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INSIDE

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Magnesium Sulfate Tocolysis

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

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

Synopsis: *Given its lack of benefit, possible harms, and expense, magnesium sulfate should not be used for tocolysis.*

Source: Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol.* 2006;108:986-989.

In the vast majority of hospitals magnesium sulfate has been the drug of choice to stop labor in patients presenting with preterm contractions. The usual regimen of the loading dose of 4-6 grams followed by 1.5-5 grams per hour has been so well entrenched in obstetrical care that the magnesium bottle is hung the minute the preterm labor patient signs her hospital admission papers. Yet, nobody has questioned this practice until recently, when David Grimes, a noted authority on evidence based medicine, decided to take on magnesium sulfate.

In an editorial in *Obstetrics & Gynecology*, Grimes reviewed the literature comparing magnesium sulfate with placebo or other tocolytics in the treatment of preterm labor. He particularly focused on the Cochrane database which included 2000 patients in 23 studies. Magnesium sulfate had no advantage over controls with regard to delivery within 48 hours, delivery before 34 weeks, or delivery prior to 37 weeks. If this was a surprise to some, the "do no harm" part was equally as attention getting. Seven studies involving 727 patients found that the relative risk of pediatric death with magnesium sulfate was 2.8 (95% CI, 1.2-6.6). Also, its usage was not associated with the decrease in reparatory distress syndrome, interventricular hemorrhage, or necrotizing enterocolitis.

Maternal mortality was increased 4.7 fold when the above standard dose was utilized for more than 24 hours (total dose of 48 grams).

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COMMENTARY

The title of the above editorial was "Magnesium sulfate tocolysis: time to quit." This may be tough to do, especially when seemingly the alternative is to do nothing. Although going "cold turkey" is very unappealing, our colleagues in hospital administration will be all too happy to shave our hospital staff by at least one nursing FTE for all the IV infusions that will not need to be started and maintained.

Dr. Grimes does offer an alternative treatment, a calcium channel blocker—nifedipine. A Cochrane database indicates a reduction in births within 7 days of therapy (relative risk, 0.76; 95% CI, 0.60-0.97) and at less then 34 weeks (relative risk, 0.83; 95% CI, 0.69-0.99) when nifedipine is used for preterm labor. Certainly the therapy is far better tolerated than magnesium sulfate. Unfortunately, the editorial did not touch upon nifedipine's ability to stop labor for 48 hours—long enough to get steroids on board. This is what we thought we were accomplishing with magnesium sulfate. ■

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Lower Doses of Estrogen Inhibit Atherosclerosis

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *This study provides an experimental basis for the assumption that low-dose CEE may be as effective as the traditional dose in inhibiting coronary atherosclerosis progression in early postmenopausal subjects.*

Source: Appt S, et al. Low dose estrogens inhibit coronary artery atherosclerosis in postmenopausal monkeys. *Maturitas*. 2006;55:187-194.

CLARKSON AND COLLEAGUES REPORT THE results of a lower-dose estrogen trial in a monkey model of coronary atherosclerosis. The animals were fed an atherogenic diet for 10 months, calculated to induce atherosclerosis comparable to that observed in early postmenopausal women. After oophorectomy, the animals were randomized to treatment for two years with a dose of conjugated equine estrogens equivalent to 0.3 mg per day in women or placebo. This dose had no effect on circulating lipid levels, nevertheless the treated animals had an average 52% reduction in coronary atherosclerosis. This degree of protection was similar to studies in this model using a dose of conjugated estrogens equivalent to 0.625 mg per day.[1]

COMMENTARY

One response to the publications from the Women's Health Initiative has been a scientific and clinical effort to assess and use lower doses of estrogen. Half of the standard dose of conjugated equine estrogens has been demonstrated to effectively treat menopausal symptoms and to prevent bone loss. It is reasonable to ask whether symptoms and bone are especially sensitive to the effects of estrogen, and whether lower doses of estrogen will beneficially impact other target tissues. The cardiovascular system is of obvious concern because it was already apparent that lower doses of estrogen do have a lesser effect on circulating lipids and lipoproteins.

