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INSIDE

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The Latest Word on Screening Mammography for Younger Women

ABSTRACT & COMMENTARY

By Eileen C. West, MD

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

Synopsis: *New guidelines from the ACP suggest that rather than universal screening, women aged 40-49 should be assessed for individual risk of breast cancer, and should be informed of the potential benefits and harms of screening mammography, then selectively screened based on the findings.*

Source: Qaseem A, et al. Screening Mammography for Women 40-49 years of Age: A Clinical Practice Guideline from the American College of Physicians. *Ann Int Med.* 2007;146:511-515.

Breast cancer is the second leading cause of cancer related death among women in the U.S. More than 40,000 die of the disease yearly.[1] Screening mammography reduces breast cancer mortality in women 50-70 years of age. Though 25% of all diagnosed cases are among women younger than 50 years of age, screening mammography in this age group has been the subject of intense debate. The USPSTF performed a meta-analysis recently which concluded that mammography every 1-2 years in women 40-49 resulted in a 15% decline the breast cancer mortality rate after 14 years, but the data varied widely with a large confidence interval, suggesting that the reduction could be as much as 27% or as little as 1%.[2] Because risks are associated with screening, the authors of this new position statement report that risks, benefits and patient preferences ought to be the basis of screening, not age alone.

The group makes four specific recommendations:

Recommendation 1: In women 40-49 years of age, clinicians should perform individualized assessment of risk for breast can-

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cer to help guide decisions about screening mammography. This assessment should be updated every 1-2 years. In this age group, women with any of the following risk factors have a higher risk than the average 50 year old woman: 2 first-degree relatives with breast cancer; 2 previous breast biopsies; 1 first-degree relative and 1 previous breast biopsy; previous diagnosis of breast cancer, DCIS, or atypical hyperplasia; previous chest irradiation or BRCA1 or BRCA2 mutation. More detailed family history patterns are found in the article, and include both sides of the family.

Recommendation 2: Clinicians should inform women 40 to 49 years of age about the potential benefits and harms of screening mammography. The primary benefit, of course, is early detection of breast cancer. The harms include biopsies, surgery, radiation exposure, false-positive results, and false reassurance, as well as procedure-associated pain and increased anxiety. The rate of false positives have been reported to range anywhere from 1% to 6.5%, and one study showed a cumulative rate of false-positive mammograms of 38% after 10 years of screening.[3] Another issue is the increased diagnosis of ductal carcinoma in situ (DCIS). The natural history of DCIS is unknown, as is the percentage of these tumors that will progress to more serious disease. DCIS is treated with mastectomy (33%), lumpectomy (64%) and/or radiation (52%). Although not all cases require aggressive treatment, reliable predictors of biological aggressiveness have not been successfully outlined.

Recommendation 3: Clinicians should base screening mammography decisions on benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile. Women will vary in their desire to start screening in the 40-49 year old age group. For those who don't wish to discuss the screening decision, screening mammography every 1-2 years is reasonable.

Recommendation 4: The group's final recommendation was for further research.

COMMENTARY

The latest screening recommendations join a long list of recommendations from other organizations, such as the Canadian Task Force of Preventive Health Care (2001), The USPSTF (2002), and the American College of Obstetrics and Gynecology (2003). These organizations reached general consensus on screening every 1-2 years with or without clinical breast exam. The American Cancer Society (2006), which favors more aggressive screening in general, recommends a yearly mammogram starting at age 40 and continuing for as long as a woman is in good health.

The biggest change with the latest guideline is the allowance for "wiggle room" for those women with few risk factors to wait a while on screening. They acknowledge that many will still choose to be screened, but believe that screening in this age group, based on existing data, is best addressed with more individualized treatment and education of the patient. They want physicians to query patients regularly on risk factors, and make patients aware that the tests, while inexpensive and easy to perform, are not without harm.

Once again we find that discussion time in the exam room saves money on testing. However, many clinicians may not take the time for this discussion, since talk isn't reimbursed well and busy schedules demand time be placed on more pressing issues. Also, the legal issues have not been addressed when screening tests are not ordered. The academic exercise has merit, however, and can be accomplished without substantial increase in time if a questionnaire is given to the patient to be filled out ahead of time outlining her risk factors. The physician can then explain, if the patient is considered low risk, that the choice is hers to have a mammogram or wait another year and reconsider. ■

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Death by Chocolate…NOT!

