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IN THE NEWS

Drug Makers Abuse FDA Approval Process

Most drug companies benefiting from the FDA's "accelerated approval" process—a means of expediting approval of drugs intended for patients with life-threatening illness—have not conducted legally required post-marketing studies on their products, according to Rep. Edward J. Markey (D-MA).*

Created in 1992, the FDA's accelerated approval process uses preliminary data indicating drug safety and efficacy to help bring drugs to the marketplace more quickly. This process greatly reduces the typical 10- to 15-year time period required to conceive, develop, and thoroughly test new drugs in animals and humans. In return for the enormous marketing advantages realized by drug makers, it was agreed that rigorous studies validating the preliminary data would continue in accordance with normal approval procedures.

Released on June 1, 2005, Rep. Markey's report, *Conspiracy of Silence: How the FDA Allows Drug Companies to Abuse the Accelerated Approval Process*, reveals that at least 17 drug companies have not completed the FDA-required post-marketing studies. Of the 91 post-marketing studies promised since 1992, only 49 have been completed. Of the 42 pending studies, half have not even been initiated, though some of the approved drugs have been on the market for years; three are in progress but behind schedule; and only 18 are currently meeting scheduled milestones.

Although the FDA has the authority to withdraw drugs from the market in the absence of supporting data, it has not done so in any cases. The need for post-approval studies is well illustrated by AstraZeneca's Iressa®, approved in May 2003 to treat non-small cell lung cancer. While preliminary data suggested that Iressa® would benefit 10% of patients, the FDA's review of the mandated follow-up studies by AstraZeneca concluded that Iressa® provided no survival benefit and that patients taking it should discuss treatment alternatives with their physicians.

The FDA must enforce its requirements for post-marketing studies by drug makers in order to protect public safety.

—Linda M. Smith, RN



Reference

* Available at: http://www.house.gov/markey/Issues/iss_health_pr050601.pdf. Accessed June 15, 2005.

Vitamin B6 Protects Women Against Colorectal Cancer



A diet rich in vitamin B6 may help prevent colorectal cancer, especially in women who consume alcohol, report researchers from Sweden and the United States.*

More than 61,000 women completed questionnaires providing long-term dietary information at the time of study enrollment (1987-1990) and again in 1997. Information was provided regarding family health history, smoking, and dietary intake of red meat, saturated fat, folate, and vitamin B6. Over a mean follow-up period of nearly 15 years, 805 study subjects, aged 41-87, were diagnosed with colorectal cancer. Women in the lowest quintile of vitamin B6 intake had a 34% greater risk of colorectal cancer than did women in the highest B6 intake quintile. Those with the highest B6 intake also had the lowest intake of saturated fat. By contrast, women in the lowest quintile of B6 intake who consumed two or more alcoholic drinks per week were at increased risk of colorectal cancer by as much as 72%.

These findings suggest that vitamin B6 may help prevent colorectal cancer, particularly among

women who drink alcohol. Vitamin B6 plays essential roles in DNA synthesis, repair, and methylation, and suboptimal B6 levels may contribute to colorectal carcinogenesis by impairing these processes. Moderate alcohol intake may exacerbate colorectal cancer risk by reducing intestinal vitamin B6 absorption and decreasing glutathione synthesis, thus making DNA more vulnerable to damage.

—Linda M. Smith, RN

Reference

* Larsson SC, Giovannucci E, Wolk A. Vitamin B6 intake, alcohol consumption, and colorectal cancer: a longitudinal population-based cohort of women. *Gastroenterology*. 2005 Jun;128(7):1830-7.

Green Tea Compound Mimics Anti-Cancer Drug



A compound found in green tea may work in a fashion similar to the anti-cancer drug methotrexate, according to researchers in Spain and England.*

While epidemiological studies have suggested that green tea prevents certain forms of cancer, its protective mechanism has been unknown. Recently, scientists found that epigallocatechin gallate (EGCG), a green tea polyphenol, inhibits the enzyme dihydrofolate reductase (DHFR), an established target for anti-cancer drugs.

Both healthy and cancerous cells require DHFR to manufacture DNA required for cell growth and replication. Certain cancer drugs such as methotrexate work by binding DHFR and blocking its activity. EGCG also binds to DHFR (though not as tightly as does methotrexate) and thus may produce less severe side effects than the drug.

Green tea's EGCG content, which is about five times greater than that of black tea, may account for its long history of use as a cancer-preventive agent. EGCG exerts its anti-cancer effects at concentrations equivalent to those found in the serum and tissues of green tea drinkers.

