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Is Your Life's Wine Bottle Half-Full or Half-Empty?

ABSTRACT & COMMENTARY

Synopsis: *Maruta and colleagues conclude that a pessimistic explanatory style, as measured by the Optimism-Pessimism scale of the MMPI, was significantly associated with increased mortality.*

Source: Maruta T, et al. *Mayo Clin Proc* 2000;75:140-143.

It has been known for many years that animals subjected to unpleasant events that were out their control often demonstrated diminished immune function and an inability to reject implanted tumors.[1,2] Anecdotal reports regarding helplessness associated with mortality in humans led researchers to study traits that turned out to be major contributors to helplessness, that is, pessimism and optimism. It was rapidly discovered that pessimistic individuals, that is, those individuals who interpret bad events as permanent and pervasive, became relatively helpless and depressed more easily than did optimists, who would look upon bad events as temporary, controllable, and regionally well defined.

Over the past 25 years, multiple studies have revealed that individuals who are pessimistic regarding life's events frequently are afflicted with poor physical health,[5,6] are prone to depression,[7] and are frequent users of both mental health care and medical delivery systems.[8] Maruta and colleagues from the Mayo Clinic studied 1145 consecutive patients self-referred to the Mayo Clinic Division of Community Internal Medicine between 1962 and 1965. Each patient was scored using the Optimism-Pessimism (PSM) scale of the Minnesota Multiphasic Personality Inventory (MMPI) and 30 years later the vital status of each of these patients was ascertained in order to determine if pessimism was a risk factor for mortality. Of the 839 patients studied, 124 were classified as optimistic, 518 as mixed, and 197 as pessimistic; at the end of 29 years, 723 were successfully contacted. After adjusting for sex, age, and expected survival, a PSM scale score that was higher by only 10 points (i.e., indicating the individual to be more pessimistic) was associated with a 19% increase in the risk of death. Maruta et al concluded that a pessimistic explanatory style, as measured by the PSM scale of the MMPI, was significantly associated with increased mortality.

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INSIDE

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

The link between mind, body, and mortality has been postulated and supported by philosophers, physicians, and life observers since the time of Plato, who claimed that mind and body are one and indivisible. Even though the exact nature of how the mind influences the body and its functions has not been clearly determined, numerous studies have suggested that the manner in which people attempt to understand or explain the causes of stressful or adverse life events, in particular, if they are subject to a pessimistic explanatory style, can significantly undermine their psychologic and physiologic functioning; in fact, a pessimistic outlook has been clearly demonstrated to adversely affect the course of many illnesses.[9] This study is extremely important since Maruta et al were successful in creating a subscale with which they were able to test the long-term effects of pessimism on physical illness and mortality.[10] Equally important, they were able to test this subscale analytic technique in a large number of patients who had taken the MMPI at least 29 years earlier. Two hundred deaths occurred among the 723 patients who were able to be contacted and, in this group, there seems to be little question that the mortality rates were significantly increased in the more pessimistic individuals.

Additional long-term studies may be necessary to confirm the findings of Maruta et al; however, even if we assume the data to be accurate, we still have no explanation as to exactly how a pessimistic explanatory mechanism acts as a risk factor for early mortality. Optimists who are less likely to develop depression and learned helplessness have less tendency to self-blame and catastrophic thinking and appear to be more positive in seeking and receiving medical care. It is quite possible that the negative effects of pessimism may increase mortality by decreasing the responsiveness of the immune system. Regardless, if the half-empty bottle manifested by pessimism shortens life and the half-full bottle of optimism prolongs life, it certainly would seem appropriate to attempt to identify pessimistic individuals early on in their lives since aggressive behavioral intervention may be helpful in creating lasting changes in their explanatory style, that is, such intervention may make them less pessimistic. In other words, it may be possible to direct pessimistic individuals into behavioral treatment programs early in their school years since appropriate clinical interventions in the early years may help to move an explanatory style more toward the optimistic pole[10,11] and therefore reduce overall mortality. There now appears to be little question that one is much better off with a positive, outgoing optimistic personality—the half-full bottle appears to have won hands down. Hopefully, Maruta et al will soon publish additional papers that will delve into the exact causes of mortality among both the optimistic and pessimistic individuals in somewhat more detail. ❖

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Are Bisphosphonates Really Toxic to the GI Tract?