As we move to the use of lower doses, keep in mind that there exists a considerable group of women who metabolize and clear estrogen at a greater rate, requiring a higher dose to achieve the desired effects. I have

argued in past issues of *OB/GYN Clinical Alert* that the only objective assessment of adequacy of dose can be found in the measurement of bone density. Women who are losing bone despite estrogen therapy, adequate calcium and vitamin D intake, and the absence of other causes of bone loss require an adjustment of the estrogen dose. ■

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Quality of Life After Tension-Free Vaginal Tape Obturator

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

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

Synopsis: *Follow-up of 100 women 12 months after they underwent TVT-O demonstrated that it was comparable to the traditional Burch colposuspension as well as the retropubic TVT procedures.*

Source: Lim JL, et al. Clinical and quality-of-life outcomes in women treated by the TVT-O procedure. *BJOG*. 2006;113: 1315-1320.

The purported advantages of the tension-free vaginal tape obturator (TVT-O) procedure include avoidance of bowel damage, reduction in risk of bladder and major vessel damage, and elimination of the need for routine cystoscopic evaluation during insertion. These Australian investigators at a tertiary care urogynecologic center prospectively evaluated stress test success rates at 6 months, but also looked for subjective issues at 6 and 12 months. Urodynamic testing was done on all 100 patients. They were able to follow patients for a mean duration of 18.5 months.

At 6 months, the negative stress test rate was 95%. The patients' subjective success rates at 6 and 12 months follow-up were 92% and 84% respectively. De novo urge incontinence occurred in 4.1% at 6 months and 4.8% at 12 months. Quality-of-life improvement was noted and patient satisfaction was 77% and 67% at 6 and 12 months. Complications included 6 recurrent UTI's, 2 patients with voiding difficulty, 3 cases of groin discomfort, and one each of tape erosion, urethral irritation, wound infection and hematoma.

The authors conclude that the TVT-O is both safe and effective in the treatment of female stress incontinence.

■ COMMENTARY

Does this study apply to you? Maybe it does, maybe it doesn't. There are some very good things about this article. The 100 cases is a large number. It was done in a single setting. All patients were documented to have stress incontinence preoperatively. The study design was prospective. The follow-up was reasonable, but not perfect. That brings me to some potential concerns that might make the reader believe that the study is not applicable to his/her practice. The study started with 100 but only saw 90 at 6 months and 82 at 12 months. It took place in Australia. This was a tertiary care center. The follow-up stopped at a relatively short time. These are not necessarily bad things, but reasons to view the data in perspective and with a bit of a jaundiced eye.

As every practitioner tries to find the next best service to provide the patient, comparisons with the gold standard traditional therapy are necessary. Part of the limitations in that search centers around the fact that each physician's "gold standard" may be different. Here, the authors report that the TVT-O appears comparable to Burch colposuspension and the retropubic TVT. The numbers compared are similar, but they are not compared head to head in a classic, randomized, controlled trial. As a result, each reader is left with the challenge of determining whether it is better or not in his/her practice. I have personally not performed a trans-obturator procedure, but am convinced that they might have a place in my practice. You might say that my statement is a bit wishy-washy and noncommittal. You would be absolutely right. I'm just not sure where it fits in my practice at this time. It certainly looks like a "sexy" procedure with a lot of upside potential.

I practice with 2 highly skilled, fellowship-trained urogynecologists. They are helping me sort through the data and clinical outcomes just as they

are trying to organize in their own minds how this technique should fit into our armamentarium of surgical offerings. With the growing number of patients needing this type of procedure, the surgical options are increasing even more. Every reader has probably already been approached about new materials, and new approaches, and better outcomes. Follow-up data beyond a year or so are sorely lacking in many cases.

As with this paper, "Let the buyer beware." In this case, the buyer is you, the surgeon, who is serving as advocate for the ultimate buyer, the patient. I am confident that we are all trying to find the best procedure for each patient. We know that one size does not fit all and we also know what works in our hands. Let's be good consumers and choose wisely, not just once, but repeatedly. Everytime we book a case in the operating room, let's ask ourself whether this is the best operation we can do for this patient. I know that the patient would want us to do so. ■

Therapeutic Role of Lymph Node Resection in Endometrioid Corpus Cancer

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb, and Ortho Biotech.

Synopsis: *The findings of the current study suggest that the extent of lymph node resection improves the survival of women with intermediate/high-risk endometrioid uterine cancer.*

Source: Chan JK, et al. Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*. 2006;107:1823-1830.