Large amounts of green tea may decrease the effectiveness of folic acid, a protective agent against birth defects. These findings may explain why women who drink considerable amounts of green tea around the time of conception and early pregnancy experience an increased risk of having a child with a neural tube disorder. This finding provides another reason for why women who might become pregnant should supplement with folic acid.

—Elizabeth Wagner, ND

Reference

* Navarro-Peran E, Cabezas-Herrera J, Garcia-Canovas F, Durrant MC, Thorneley RN, Rodriguez-Lopez JN. The anti-folate activity of tea catechins. *Cancer Res*. 2005 Mar 15;65(6):2059-64.

Melatonin Lessens Pain from Irritable Bowel Syndrome

Melatonin helps ameliorate abdominal pain associated with irritable bowel syndrome (IBS), report researchers at the National University Hospital in Singapore.¹

Best known as a sleep-promoting neurohormone derived from the pineal gland, melatonin is also synthesized in the gastrointestinal tract, where concentrations may be as much as 100 times those in the blood.² In the gastrointestinal tract, melatonin supports stomach lining repair, prevents ulcerations, and increases microcirculation; researchers have speculated that melatonin may have promise in managing gastrointestinal tract disorders.²

In the recent Singapore study, 40 subjects with both IBS and sleep disturbances were randomly assigned to one of two groups. The study group received 3 mg of melatonin at bedtime for two weeks, while the control group received placebo. Before beginning the study and upon its completion, each subject completed four questionnaires to assess bowel symptoms, psychological status, sleep quality, and level of daytime sleepiness. Each subject also underwent rectal pressure determination and a recorded

overnight sleep study.¹

After just two weeks of supplementation, the melatonin-supplemented subjects experienced 58% less abdominal pain, compared to 18% in the placebo group. Such pain indicates gastrointestinal tract hypersensitivity and is the most frequent complaint of IBS sufferers. Other parameters of bowel dysfunction improved in the melatonin group, though this difference was not statistically significant. The two groups reported no differences regarding sleep parameters.¹ Melatonin thus shows promise in alleviating the gastrointestinal discomfort associated with IBS.

—Linda M. Smith, RN

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2. Bubenik GA. Gastrointestinal melatonin: localization, function, and clinical relevance. *Dig Dis Sci*. 2002 Oct;47(10):2336-48

IN THE NEWS

Magnesium May Help Obese Children Avoid Diabetes



Increasing dietary or supplemental magnesium intake may help prevent type II diabetes in obese children, according to a recent study from the University of Virginia.¹ While large studies have established a relationship between low dietary magnesium and increased risk for type II diabetes in adults,² a similar relationship in children has not previously been investigated.

In the Virginia study, 24 obese, nondiabetic children demonstrated significantly lower serum magnesium and dietary magnesium intake than did 24 lean children matched for age and sex. Compared with obese children, lean children consumed more magnesium from leafy green vegetables, fish, beans, yogurt, nuts, and peanut butter. Children with lower levels of serum magnesium and lower dietary magnesium intake had markedly higher levels of fasting insulin and reduced insulin resistance, a precursor to type II diabetes.¹ Approximately 27% of healthy lean children and 55% of obese children had low serum magnesium, “indicating that serum magnesium

deficiency may be more prevalent in children than previously suspected.”¹

Magnesium supplementation in people with insulin resistance may improve insulin sensitivity.³ In animal models, increased magnesium intake reduces the rate of developing type II diabetes.⁴ Magnesium’s role in preventing diabetes is unclear, but it is required for enzyme reactions involved in carbohydrate metabolism.

—Laurie Barclay, MD

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2. Lopez-Ridaura R, Willett WC, Rimm EB, et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care*. 2004 Jan;27(1):134–40.
3. Guerrero-Romero F, Tamez-Perez HE, Gonzalez-Gonzalez G, et al. Oral magnesium improves insulin sensitivity in non-diabetic subjects with insulin resistance. A double-blind placebo-controlled randomized trial. *Diabetes Metab*. 2004 Jun;30(3):253–8.
4. Balon TW, Gu JL, Tokuyama Y, Jasman AP, Nadler JL. Magnesium supplementation reduces development of diabetes in a rat model of spontaneous NIDDM. *Am J Physiol*. 1995 Oct;269(4 Pt 1):E745-52.

Vitamin D Cuts Fracture Risk in Elderly



Vitamin D supplementation reduces the risk of hip or nonvertebral fracture in older people by approximately 25%, according to a meta-analysis recently published in the *Journal of the American Medical Association*.*

While vitamin D supplementation has long been supported as a possible preventive measure in reducing the risk of bone fracture—a major cause of morbidity and mortality in the elderly—some studies have failed to correlate supplementation with a reduced risk of fractures. To clarify the relationship between vitamin D supplementation and fracture risk, researchers at the Harvard School of Public Health and other institutions performed a meta-analysis of all related medical articles published between 1960 and 2005.