ABSTRACT & COMMENTARY

Synopsis: *Lowe and colleagues conclude that alendronate does not cause predictable esophageal, gastric, or duodenal mucosal damage when used as directed.*

Source: Lowe CE, et al. *Am J Gastroenterol* 2000;95: 634-640.

Lowe and colleagues conducted a double-blind, randomized, placebo-controlled trial with 32 healthy female volunteers aged between 40 and 65 years. They were randomized to receive either placebo or alendronate 10 mg daily for one month. Endoscopic mucosal abnormalities in the esophagus, stomach, and duodenum were scored and compared using validated endoscopic grading systems before and after one month of treatment. Symptom scores were also evaluated, and small intestinal permeability assessed. Lowe et al found no difference in symptom or endoscopic scores for the esophagus, stomach, or duodenum before and after treatment with alendronate or between the alendronate and placebo groups. There were also no significant changes in mucosal permeability in the stomach or small intestine. Lowe et al conclude that alendronate does not cause predictable esophageal, gastric, or duodenal mucosal damage when used as directed.

COMMENT BY EAMONN M.M. QUIGLEY, MD

Bisphosphonates have assumed an important role in the management of osteoporosis, an increasingly common problem among the elderly female population. Initial reports suggested that their use was associated with significant upper gastrointestinal (GI) mucosal damage, especially involving the esophagus. However, large randomized controlled trials have failed to support these data. This carefully performed study suggests that, when the dose of alendronate is not excessively high, and when the drug is taken as directed (i.e., medication taken with a full glass of water and the patient remains upright for 30 minutes post-ingestion), its use is not associated with GI symptoms, endoscopic damage, mucosal pathology, or altered mucosal permeability. While these findings are reassuring, it must be conceded that they do not rule out the possibility of mucosal injury in particularly susceptible individuals or with higher doses. ❖

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Comparing Oral Montelukast with Inhaled Salmeterol for Exercise-Induced Bronchoconstriction

ABSTRACT & COMMENTARY

Synopsis: *This study concluded that montelukast provides a consistent inhibition of exercise-induced bronchoconstriction at the end of eight weeks without tolerance.*

Source: Edelman JM, et al. *Ann Intern Med* 2000;132: 97-104.

Exercise-induced bronchoconstriction occurs in a majority of adults with chronic asthma. It is defined as bronchial narrowing in association with vigorous exercise. The stimulus for exercise-induced bronchoconstriction is not the exercise itself but the cooling and drying of the airway mucosa hypothesized to stimulate the activation of mast cells and release of bronchoconstricting mediators. These mediators include histamine and the cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4).

The selective β-2 adrenergic agonists, particularly the long-acting type such as inhaled salmeterol, have been used to prevent bronchoconstriction that occurs at night or after exercise. It has been recognized that a single dose of salmeterol attenuates exercise-induced bronchoconstriction for at least 12 hours. However, it has been shown that with extended administration of salme-

terol, the duration of protection decreases.[1]

Montelukast is a potent, oral, leukotriene receptor antagonist for the treatment of asthma. It has been shown that once-daily treatment with montelukast provides significant protection against exercise-induced bronchoconstriction over a 12-week period and tolerance to the medication is not seen after this long-term administration.[2]

The present study was a comparative trial of the effect of inhaled salmeterol vs. oral montelukast for exercise-induced bronchoconstriction asthma. It involved 17 asthma treatment centers in which 191 adults with asthma and documented exercise-induced bronchoconstriction were randomly assigned to double-blind treatment with montelukast (10 mg once every evening) or inhaled salmeterol (50 mg [2 puffs] twice daily).

Changes in pre- and post-exercise values, mean change from baseline in maximal percentage decrease in FEV_1, area under the FEV_1 curve, and time to recovery of FEV_1 were assessed at days 1, 2, 3, 28, and 56. Within three days of therapy, both treatments provided significant attenuation of exercise-induced bronchoconstriction for all study end points. At weeks 4 and 8, sustained improvement was demonstrated by montelukast and a loss of bronchoprotective effect in the salmeterol group was noted. The percentage inhibition of the maximal percentage decrease in FEV_1 at week 8 was 57.2% in the montelukast group and 33.0% in the salmeterol group, representing greater bronchoprotective effect for montelukast.

