of Neuropathic Symptoms and Signs, and exclusionary criteria included drug abuse, pregnancy, breastfeeding, recent cardiac or cerebral ischemic events, recurrent hypoglycemic episodes requiring third-party assistance, or end-stage disease of a major organ system. Subjective pain, assessed by the Brief Pain Inventory, was the primary outcome measure. Secondary outcomes measures, including quality of life, measured by the short-form, 36-item general health survey, and subjective sleep, mood, and daytime sleepiness, assessed by the Leeds Sleep Evaluation Questionnaire, the Linear Analog Rating Scale, and the Karolinska Sleepiness Scale. Daytime functioning was evaluated during a 2-day inpatient period using a psychometric test battery including continuous tracking, choice reaction time, central nervous system arousal and information processing, Stroop task, digit symbol substitution testing, and working and explicit memory tasks. Statistical analysis comprised a preplanned statistical analysis plan, with statistical significance set at $P < 0.05$.

Among 83 patients enrolled and randomized between February 2007 and March 2009, 65 completed all treatment periods, with 27 randomized to pregabalin and 28 each to amitriptyline and duloxetine. No significant difference between treatment groups was found for the primary outcome of subjective pain. Pregabalin facilitated falling asleep and improved sleep continuity, but no significant differences between treatments were appreciated for any of the sleep components. Duloxetine significantly reduced sleep time and increased wake time, but nevertheless enhanced central nervous system (CNS) arousal and performance on sensory motor tasks. Duloxetine (60 and 120 mg) was associated with a small but significant decrease in nocturnal blood glucose, whereas pregabalin (600 mg only) was associated with a small but significant increase in nocturnal blood glucose. No serious adverse events were felt to be due to the study medication. Pregabalin, amitriptyline, and duloxetine are equally efficacious in reducing diabetic neuropathic pain, but sleep is improved with pregabalin.

■ COMMENTARY

Microgliosis denotes the process whereby microglia, the CNS macrophages, respond to pathogens or injury by proliferating and altering their surface proteins, gene expression, and morphology. When peripheral nerves are injured, microgliosis occurs within the dorsal and ventral horns of the spinal cord, where these nerves terminate, as well as in the thalamus, hypothalamus, rostral ventromedial medulla, and periaqueductal grey. Mediators such as neuregulin-1, MMP-9, CCL2, and fractalkine induce this microglia transformation, as may tissue injury products including ATP, misfolded proteins or nuclear factors, complement components, and reactive oxygen species. These mechanisms, in part, explain chronic pain as a consequence of peripheral nerve injury, and blocking the microglial response can prevent injury-induced hypersensitivity in animal models. However, not all models of peripheral neuropathic pain evoke such a significant immune response in the CNS, and the extent to which CNS inflammation occurs in human peripheral neuropathic pain remains to be elucidated.[1] ■

Reference

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Tbo-filgrastim Injection

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 relationships relevant to this field of study.

A MODIFIED RECOMBINANT HUMAN GRANULOCYTE COLONY-stimulating factor (G-CSF) has been approved by the FDA. The new tbo-filgrastim differs from filgrastim by the addition of a N-terminal methionine residue and lack of glycosylation at residue 133 (r-metHuG-GCSF). The drug was approved by way of a full biologic license application, although it fits the definition of a biosimilar molecule. The product is approved in Europe as a biosimilar to filgrastim (Neupogen®). Tbo-filgrastim is manufactured by Sicor Biotech and marketed by Teva.

Indication

Tbo-filgrastim is indicated for the reduction in the duration of severe neutropenia in patients with non-myeloid malignances receiving myelosuppressive anti-cancer therapy with a clinically significant risk of febrile neutropenia.[1]

Dosage

The recommended dose is 5 mcg/kg/day given subcutaneously. Administration should be started no earlier than 24 hours following myelosuppressive therapy.

Tbo-filgrastim is available as 300 mcg/0.5 mL and 480 mcg/0.8 mL in single-use prefilled syringes.

Potential Advantages

Tbo-filgrastim provides an alternative to filgrastim and is expected to be priced competitively to filgrastim.