After analyzing seven studies involving nearly 10,000 patients, the investigators concluded, “oral vitamin D supplementation between 700 to 800 IU per day appears to reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons.” Those taking 700 to 800 IU a day of vitamin D had a 26% reduction in hip fractures and a 23% reduction in nonvertebral fractures compared to participants taking calcium alone or placebo. The researchers hypothesize that vitamin D may exert its protective effects by either decreasing bone loss in the elderly or reducing the chance of a person falling by exerting a

beneficial effect on muscle strength and balance.

“An oral vitamin D dose of 400 IU per day is not sufficient for fracture prevention,” wrote the researchers. “Our results are compelling for general vitamin D supplementation in the range of 700 to 800 IU per day in elderly persons.”

In all but one of the analyzed studies, the participants took calcium in combination with vitamin D. Because of the lack of studies examining vitamin D alone, the researchers were unable to determine whether vitamin D acts independently or together with calcium in reducing fracture risk.

—Marc Ellman, MD

Reference

* Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA*. 2005 May 11;293(18):2257-64.

Dietary Vitamin E May Protect Against Parkinson's



Consuming a diet rich in vitamin E may help reduce the risk of developing Parkinson's disease, reports a review article recently published in the *Lancet Neurology* journal.*

Investigators at the Royal Victoria Hospital in Quebec, Canada, conducted a systematic review and meta-analysis of observational studies published between 1966 and 2005. Using data from eight studies, they concluded that both moderate and high levels of dietary vitamin E intake helped reduce the risk of developing Parkinson's disease. By contrast, the studies did not suggest that vitamin C or beta-carotene confers protection against Parkinson's.

Gamma tocopherol is the predominant form of vitamin E in food sources, while alpha tocopherol is the most prevalent form in nutritional supplements. Foods rich in vitamin E include nuts, seeds, wheat germ, and spinach and other leafy green vegetables.

Parkinson's is a chronic, irreversible neurodegenerative disease affecting about 1% of all adults over the age of 65 worldwide. Its symptoms include tremors, stiffness, slow movement, and poor coordination and balance.

This study suggests that dietary vitamin E provides a neuroprotective effect against the development of Parkinson's disease. Randomized controlled trials are indicated to confirm these results.

—Elizabeth Wagner, ND

Reference

* Etninan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. *Lancet Neurol*. 2005 Jun;4(6):362-5.

Grapes Guard Against Atherosclerosis in Animals



Grapes may help protect against the development of atherosclerosis, a thickening and hardening of the arteries that is a leading cause of morbidity and mortality worldwide, according to a recent study conducted at the Lipid Research Laboratory at Israel's Rambam Medical Center.* This finding may help account for epidemiological studies that have suggested a protective effect of red wine against heart attack.

In their study, the Israeli scientists used mice bred to develop atherosclerosis. Thirty mice were assigned to consume water alone, a placebo, or a polyphenol-rich, freeze-dried extract of fresh California grapes in drinking water for 10 weeks.

Consumption of grape powder reduced the atherosclerotic lesion area by 41% compared to the control and placebo groups. The

anti-atherosclerotic effect was at least partly due to a significant 8% reduction in serum oxidative stress and an increase in serum antioxidant capacity of as much as 22%. Furthermore, the grape powder protected both plasma LDL (low-density lipoprotein) and macrophages from oxidative stress.

“Grapes contain an abundance of powerful antioxidants that appear to inhibit an array of critical factors that can cause atherosclerosis,” noted principal investigator Bianca Fuhrman. Phytochemicals called polyphenols may be responsible for the potent antioxidant effects of grapes.

—Elizabeth Wagner, ND

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* Fuhrman B, Volkova N, Coleman R, Aviram M. Grape powder polyphenols attenuate atherosclerosis development in apolipoprotein E deficient (E0) mice and reduce macrophage atherogenicity. *J Nutr.* 2005 Apr;135(4):722-8.

IN THE NEWS

Dietary Antioxidants May Mitigate Stroke Damage



Intake of antioxidant-rich foods reduces brain damage from ischemic stroke and improves post-stroke movement recovery in test animals, according to scientists at the National Institute on Drug Abuse in Baltimore, MD.¹

Previous studies have demonstrated that an antioxidant-rich diet protects aging animals from neurodegenerative changes. The Maryland study investigated a potential protective role of antioxidant-rich foods against ischemia, or lack of oxygen, as occurs with stroke.