Edelman and colleagues conclude that once-daily long-term therapy with montelukast may provide better bronchoprotection against exercise-induced asthma than long-term inhaled salmeterol.

COMMENT BY DAVID OST, MD

The prevalence of exercise-induced bronchoconstriction among asthmatics has been reported to range from 40-90%.[3] It was evident that about half of the subjects in this study had mild intermittent asthma and about half had mild persistent asthma (based on FEV_1 and symptoms). None of the patients was on inhaled steroids.

The article demonstrates that in this group of patients, montelukast rendered significantly greater inhibition of exercise-induced bronchoconstriction compared with salmeterol at four and eight weeks of therapy. Previous findings with salmeterol have suggested that partial tolerance develops at four and eight weeks. This is in contrast to montelukast, in which the bronchoprotective effect was maintained. They also noted that fewer patients on montelukast required β-agonist rescue after exercise compared with the salmeterol group.

Oral montelukast is more convenient to take than inhaled salmeterol and this study suggests that tolerance to montelukast does not develop as readily as it does to salmeterol. For mild asthmatics with primarily exercise-induced symptoms, montelukast may represent a good initial treatment. ❖

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Postmenopausal Estrogen-Progestin Therapy and Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *Ross and colleagues conclude that the addition of a progestin to an estrogen postmenopausal regimen increases the risk of breast cancer compared with the use of estrogen alone.*

Source: Ross RK, et al. *J Natl Cancer Inst* 2000;92:328-332.

Ross and colleagues from the university of southern California reported the results of a population-based, case-control study of breast cancer risk associated with postmenopausal hormone therapy, both estrogen alone and combined estrogen-progestin in sequential and daily, continuous regimens. Combined estrogen-progestin therapy was associated with a higher odds ratio per five years of use (OR = 1.24; CI = 1.07-1.45) compared with estrogen alone (OR = 1.06; CI = 0.97-1.15). Sequential estrogen-progestin regimens were associated with a higher odds ratio per five years of use (OR = 1.38; CI = 1.13-1.68) compared with a daily, continuous combined regimen (OR = 1.09; CI = 0.88-1.35). The difference between sequential and continuous regimens was not statistically significant. Ross et al conclude that the addition of a progestin to an estrogen postmenopausal regimen increases the risk of breast cancer compared with the use of estrogen alone.

COMMENT BY LEON SPEROFF, MD

In the introduction to this case-control study, Ross et al, with some obvious pride, claim that this study provides the most definitive and detailed data yet available between estrogen-progestin use and breast cancer risk. If

that is the case, then their conclusion that this study "provides strong evidence that the addition of a progestin enhances markedly the risk of breast cancer relative to estrogen use alone" hardly warrants the modifying adjective and adverb so carefully chosen by Ross et al.

Let me point out some of the weaknesses that were interpreted as strengths. The difference between sequential and daily estrogen-progestin regimens was not statistically significant, but Ross et al were obviously unencumbered by this fact in their emphasis upon a difference between the regimens, especially and unfortunately, in the press release originating from the University of Southern California. The increased relative risks (RR) associated with sequential and daily estrogen-progestin regimens for more than 10 years were based on 27 cases/14 controls and 13 cases/20 controls, respectively; hardly the robust numbers claimed by Ross et al in their introduction. Indeed, where the numbers of cases were substantial, the estrogen-only users, the analysis of estrogen alone regimens indicated no statistically significant increased risk of breast cancer, even with increasing duration of use up to more than 15 years (OR = 1.06; CI = 0.97-1.15). When analyzed by stage of disease, combined estrogen-progestin regimens were associated with a barely significant increase in localized disease and no significant increase in in situ or advanced disease; sequential estrogen-progestin regimens with a significant increase in localized disease and no significant increase in in situ or advanced disease; and daily estrogen-progestin regimens with no significant increase in any of the categories. This variation and the strength of the associations (RRs that range from 0.98 to 1.44) do not provide evidence of a major effect.

The emphasis and interpretation of the current reports examining the effect of estrogen and progestin could have been of a totally different nature. The numbers indicated no significant increased risk with estrogen therapy, even of long duration, a conclusion based on more cases compared with the number of cases in estrogen-progestin users. If one placed the emphasis where the greater numbers are, the message would be a reassuring one.