Potential Disadvantages

The immunogenicity and the potential of tbo-filgrastim to prolong QTc interval have not been adequately assessed.[1] These are to be evaluated as part of the post-marketing requirements.[2]

Comments

The approval of tbo-filgrastim was based on a Phase 3, multicenter, randomized, controlled study in chemotherapy-naïve patients with high-risk stage II or stage IV breast cancer receiving doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2).[1,2] Subjects (n = 348) were randomized to placebo, tbo-filgrastim, and a non-U.S.-approved filgrastim. The primary endpoint was the duration of severe neutropenia. The mean duration of severe neutropenia in cycle 1 was 1.1 days vs 3.8 days for placebo. The FDA did not consider the non-U.S.-approved filgrastim comparator relevant to the demonstration of efficacy and safety.[2] The most common adverse event was bone pain, which was observed in 24% of patients.[2] Tbo-filgrastim has been shown to be bioequivalent to filgrastim in terms of pharmacokinetic parameters and pharmacodynamic parameters (absolute neutrophil count).[3,4] A meta-analysis of three clinical trials conducted with tbo-filgrastim and filgrastim in patients for the prophylaxis of febrile neutropenia during the first cycle in patients being treated with myelosuppressive chemotherapy for breast, lung cancer, and non-Hodgkin's lymphoma suggests non-inferiority for tbo-filgrastim.[5] Two studies conducted in Europe reported similar efficacy and safety in patients with lung cancer receiving platinum-based chemotherapy (n = 240) and chemotherapy for non-Hodgkin's lymphoma (n = 92).[6,7] Subjects received either tbo-filgrastim or filgrastim (5 mcg/kg/day) daily for 5-14 days for the first cycle. Efficacy endpoint was duration of severe neutropenia or incidence of neutropenia in the first cycle.

Clinical Implications

Tbo-filgrastim has been available in Europe for several years as an approved biosimilar. It was recently approved in the United States after a full Biologic License Application, as the biosimilar pathway was not available at the time of submission. Due to a patent litigation settlement between Amgen and Teva, tbo-filgrastim will not be available until November 2013. ■

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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 Questions

1. **The main result of the SOS study was a reduction in the incidence of type 2 diabetes over 15 years in:**
   a. only men with a body mass index (BMI) > 40.
   b. both men and women with a BMI > 40.
   c. only women with a BMI > 36.
   d. both men and women independent of BMI.

2. **The current meta-analysis of cognitive decline associated with breast cancer chemotherapy was remarkable in that it demonstrated which of the following?**
   a. Moderate-to-severe decline in eight domains of cognitive functioning
   b. Definite but small in magnitude decline in eight domains of cognitive functioning apparent at a minimum of 6 months after chemotherapy
   c. Definite but small in magnitude decline in two domains of cognitive functioning (verbal and visuospatial ability) apparent at a minimum of 6 months after chemotherapy
   d. Dramatic decline in two domains of cognitive functioning (verbal and visuospatial ability) apparent at a minimum of 6 months after chemotherapy

3. **In double-blind, placebo-controlled trials, which agent best controls pain in diabetic peripheral neuropathy?**
   a. Pregabalin
   b. Amitriptyline
   c. Duloxetine
   d. All are equally efficacious in controlling the pain of diabetic peripheral neuropathy.

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

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Risk of Cancer in RA Patients Treated with Disease-Modifying Drugs

Source: Lopez-Olivo MA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: A meta-analysis. *JAMA* 2012;308:898-908.

In the early years of treatment experience with biologic response modifiers (BRMs) for rheumatoid arthritis (RA), concern was raised that the immune-modulating effects responsible for dramatic symptomatic improvement might also lead to increased risk for cancer. Indeed, based on excess cases of lymphoma reported in the Adverse Event Reporting System database among children and adolescents treated with BRMs, the FDA recommended a warning label for all TNF-inhibitors. Should we be worried about cancer risk in patients treated with BRMs?

Lopez-Olivo et al performed a data analysis on randomized, controlled trials (n = 63 trials) of BRM treatment in RA patients in which a BRM was compared with placebo or another traditional therapy such as methotrexate (n = 29,423). A wide variety of BRMs was included in the analysis (e.g., abatacept, adalimumab, anakinra).

This dataset was restricted to trials with at least 6 months' duration. No signal for increased risk of cancer was discerned. Although a trend for increased risk of lymphoma was found, the numbers did not achieve statistical significance. It is not possible to determine whether longer-term outcomes in relation to BRMs will be impacted by cancer risk, since this dataset is comprised of studies of 3 years' duration or less. Additionally, whether RA patients who have already suffered a cancer are at greater risk of recurrence subsequent to BRM treatment is unknown. The dramatic RA disease remission we have come to commonly see thanks to treatment with BRMs appears to be safe from an increased risk for cancer. ■

A Different Kind of Fish Story

Source: Rizos EC, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *JAMA* 2012;308:1024-1033.