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

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

Synopsis. *In a small sample of adults who were healthy except for elevated blood pressure, addition of small amounts of dark chocolate to their usual diet resulted in lowered blood pressure and improved formation of vasodilative nitric oxide.*

Source: Taubert D, et al. Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide. A Randomized Controlled Trial *JAMA.* 2007;298:49-60.

German investigators recruited 44 older adults who had untreated stage 1 hypertension but were otherwise healthy. Participants were randomly assigned to receive either 6.3 grams (30 kcal) per day of dark chocolate containing 30 mg of polyphenols or matching polyphenol-free white chocolate for 18 weeks. At the end of 18 weeks, those subjects who were assigned to the dark chocolate group experienced a fall in systolic blood pressure of 2.9 (1.6) mm Hg ($P < .001$); their diastolic blood pressure fell –1.9 (1.0) mm Hg ($P < .001$). There were no changes in body weight, plasma levels of lipids, glucose, or 8-isoprostane. In the dark chocolate group, overall hypertension prevalence fell from 86% to 68%. In addition, plasma markers of vasodilating substances increased. White chocolate intake caused no changes in blood pressure or plasma biomarkers. The authors concluded that including amounts of polyphenol-rich dark chocolate as part of a usual diet can lower blood pressure and increase formation of vasodilative nitric oxide.

COMMENTARY

Chocolate lovers are feeling vindicated by the findings of this study. Indeed, this report has received attention in the lay press. There are a couple of points to emphasize here, however:

1. Only dark chocolate was associated with lowered blood pressure in this study;

2. Small amounts of chocolate were used. In other words, this paper cannot be used as justification to eat an entire white chocolate Easter bunny, and we are left not knowing anything about the effects of milk chocolate on blood pressure.

What is the rationale for using chocolate to lower blood pressure? Polyphenols in fruits and vegetables are believed to be major contributors to the health benefits of dietary plant intake, including lowered cardiovascular risk.[1-3] It turns out that cocoa contains significant amounts of phenol as well.[4-6] Indeed, cocoa intake has been shown to lower blood pressure and improve endothelial function in human intervention studies, but these studies have heretofore been short term (no more than 2 weeks) and involved huge doses of cocoa.[7-9] What the current study adds to the literature is longer-term (more than 4 months) follow-up and evidence that there were no adverse effects on body weight, lipids, or blood glucose associated with dietary intake of chocolate. Further, it helps to establish that the fall in blood pressure was associated with increases in circulating levels of vasodilative S-nitrosoglutathione, suggesting a causative role of S-nitrosoglutathione for blood pressure regulation.

In this randomized, controlled trial, these investigators have demonstrated that small amounts of commercial cocoa have comparable benefit in lowering blood pressure as do comprehensive dietary modifications that have proven efficacy to reduce cardiovascular event rate.[10, 11] Those of us who spend our days trying to get humans to change their behavior may find it easy to recommend that our patients eat (a small amount of dark) chocolate, along with our usual, predictable admonitions about exercise, smoking cessation, alcohol restriction, and adequate sleep. ■

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Symptom-driven Steroid Combination Inhalers for Mild Persistent Asthma

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

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

Synopsis: *Use of a symptom-driven dose of a combined steroid and albuterol inhaler was equally effective for mild persistent asthma compared to a twice daily steroid inhaler, and resulted in a smaller cumulative dose of inhaled steroids in the six month study period.*

Source: Papi A, et al. *N Engl J Med.* 2007;356:2040-2052.

Four combinations of inhaled treatments were tested in a double blind, randomized controlled trial of 455 subjects between ages 18-65 years in 25 worldwide centers. Mild persistent asthma was identified as a prebronchodilator FEV[1] 75% or more of predicted, with a 12% increase of predicted value after 200 micrograms inhaled albuterol or a positive metacholine challenge. Participants recorded medication use, symptom scores and measured peak flows in morning and evening. Before being assigned to one of the four study arms, participants had 4 weeks of standard care (twice daily inhaled beclomethasone dipropionate 250 micrograms and rescue albuterol inhaler), and were excluded if asthma was not controlled on this regimen.

Current standard care was compared to two groups given placebo inhalers twice daily, with rescue inhalers either a combination of beclomethasone dipropionate 250 micrograms with albuterol 100 micrograms, or albuterol 100 micrograms alone. The fourth group used the combination inhaler twice daily. Approximately 100 subjects in each of the 4 groups completed the study, and were similar in demographic and clinical characteristics.