THE THERAPEUTIC ROLE OF LYMPHADENECTOMY IN patients with endometrial cancer is controversial and challenging to study given the relative infrequency of metastatic disease and the generally good prognosis of newly diagnosed patients. Nevertheless, prior work in limited sized cohorts has suggested that the number of nodes resected may be prognostic and informative in planning subsequent adjuvant treatment. To address these questions, Chan and colleagues evaluated over 12,000 women registered in the SEER database in whom nodal sampling accompanied their primary surgical procedure from 1988-2001. Patients with Stage I to IV disease and endometrioid histology (all grades) were included in the study cohort. Importantly, women with uterine serous histology and uterine sarcoma were excluded. In light of the large sample size, 5 categories of node counts could be evaluated. Risk groups were considered as well, defined as: Low Risk (Stage IA, all grades, Stage IB, Grade 1-2), Intermediate Risk/High risk (Stage IB, Grade 3, Stage IC-IV, all Grades) and High Risk (Stage IIIC-IV). The authors documented that the percentage of patients undergoing nodal sampling significantly increased over the years of the study (23% to 41%; $P < 0.001$). The number of nodes resected was significantly associated with improved survival for intermediate/high-risk and high-risk patients. No benefit in disease-specific survival was seen for the low-risk cohort. Age at diagnosis, race, year of diagnosis, grade, identified metastatic nodal disease, and adjuvant therapy were significant covariates in the study; however, in the multivariate analysis, node count remained a significant prognostic factor to disease specific survival in the intermediate/high-risk cohort after adjustment for these effects. The authors concluded that node count acts as a surrogate for extent of node resection and improves the survival of women with intermediate/high-risk endometrioid uterine cancer.

COMMENTARY

One of the most important prognostic factors for uterine cancer limited to the corpus is identification of extrauterine disease, particularly retroperitoneal adenopathy. Fortunately, the identification of metastatic disease occurs in just 1 in 5 women with endometrioid primary cancers. However, the price for undetected metastatic disease is high. This has led to two approaches or management philosophies regarding intervention: broader application of more extensive nodal sampling or more frequent utilization of adjuvant therapy in patients where staging information is missing. Both approaches have merit but risk overtreatment. The former strategy ensures accurate diagnostic information in all cases but 80% of women will receive limited benefit from the procedure; the latter, ensures high-risk areas are treated without the attendant morbidity of extensive surgery but does so blindly as the target volume is "guesstimated" (vaginal cuff and/or pelvis field and/or paraortic field). The current article pro-

vides some guidance to this dichotomous treatment approach for women with endometrioid tumors.

One relevant observation the authors identify is that there appears to be a cohort of patients (totaling 5,556/12,333 or 45% of the population) in whom nodal sampling or dissection offers no therapeutic value—patients with stage IA, all grades and stage IB, grades 1 and 2. Survival in this low-risk cohort ranges from 94% to 97%, irrespective of the extent of nodal resection. However, for all other risk cohorts, node count has a profound effect on survival. Most impressive is the effect of node count on patients with identified metastatic disease. Of 1221 patients with stage IIIC/IV disease, 5-year disease-specific survival ranged from 51% in women with 1 resected node to 72% in women with more than 20 resected nodes. To minimize sampling bias, they additionally evaluated the ratio of positive nodes to the total number of nodes resected. In this analysis women in whom the metastatic node ratio was greater than 20% had a survival of 51% compared to those in whom the number of metastatic nodes were 5% or less of the total node resection. While this kind of analysis can be confounded by misclassification of patients with high positive node counts, their specific occurrence is historically uncommon and may still be positively offset by more thorough lymphadenectomy.

The second point raised in this analysis is that patients without formal staging may be misclassified as having optimistic outcomes in apparent early stage disease and poor outcome in advanced stage disease. Women undergoing formal evaluation by lymphadenectomy resulting in an early stage (Stage I) designation similarly have favorable outcomes; however, the survival for those identified advanced disease (Stage II-IV) is substantially better. This result is likely the combination of stage migration and the therapeutic value of resection—even unaffected nodes. It also speaks to better defining the treatment volume of "at-risk" tissues, which has the potential to reduce treatment-related toxicity.