The idea that omega-3 polyunsaturated fatty acids — a.k.a. fish oil — are beneficial stems from *some* positive randomized clinical trials. But the word "some" is limiting in the previous sentence, since some other trials do not report benefit. Rizos et al performed a systematic review and meta-analysis based on 28 studies (n = 68,680) in which adults were treated with omega-3 fatty acids for primary or secondary prevention of cardiovascular disease.

Studies were reported between 1999-2010, and averaged 2 years of follow-up, although some data went as long as 6.2 years. The majority of trials were secondary prevention trials, which — because they represent a higher risk group — might be anticipated to more readily demonstrate risk reduction.

Contrary to popular opinion, this meta-analysis was unable to confirm any positive effects of omega-3 fatty acids, whether the metric was all-cause mortality, cardiac death, sudden death, MI, or stroke. Most of the trials used combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leaving open the possibility that an EPA or DHA individually might have produced different results. The authors conclude that their data support neither the routine inclusion of omega-3 fatty acids in clinical practice nor guideline recommendations that advocate their use. ■

Antidepressants and Auto Accidents

Source: Orriols L, et al. Risk of injurious road traffic crash after prescription of antidepressants. *J Clin Psychiatry* 2012;73:1088-1094.

Driving simulation tests performed with *healthy, non-depressed volunteers* indicate varying degrees of deleterious effect on driving skills with tricyclics (TCA) and mirtazapine, but less so with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. In direct contrast, but perhaps more pertinent to clinical medicine, trials of driving performance in *depressed patients* on antidepressants suggest better driving skills on SSRIs or mirtazapine than TCAs or venlafaxine. To gain more insight into the effects of antidepressant treatments on auto crashes, Orriols et al reviewed the database of accidents accrued by the French police force from 2005-2008 (n = 210,818).

Being on an antidepressant increased the odds ratio of being the at-fault driver by 34% compared with persons not on antidepressants. The immediate time period around initiation or change of treatment was particularly high risk. Subgroup analysis found the greatest risk among persons receiving serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and the least risk among TCA recipients (e.g., amitriptyline). Even though driving simulation tests suggest that depressed patients who are being treated perform better than untreated patients, clinicians must still exercise vigilance and should consider informing patients — especially upon initiation of or change in treatment — about driving risks. ■

In Future Issues:

Sedentary Time in Adults and the Association with Diabetes, Cardiovascular Disease, and Death

PHARMACOLOGY WATCH

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Do Benzodiazepines Cause Dementia in the Elderly?

In this issue: Dementia and benzodiazepines; effectiveness of omega-3 fatty acid and *Ginkgo biloba* supplements; and FDA actions.

Benzodiazepines and dementia

Can benzodiazepines increase the risk for dementia? Researchers in France studied 1063 men and women with an average age of 78 who were free of dementia and did not start taking benzodiazepines until they had been followed for at least 3 years. During a 15-year follow-up, 253 cases of dementia were confirmed. New use of benzodiazepines occurred in 9% of the study population and was associated with an increased risk of dementia (32% benzodiazepine group vs 23%, adjusted hazard ratio 1.60, 95% confidence interval [CI] 1.08-2.38). After correcting for the existence of depressive symptoms as well as age and diabetes, the hazard ratio was unchanged. A secondary analysis looking at participants who started benzodiazepines at different times during follow-up also showed an elevated risk of dementia. Results of the complementary, nested, case-control study showed that ever use of benzodiazepines was associated with an approximate 50% increased risk of dementia compared with never users. The authors conclude that in this prospective, population-based study new use of benzodiazepines was associated with a significantly increased risk of dementia. They further conclude that "indiscriminate widespread use should be cautioned against" (*BMJ* 2012;345:e6231). The obvious criticism of the study was the presence of confounders — whether use of benzodiazepines was a marker for early onset dementia rather than a cause. While the authors feel the study was carefully controlled, selection bias cannot be completely ruled out. They further state that the research should be done on younger patients to see if starting benzodiazepines at ages younger than 65 may have deleterious effects. They also recommend that "physicians and regulatory agencies should consider the increasing evidence of potential adverse effects of this drug class for the general population." ■

Popular supplements' use questioned

Two popular supplements — omega-3 fatty acids and *Ginkgo biloba* — may be of limited value, according to two recent studies. Omega-3 fatty acids are thought to have a number of benefits, including lowering triglyceride levels, preventing arrhythmias, decreasing platelet aggregation, and lowering blood pressure. But the fish oil supplement's ability to prevent major cardiovascular events has been debated in the literature. Twenty studies of nearly 67,000 patients were included in a meta-analysis looking at the effect of omega-3 on all-cause mortality, cardiac death, sudden death, myocardial infarction, and stroke. After correcting for dose and comorbidities, there was no difference in the absolute or relative risk of any of the outcomes associated with omega-3 supplementation. The authors concluded that marine-derived omega-3 polyunsaturated fatty

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acid supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke (*JAMA* 2012;308:1024-1033).