The group receiving rescue albuterol alone had the most severe exacerbations (10 out of 17 total), and the most nocturnal awakenings. The three other groups had similar numbers of exacerbations and all with similar improvements in lung function. The group receiving standard care with twice daily beclomethasone used less rescue medications, but all groups except the albuterol alone had improved numbers of symptom-free days and nights. The cumulative inhaled total over the 6 month study for beclomethasone was 19 mg for the symptom-driven combination group, compared to 77 mg for the twice daily groups.

COMMENTARY

This article supports less frequent use of inhaled steroids for mild persistent asthma, either as-needed or once daily in combination with inhaled albuterol. The authors state that acute asthma is a combination of bronchoconstriction and airway inflammation, and they used a higher inhaled beclomethasone dose at 250 micrograms for more immediate effect than the commercially available twice-daily inhaler at 40 or 80 micrograms. Smaller doses may also be effective, but this has not been studied, nor has the long-term effects on the course of the disease.

It was published alongside a similar study from the American Lung Association[1] (see Clinical Briefs on page 112), which also gave support for reducing medication use in controlled mild persistent asthma. The Lung Association study used inhaled fluticasone 100 micrograms instead of beclomethasone, and showed feasible options for substitution with once daily inhaled fluticasone combined with the long-acting beta2 agonist salmeterol 50 micrograms, or with a daily oral leukotriene-receptor antagonist using inhaled albuterol only for rescue. The latter option avoids steroids altogether but results in less asthma control (30% less control compared to 20%), but did give 79% symptom-free days compared to 83-86% for the other options.

All of these alternatives for step-down therapy reduce the cumulative amount of inhaled corticosteroids, which in large amounts has been suggested to increase the rate of fracture after 25 years along with other complications.[2] The benefits of inhaled steroids used as-needed have been shown to be feasible in a previous study of budesonide,3 challenging past assumptions that steroids needed to be given regularly for maximal benefit. All of this evidence suggests that an individualized approach to minimize medications for mild persistent asthma will

result in smaller doses with acceptable asthma control. ■

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The Efficient Diagnosis of Tuberculosis

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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

Source: Brown M, et al. Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. *Clin Infect Dis.* 2007;44:1415-1420.

Synopsis: *In patients with suspected pulmonary tuberculosis who are unable to expectorate sputum, culture of 3 induced sputum samples, all collected on the same day, is an effective and efficient means of diagnosis.*

Brown and colleagues evaluated the most efficient means of microbiological diagnosis of tuberculosis in patients. Adults in whom the presence of pulmonary tuberculosis was suspected based on the presence of compatible abnormalities on chest X-ray who were unable to produce an expectorated sputum sample were evaluated in order to determine the relative value of specimens obtained by sputum induction, gastric washing, and bronchoalveolar lavage (BAL). Also studied was the relative value of sputum induction on 3 consecutive days as opposed to obtaining all 3 samples on the same day, approximately 4 hours apart.

Three induced sputum specimens were obtained on a single day, followed by additional morning samples on 2 subsequent days. Analysis of the 79 patients from whom all 5 samples were obtained found that at least one of the 3 specimens collected on a single day were positive in 27 (34%) of patients compared to a positive result in 29 (37%; $P = 0.63$) in at least one of the 3 daily induced sputum specimens. There was no correlation between the volume of sputum obtained for testing and the results.

Twenty-one patients whose smears were negative underwent bronchoscopy, and BAL cultures proved to be positive in 5 (24%) —but all 5 had positive day-one induced sputum cultures. In addition, 2 individuals with positive day-one induced sputum samples had negative BAL cultures.

At least 3 induced sputum specimens and 3 gastric washing specimens were available for 107 of the 140 patients enrolled; *Mycobacterium tuberculosis* was recovered in culture from one or more cultures obtained from 46 (43%) of the 107. At least one of the first 3 induced sputum samples obtained were culture positive in 42 (39%) patients compared to gastric washings from 32 (30%; $P = 0.03$) patients.

■ COMMENTARY

This is a valuable study from which a number of conclusions regarding the diagnosis of pulmonary tuberculosis in patients unable to provide an expectorated sputum sample can be drawn:

- Culture of 3 induced sputum samples was more sensitive than culture of 3 gastric washings;
- Culture of BAL specimens did not contribute to the diagnosis obtained from the induced sputum samples;
- Collecting induced sputum samples on consecutive days was not superior to obtaining all 3 specimens on a single day.