The available epidemiologic evidence summarized in tables 1 and 2 on the effect of combined estrogen-progestin treatment on the risk of breast cancer indicates a mixed story, not a uniform and consistent result (10 negative studies and 4 positive studies). Those who implicate progestins have given great weight to the observation that proliferation and mitotic activity peak in the luteal phase. Recent studies, however, indicate that prolonged exposure to a constant level of progestin (unlike pregnancy or a menstrual cycle) provides an inhibiting influence, a possible advantage for the postmenopausal regimen of the daily, continuous administration of estrogen-progestin.

Table 1

Relative Risks of Breast Cancer Associated with Postmenopausal Estrogen-Progestin Treatment (Statistically Significant)

Reference	Relative Risk	(Confidence Interval)
Colditz GA, et al, 1995.[1]	1.41	(1.15-1.74)
Persson I, et al, 1999.[2]	1.7	(1.1-2.6) > 6 yrs
Magnusson C, et al, 1999.[3]	1.68	(1.39-2.03)
Schairer C, et al, 2000.[4]	1.40	(1.1-1.8)

Table 2

Relative Risks of Breast Cancer Associated with Postmenopausal Estrogen-Progestin Treatment (Not Statistically Significant)

Reference	Relative Risk	(Confidence Interval)
Kaufman DW, et al, 1984.[5]	1.7	(0.9-3.3)
Ewertz M, et al, 1988.[6]	1.36	(0.98-1.87)
Bergvist L, et al, 1989.[7]	4.4	(0.9-22.4)
Yang CP, et al, 1992.[8]	1.2	(0.6-2.2)
Stanford JL, et al, 1995.[9]	0.9	(0.6-1.2)
Newcomb PA, et al, 1995.[10]	0.75	(0.49-1.15) < 5 yrs
	1.12	(0.72-1.76) > 5 yrs
LaVecchia C, et al, 1995.[11]	1.6	(0.4-6.3)
World reanalysis, 1997.[12]	1.53	(0.80-2.92)
Brinton LA, et al, 1998.[13]	0.99	(0.7-1.3)
Persson I, et al, 1999.[2]	1.4	(0.9-2.3) 1-6 yrs

There is another aspect of this controversial issue that deserves more publicity. Most of the studies that have examined the breast cancer mortality rates of women who had used postmenopausal hormone therapy have documented improved survival rates.[14-23] Even studies that detect an increased risk of breast cancer in hormone users indicate a paradoxical better outcome. This undoubtedly partly reflects earlier diagnosis in users because the greater survival rate in current users is associated with a lower frequency of late stage disease.[12,15,19,22,24-27] There is also evidence to suggest that estrogen users develop smaller, better-differentiated (lower grade) tumors, and that surveillance/detection bias is not the only explanation for better survival.[25,27-31] These biologic differences imply that hormone treatment promotes the growth of a malignant locus already in place, and it presents clinically with a more favorable biology. This conclusion is consistent with the fact that virtually all

the positive studies find that any increase in risk disappears within five years of discontinuing hormone therapy, and tumors occur at an earlier stage and a younger age in women using hormone therapy. Lower grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers, or when the data are adjusted for the method of detection.[21,23,31] Thus, an important effect is on grade of disease, tumor differentiation, and aneuploidy. An excess of grade I tumors has been documented equally in users of estrogen alone and in users of combined estrogen and progestin.[32]

It is, in my view, appropriate to emphasize the benefits of postmenopausal hormone therapy, point out the continuing concern regarding the relationship between estrogen use and breast cancer (particularly long-term use), and to emphasize the absence of definitive evidence linking such therapy to an increased risk of breast cancer, as well as the uniform data indicating better outcomes in hormone users who develop breast cancer. Additional case-control and cohort studies will only confirm the variability and inconsistency of the findings. Thus, a definitive answer must await the results of the ongoing randomized trials. (*Dr. Speroff is Professor of Obstetrics and Gynecology, Oregon Health Sciences University, Portland, OR.*) ❖

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Pharmacology Update

Mometasone Furoate Nasal Spray (Nasonex—Schering)

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

The fda has approved a nasal steroid for use in children as young as 3 years of age. Schering's mometasone furoate nasal spray (Nasonex) is the first drug in this class to be approved for use in children this young for the treatment of allergic rhinitis. The approval was prompted by recent studies that reported that mometasone, in contrast to beclomethasone, did not affect bone growth in children after one year of treatment.[1,2] Other nasal steroids are approved for use in children but beginning at somewhat older ages—fluticasone is approved for use down to the age of 4 and the others (flunisolide, triamcinolone, budesonide, becomethasone) down to the age of 6. Mometasone has been marketed for use in adults and children 12 years of age and older since 1997.