Ginkgo biloba for the prevention of Alzheimer's disease (AD) was studied in a randomized, parallel group, double-blind, placebo-controlled trial of adults age 70 years or older who spontaneously reported memory complaints to their primary care physician in France. Patients were randomized to a twice per day 120 mg standardized *Ginkgo biloba* extract or matching placebo and followed for 5 years. The primary outcome was conversion to probable AD. More than 2800 patients were enrolled with about 1400 patients in each group. By 5 years, 61 participants in the ginkgo group were diagnosed with AD vs 73 in the placebo group (hazard ratio 0.84, 95% CI 0.60-1.18; $P = 0.306$). Adverse events were the same between both groups and mortality was roughly the same as well. Sixty-five participants in the ginkgo group had a stroke compared to 60 in the placebo group ($P = 0.57$). The authors conclude that long-term use of standardized *Ginkgo biloba* extract did not reduce the risk of progression to AD compared to placebo (*Lancet Neurology* 2012;11:851-859). ■

FDA actions

The FDA has approved teriflunomide for the treatment of relapsing forms of multiple sclerosis (MS). The approval was based on a 2-year study in which the drug reduced relapses by nearly a third compared to placebo — results that are about the same as other MS drugs and no better than Merck's popular injectable interferon beta 1a (Rebif). Side effects include diarrhea, abnormal liver function tests, nausea, and hair loss. It should not be used during pregnancy. Teriflunomide has the advantage of being a once-daily oral medication, the second oral MS medication after Novartis' fingolimod (Gilenya). Teriflunomide will be marketed by Sanofi Aventis as Aubagio. A third oral MS medication, Biogen Idec's BG-12, was recently found to reduce MS relapses by about 50% (*N Engl J Med* 2012;367:1087-1097; 1098-1107). BG-12 is not yet approved by the FDA, but a decision is expected before the end of the year.

The FDA has delayed the approval of apixaban (Eliquis) once again. Pfizer and Bristol-Myers Squibb's novel oral anticoagulant (NOAC) was expected to be approved last spring after publication of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, which showed that the drug was effective in preventing strokes in patients with non-valvular atrial fibrillation — data that suggested that the drug was perhaps even more effective than the two other NOACs, dabigatran (Pradaxa) and rivaroxaban (Xarelto). In June, the FDA told the manufacturers they needed "additional information on data management and verification from the ARISTOTLE trial." Now, the agency says that the review date will be March 17, 2013. No reason was given by the FDA for the delay.

About 25% of Internet consumers have purchased prescription medications online, while at the same time, the prevalence of fraudulent Internet pharmacies has grown. The FDA has now launched a national campaign to raise public awareness called BeSafeRx – Know Your Online Pharmacy, a resource that provides patients and caregivers with a better understanding of who they are buying from, and makes sure the medication they buy matches what their doctor prescribed. The FDA recommends that patients only buy medications from online pharmacies that require a prescription, are located in the United States, have a licensed pharmacist available for consultation, and are licensed by the patient's state board of pharmacy. More information can be found at www.FDA.gov/BeSafeRx.

The FDA has approved enzalutamide to treat men with late-stage, castration-resistant prostate cancer under the agency's priority review program. The drug was approved based on a study of nearly 2000 men with metastatic prostate cancer who had been previously treated with docetaxel. Men treated with enzalutamide lived an average of 18.4 months vs 13.6 months for men treated with placebo. Enzalutamide is co-marketed by Astellas and Medivation as Xtandi.

The FDA has also approved a new agent for the treatment of advanced colorectal cancer. Regorafenib is a multi-kinase inhibitor that was also approved under the FDA's priority review program. In a study of 760 patients with previously treated metastatic colorectal cancer, regorafenib extended survival about 45 days to 6.4 months from 5 months for placebo as well as progression-free survival of 2 months vs 1.7 months for placebo. Regorafenib is marketed by Bayer as Stivarga. ■