These results have practical implications for the diagnostic management of patients with suspected pulmonary tuberculosis. The referral center in the UK where this study was performed has, in fact, altered their procedures as a consequence of these results. In patients unable to expectorate sputum, they no longer perform gastric washings and instead obtained 3 induced sputum specimens—all on the same day. Bronchoscopy is performed only in limited circumstances. Thus, in most cases, their entire evaluation is performed in one day. ■

Pharmacology Update

Lisdexamfetamine Dimesylate Capsule (Vyvanse™) CII

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

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

A prodrug of dextroamphetamine has been approved by the FDA for the treatment of attention-deficit/hyperactivity disorder (ADHD). Lisdexamfetamine is the d-amphetamine covalently bound to l-lysine. It is marketed by Shire US Inc as Vyvanse .

Indications

Lisdexamfetamine is approved for the treatment of ADHD in children 6-12 years of age.[1]

Dosage

The recommended starting dose in children (6-12 years of age) is 30 mg once daily in the morning. The dose may be increased to 70 mg daily if clinically appropriate. The dose should be increased in increments of 20 mg at weekly intervals. Doses greater than 70 mg are not recommended.[1] The capsule may be swallowed whole or the contents dissolved in water and taken without regard to meals.

Lisdexamfetamine is supplied as 30 mg, 50 mg, and 70 mg capsules.

Potential Advantages

Lisdexamfetamine is a prodrug that provides a gradual release of d-amphetamine and may reduce abuse potential.[2,3]

Potential Disadvantages

The drug shares the same warnings as amphetamine (eg, abuse potential, dependence, sudden death and cardiovascular risks).[1] Lisdexamfetamine has not been studied in children older than 12.

Comments

Lisdexamfetamine is the latest drug approved for the treatment of ADHD. It is not a new chemical entity but a prodrug for d-amphetamine. Its efficacy was shown in two double-blind, placebo-controlled studies in children ages 6-12 years. In the first study, subjects were randomized to 30 mg, 50 mg, or 70 mg for 4 weeks ($N = 290$). The primary endpoint was the change from baseline in the ADHD rating scale (AHDD-RS) total score. Reductions from baseline were 21.8, 23.4, and 26.7 vs 6.2 points for 30 mg, 50 mg, 70 mg and placebo respectively.[1,2] These represented a 50% to 60% reduction for lisdexamfetamine to about 15% for placebo. The response rates (30% or greater decrease in ADHD-RS total score) were 66%, 72%, 77%, and 18% respectively. In the second study ($n = 52$), subjects were randomized to lisdexamfetamine (30 mg, 50 mg, 70 mg), placebo, or continued Adderall XR treatment after a 3-week open label dose titration with Adderall XL.[1] Lisdexamfetamine was reported to be significantly better than placebo and similar to Adderall XR. Lisdexamfetamine gradually releases dextroamphetamine via rate limiting hydrolysis of the lysine group. The systemic exposure of dextroamphetamine over the first 4 hours is about 2/3rd that for a comparable amounts of dextroamphetamine.[2,3]

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

In a study to assess abuse potential, lisdexamfetamine 50 mg and 100 mg were not significantly different from placebo in adult stimulant abusers (n = 36) in terms of likability (Drug Rating Questionnaire-Subject Liking scale)[3]. However the 150 mg dose, d-amphetamine (40 mg), and diethypropion (200 mg) was significantly greater than placebo.[3] Adverse events for lisdexamfetamine are similar to those for d-amphetamine (decrease appetite, insomnia, irritability, decreased weight, and dizziness).[3] Lisdexamfetamine is priced the same for all strengths and is the same as Adderall XR, $3.41 per day (both distributed by Shire). Lisdexamfetamine 50 mg tablets and dextroamphetamine sulfate 20 mg contains about the same amount of amphetamine base.[3]

Clinical Implications

It's not clear if lisdexamfetamine offers any significant clinical advantage over other ADHD drugs in general or specifically over d-amphetamine. The possibility of reduced abuse potential is interesting and may be dose dependent. Still, the drug's clinical relevance remains to be established. ■

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CME Question:

36. Which of the following is NOT one of the risk factors commonly identified for breast cancer:

a. history of breast biopsy
b. first degree relative with breast cancer
c. age
d. painful breasts

37. Which of the following is true about chocolate consumption and health?

a. Small amounts of dietary white, milk, or dark chocolate lower blood pressure.
b. Chocolate intake is associated with lowered blood pressure, but large amounts (up to 400 grams/day) are necessary.
c. Milk chocolate intake can lower blood pressure, but is associated with worsened lipid profiles and glucose tolerance. .
d. Small amounts of dark chocolate can lower blood pressure without adverse effects on lipids, weight, or serum glucose.