Indications

Mometasone is indicated for the treatment of the nasal symptoms of seasonal allergic and perennial allergic rhinitis in adults and pediatric patients 3 years of age and older.

Dosage

The recommended dose for adults and children 12 years of age and older is two sprays in each nostril once daily (200 mcg per day). For children 3-11 years of age the recommended dose is one spray in each nostril once

daily (100 mcg per day).[3]

The pump needs to be primed by actuating 10 times or until a fine spray appears. If the spray has not been used for more than one week the pump should be reprimed by actuating two times.[3] Mometasone is supplied as a metered dose nasal spray (17 g) containing 120 sprays (50 mcg per actuation).

Potential Advantages

Mometasone has low bioavailability (≤ 0.1%) and is also extensively metabolized, which minimizes systemic exposure.[4] In a one-year study in children (3-9 years of age) with perennial allergic rhinitis, mometasone 100 mcg daily did not affect growth or lead to suppression of the hypothalamic pituitary adrenal (HPA) axis.[1] Height was measured at baseline and at 4, 8, 12, 26, 39, and 52 weeks with a calibrated stadiometer. HPA suppression was assessed by cosyntropin stimulation testing at baseline and at 26 and 52 weeks. Mometasone is approved for use in children as young as 3 years of age.

Potential Disadvantages

Nasal steroids in general have a slower onset of action than antihistamines for the treatment of allergic rhinitis. Maximum effect occurs about 7 to 14 days after initiation of treatment although effect may be noticed the first day.[4]

Comments

Mometasone furoate is a corticosteroid for intranasal administration which is dosed once daily and appears to have minimal systemic activity. Recently it gained FDA approval for use in pediatric patients as young as 3 years of age. Data from comparative trials indicate that mometasone is comparable to other intranasal steroids (e.g., beclomethasone, fluticasone) in the treatment of perennial allergic rhinitis and seasonal allergic rhinitis.[4,6] Median time to at least moderate symptom relief was 36 hours compared to 72 hours for placebo. Approximately 64% of treated patients experienced moderate symptom relief at 72 hours.[5] In an acute exposure setting, mometasone was reported to produce statistically significant improvement in nasal symptoms in patients with seasonal allergic rhinitis by seven hours.[7]

Clinical Implications

The findings of a recent study, supported by Schering and Glaxo Wellcome, indicated that treatment with intranasal beclomethasone (168 mcg twice daily) can slow growth rate in prepubescent children without showing suppression of the HPA axis.[2] The mean change in standing height after one year was 5.0 cm in the beclomethasone group compared to 5.9 cm in the placebo-treated group. The difference was evident as early as the first month of treatment. In another study of essentially identical design supported by Schering, mometasone (100 mcg daily) showed no suppression of growth.[1] At the one-year point, the change in height was 6.95 cm vs. 6.35 cm for mometasone and placebo, respectively. Some data suggest that patients who experienced delays in growth may still achieve final height.[8] The FDA is encouraging further studies in this area and has added a class labeling stating that these agents may cause a reduction in growth velocity in pediatric patients.

It is recommended that pediatric patients minimize exposure to total corticosteroids, from various routes, and physicians titrate each patient to the lowest effective dose. ❖

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CME Questions

26. The following statements regarding the risk of breast cancer associated with postmenopausal hormone therapy are true *except*:

a. The data available from case-control and cohort studies do not provide uniform, consistent results.
b. Women who use postmenopausal hormone therapy and develop breast cancer while using hormone therapy have a reduced risk of dying of breast cancer.
c. Postmenopausal hormone users have more breast exams and mammograms.
d. The relative risks of breast cancer associated with postmenopausal hormone therapy are in the range recognized as strong associations (> 2.0).