For four weeks, adult rats were fed either a control diet or one supplemented with blueberry, spinach, or spirulina. Strokes were then surgically simulated in the rats. Those that received the blueberry-, spinach-, or spirulina-enriched diets had a significantly reduced volume of infarction in the cerebral cortex and an increase in post-stroke locomotor activity. Rats supplemented with blueberry or spinach had half as much brain damage as the control group, while the spirulina group had stroke lesions that were 75% smaller than those in the untreated group.¹

Fruits and vegetables are rich sources of antioxidants, and abundant intake of these plant-based foods has been reported to help improve health and reduce the incidence of disease.² Blueberries, spinach, and spirulina are rich in phytochemicals—including carotenoids, flavonoids, and anthocyanins—and have demonstrated particularly powerful antioxidant and free radical-scavenging activity.^{2,3} The Maryland study suggests a role for antioxidant-rich foods in protecting the brain against the effects of stroke.¹

—Christie C. Yerby, ND

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3. Reddy MC, Subhashini J, Mahipal SV, et al. C-Phycocyanin, a selective cyclooxygenase inhibitor, induces apoptosis in lipopolysaccharide-stimulated RAW 264.7 macrophages. *Biochem Biophys Res Commun*. 2003 May 2;304(2):385-92.

Sigmoidoscopy Overlooks Colon Cancer in Women



Sigmoidoscopy fails to detect colon tumors in nearly two thirds of women who have them, according to a recent study published in the *New England Journal of Medicine*.^{*} Sigmoidoscopy and colonoscopy are widely used screening tools to detect colon tumors. Both procedures use a long, flexible tube to inspect the colon for growths or polyps. The colonoscope is longer and is able to examine the entire six-foot length of the colon, while the sigmoidoscope examines only the lower two feet of the colon. Sigmoidoscopy is faster and less expensive than colonoscopy, and does not require the use of sedatives as colonoscopy does. However, the effectiveness of sigmoidoscopy is already in question, as studies in men have shown that it succeeds in detecting tumors in only 66% of average-risk men who have them.

The researchers studied nearly 1,500 women, aged 50-79, who were considered at average risk of colon cancer. Using colonoscopy, these asymptomatic women were screened for growths of the colon. The investigators then calculated how many women who had colon lesions would have been detected had sigmoidoscopy been used instead. Lesions were considered detectable by sigmoidoscopy if they were in the distal colon or if proximal colon tumors were accompanied by concurrent small adenomas in the distal colon, a finding that would have led to a colonoscopy.

Using colonoscopy as the primary screening tool, advanced neoplasia was found in 72 (4.9%) of 1,463 women. Had flexible sigmoidoscopy been used as the primary screening tool, advanced neoplasia would have been detected in only 25 (1.7%) of

these women and missed in 47 (3.2%). Thus, only 35.2% of women with advanced neoplasia of the colon would have been identified using sigmoidoscopy alone. Colonoscopy thus appears to be more effective than sigmoidoscopy in screening women for colon cancer.

—Elizabeth Wagner, ND

Reference

* Schoenfeld P, Cash B, Flood A, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med*. 2005 May 9;352(20):2061-8.

Selenium Aids in Treating Prostate Cancer

Emerging research suggests that the trace mineral selenium may be invaluable in the fight against prostate cancer.¹ Selenium may help make prostate cancer cells more vulnerable to self-destruction, or apoptosis, report researchers at the Fox Chase Cancer Center in Philadelphia, PA.¹

Selenium helps prostate cancer cells overcome their resistance to tumor necrosis factor-related apoptosis-inducing li-gand (TRAIL). An endogenously (internally) produced promoter of cell death, TRAIL is being researched as an experimental cancer drug. While TRAIL has shown promise against a wide variety of cancer cells, some cell types seem resistant to its effects.

Previous studies have demonstrated that selenium helps reduce prostate cancer risk, possibly by protecting prostate cells against DNA damage.² The Philadelphia study took selenium research a step further, demonstrating that selenium sensitizes resistant prostate cancer cells to TRAIL, enabling the compound to destroy them.¹ The researchers found that selenium contributed to an “amplification” loop in which the TRAIL drug set off a chain reaction of cell death among prostate cancer cells. Interestingly, neither selenium nor TRAIL was as effective on its own, indicating a synergistic effect of the two compounds.¹

“The combination of a TRAIL and [selenium] may be a novel strategy for the development of innovative therapeutic modalities targeting apoptosis-resistant forms of prostate cancer,” concluded Vladimir M. Kolenko, MD, PhD, a lead author on the study.¹

—Jon VanZile

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