38. Which of the following would be appropriate step-down therapy for a case of mild persistent asthma that is well controlled on twice daily inhaled beclomethasone dipropionate?

a. Oral leukotriene-receptor antagonist daily with inhaled albuterol as needed
b. Inhaled beclomethasone combined with albuterol as needed
c. Inhaled fluticasone combined with long-acting beta2 agonist daily
d. All of the above
e. None of the above

Answers: 36 (d); 37 (d); 38 (d)

Clinical Briefs

By Louis Kuritzky, MD, *Clinical Assistant Professor, University of Florida, Gainesville*
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Step-Down Therapy for Controlled Mild Persistent Asthma

For persistent asthma, clinical guidelines recommend low-dose inhaled corticosteroids (LDIC) as initial maintenance therapy. If asthma is well controlled with this treatment, it is suggested that clinicians pursue "step-down therapy," ie, try to reduce the intensity of pharmacotherapy without incurring an increase in asthma symptomatology.

To test the viability of two different step-down regimens, 500 patients with mild persistent asthma that was well controlled on fluticasone 100 mcg b.i.d. were randomized to try either montelukast 5-10 mg once daily or fluticasone 100 mcg + salmeterol 50 mcg once daily. The "control" population continued to receive 100 mcg fluticasone b.i.d. Treatment failure was defined as including any of: hospitalization or acute care asthma visit, need for systemic increased steroids (oral or inhaled), 20% decrease from baseline FEV1, 35% decrease from baseline peak expiratory flow, or frequent use of rescue beta-agonist.

During 4 months of follow-up, treatment failure occurred in the same number of individuals who stepped down to fluticasone + salmeterol (20%) as those who continued on "full dose" inhaled steroid. On the other hand, 30% of the subjects stepped down to montelukast experienced treatment failure.

Use of montelukast for step-down therapy is associated with greater risk of treatment failure than step-down to once daily fluticasone + salmeterol. ■

The American Lung Association Asthma Clinical Research Centers. N Engl J Med. 2007;356:2027-2039.

Risk-management for Persons at High Risk of GI Bleeding

Persons with a history of ulcer bleeding are at great risk of rebleeding if a traditional NSAID is administered: as much as 19% over 6 months. Current guidelines suggest that appropriate steps for risk reduction in such individuals include utilization of a COX-2 inhibitor instead of an NSAID or combining a proton pump inhibitor (PPI) with an NSAID. Trials of such interventions are encouraging, and have shown bleeding rates as low as 5% over 6 months.

Whether combining a PPI with a COX-2 inhibitor would reduce risk still further was the hypothesis question of this trial by Chan et al. Subjects admitted for GI bleeding (n = 273) due to an ulcer on NSAIDs (all of whom were helicobacter negative) were randomized to celecoxib 200 mg b.i.d. plus placebo or esomeprazole 20 mg b.i.d. and followed for 1 year. The primary endpoint was recurrent bleeding within 13 months of study enrollment.

None of the study subjects who received celecoxib + esomeprazole experienced a GI bleed, compared with 8.9% of subjects treated with celecoxib alone. The authors suggest that this data should provide evidence to support recommending celecoxib in combination with a PPI for optimum risk reduction in persons at high risk of GI bleeding. ■

Chan FKL, et al. Lancet 2007;369:1621-1626.

Group visits: Assessment of Patient Acceptance

Group visits (GVIS) have appeal from a variety of vantage points, both patient and provider related. In an era of pressing time constraints and often shrinking resources, GVIS offers some respite. High-profile disorders such a s hypertension, diabetes, obesity, and dyslipidemia (which occupy a compelling place due to both epidemiologic presence and significant consequences) lend themselves well to consideration of GVIS. Clinician advocacy is important in development and utilization of GVIS, but patient acceptance is at least as important.

Kawasaki, et al conducted a survey by a single trained interviewer using a scripted interview of 296 persons with hypertension. After describing GVIS, subjects were asked whether they would be willing to attend one. Subsequently, those who said no were queried as to whether incentives, such as a monetary compensation for parking/transportation, more time with their physician, or less visit waiting time, would induce them to change their mind about GVIS.

With no mention of incentives, 68% of respondents were willing to participate in GVIS. Willingness did not vary across ethnicity, age, or gender. After incentive offering, an additional 37% responded affirmatively to GVIS, with economic subsidy being the least common reason chosen.

These data suggest that patients are receptive, at least in principle, to GVIS, and that individuals with an initially tepid response might warm to the idea if incentives to greater address their personal needs are included. ■

Kawasaki Lm, et al. Am J Managed Care. 2007;13:257-262.

In Future Issues: **Outcomes of Using High- or Low-Dose Atrovastatin**