27. Which is *not* true about mometasone?

a. It has been approved for use in children as young as 3 years old.
b. It affected bone growth in children after one year of treatment.
c. It is a nasal spray.
d. The maximum effect occurs about seven to 14 days after initiation of treatment.

By Louis Kuritzky, MD

Orlistat in the Long-Term Treatment of Obesity in Primary Care Settings

Obesity is a problem in about 30% of the U.S. population, but few successful long-term strategies have been identified. Recently, focus has been shifted from achievement of ideal body weight to achievement and maintenance of 5-15% reductions in body mass index (BMI), which translate into meaningful improvements in traditional cardiovascular risk factors. Most studies of pharmacotherapy for obesity have been short term, and have studied populations in non-primary-care settings. This report details a primary care setting study of obese persons (BMI ≥ 30) who were treated with diet combined with orlistat 60 mg or 120 mg thrice daily for two years (n = 635).

The larger dose of orlistat produced a 7.9% decrease from initial body weight, compared with a 4.2% decline in the placebo group at the one-year mark (both groups received dietary intervention). Maintenance of weight loss was significantly better for orlistat recipients than placebo. Approximately half of orlistat-treated patients lost at least 5% of their initial body weight by one year, compared with 30.7% in the placebo group. Lipid levels and blood pressure were favorably affected by drug treatment.

Tolerance of treatment was excellent; rates of withdrawal due to adverse events were not statistically different between placebo and treatment groups. GI effects, the most frequent adverse experience, were generally transient and mild to moderate, resolving without intervention.

Orlistat is effective and well tolerated over the long term in the primary care setting. ❖

Hauptman J, et al. Arch Fam Med 2000;9:160-167.

Dissociation in Near-Death Experiences

The term dissociation has been described as "a separation of thoughts, feelings, or experiences from the normal stream of consciousness and memory." The ranges of this experience extend from simple daydreaming to multiple personalities. Dissociation is not always considered pathologic, and has been described in victims of trauma, rape, or other intense emotional/physical assault.

Near-death experiences (NDE) are often described as a perception of having left the physical boundary and transcending time/space boundaries. There has been the suggestion that NDE are, in fact, dissociations. Greyson studied the frequency of dissociation among people who reported NDE, comparing this with the frequency of dissociation in persons who had been close to death but did not experience NDE. The instrument used to measure dissociation was the Dissociative Experiences Scale (DES), a 28-item visual analogue scale measuring a variety of different dissociative experiences.

Evaluation of 134 individuals who reported having been close to death determined that 72% described NDE. Scores on the DES for persons experiencing NDE were significantly higher than for individuals who had not experienced NDE, but the DES scores were not as high as those seen in persons with pathologic dissociative disorders. Greyson concludes that NDE are not a manifestation of a dissociative disorder nor are they a pathological type of dissociation. ❖

Greyson B. Lancet 2000;355:460-463.

Oral Androstenedione Administration and Serum Testosterone Concentrations in Young Men

Androstenedione (ansd) has recently become popular among the lay public for (unsubstantiated) claims that it will have anabolic effects similar to those of anabolic steroids, reportedly increasing testosterone levels. Since ANSD is available over the counter as a dietary supplement, substantial numbers of individuals may be using it in an attempt to enhance athletic ability, without proof of efficacy. The current study examined the effect of 100-300 mg per day ANSD orally on testosterone levels in healthy young men (n = 42). Measured responses included testosterone, estradiol, estrone, LH, FSH, and sex-hormone-binding globulin.

Serum testosterone was significantly increased by the 300-mg dose ANSD, but not by the 100-mg dose. Both ANSD doses significantly increased estradiol and estrone levels. Other measured markers did not change with ANSD supplementation. This study documents that short-term administration of higher doses (at least 300 mg) of ANSD are associated with increased levels of testosterone. Such elevations in women could have virilizing effects; in men, the elevated estrogen could also have feminizing effects (e.g., gynecomastia); in children, premature epiphyseal closure due to supraphysiologic amounts of gonadal steroids could lead to reduced ultimate height. ❖

Leder BZ, et al. JAMA 2000;283: 779-782.

In Future Issues: Monitoring Osteoporosis Therapy with Bone Densitometry