This current report suffers the fate of similar SEER-based analyses with inconsistent or absent central pathology review, missing data of adjuvant hormonal and chemotherapy, undefined skills of the surgeon, unknown progression-free survival and incomplete detail of subsequent therapy for recurrence. In addition, while node counts may serve as a surrogate of completeness of resection, it is highly operator-dependent. Large node counts can be achieved if they are specifically sought in gross processing, particularly if defattying agents are utilized. Reproducible criteria which ensure the completeness of resection are unavailable and probably better represented by specified sampling in specific nodal regions such as: external iliac, obturator, junctional, common iliac, low paraortic (below the inferior mesenteric artery) and paraortic (ovarian). However, the data are provocative and are positive reinforcement for the trend identified in this study of a greater proportion of patients being referred for expert surgical care by trained gynecologic oncologists. ■

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Survival Patterns after Oophorectomy in Premenopausal Women: A Population-Based Cohort Study

ABSTRACT & COMMENTARY

By Sarah L. Berga, MD

James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta

Dr. Berga is a consultant for Pfizer, Organon, and is involved in research for Berlex and Health Decisions, Inc.

Synopsis: *Risk of death was increased in women who had a bilateral oophorectomy before the age of 45 years but not in those who had a unilateral oophorectomy. The increased risk of death was also not seen in women who received estrogen treatment up to age 45 years.*

Source: Rocca WA, et al. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol.* 2006;7:821-827.

THIS STUDY WAS MADE POSSIBLE BY THE MAYO Clinic Cohort Study of Oophorectomy and

Aging, the main aim of which is to detect new cases of age-related diseases, especially Parkinson's disease and dementia. This report focused on the mortality outcomes. The cohort included women who underwent bilateral or unilateral oophorectomy and a group of referent women who did not undergo oophorectomy. All study participants were born before 1962 (were at least 40 years old by January 1, 2002) and resided in Olmsted County, Minnesota, which is mainly middle class, well-educated, and has excellent access to health care. Cases were carefully matched with referent women. The indication for oophorectomy had to be non-cancer and included benign ovarian conditions such as cysts, endometriosis, and benign tumors; about half had an oophorectomy prophylactically.

The follow-up procedures were exhaustive. Ascertainment of outcomes was high and participants were asked about hormone use. The final groups included 1091 women who had a bilateral oophorectomy, 1274 with a bilateral oophorectomy, and 1755 referent women. The Kaplan-Meier survival curves show decreased survival across time for women who underwent a bilateral oophorectomy. The hazard ratio for mortality in those who underwent bilateral oophorectomy was 1.93 (1.25-2.96, 79 cases) for women younger than 45 years, 1.02 (0.78-1.32, 243 cases) for those between 45 and 50 years, and 0.90 (0.68-1.19, 170 cases) for those older than 50 years. In contrast, the hazard ratio for mortality for those who had a unilateral oophorectomy younger than age 45 was 0.94 (0.65-1.37, 218 cases).

Further, analyses stratified by age at estrogen deficiency showed that the increased risk of death was restricted to women who had bilateral oophorectomy before the age of 45 years and did not receive estrogen treatment up to this age. Women who had estrogen deficiency before age 50 had a smaller but significantly increased risk of death. Women who underwent unilateral oophorectomy with hysterectomy had a survival advantage compared to referent women or women who underwent only a unilateral oophorectomy. Although the numbers are small, mortality for neurological or mental disorders was significantly increased in women who underwent bilateral oophorectomy before age 45 years, hazard ratio, 6.28 (1.83-21.5, 12 cases; $P = 0.003$). When this analysis was confined to those who had estrogen deficiency before age 45, the hazard ratio was 2.34 (9 cases, nonsignificant statistically).

COMMENTARY

This is a fascinating and provocative study that lends fuel to the hormone therapy fire. I look forward to future analyses, especially those which explore the role of estrogen deficiency upon the risk of dementia. The current results seem relatively straightforward. Bilateral prophylactic oophorectomy in unselected women (those not identified by molecular screening to be at high risk for breast and ovarian cancer) reduces survival if done in women younger than age 45 years, presumably because most women do not take hormones afterward and are thus exposed to estrogen deficiency. Said another way, premature estrogen deficiency seems to promote mortality.

The study is limited by the small number of cases, but it is otherwise carefully conducted, makes a valuable contribution to our fund of knowledge, and should hopefully alter practice patterns. For years, there have been two camps regarding the practice of prophylactic oophorectomy in women undergoing hysterectomy for benign indications. The glib answer was that the ovaries should be removed after age 35 years and the women placed on hormones, thus promoting survival and freeing them from the risk of ovarian cancer. However, because compliance is low, this strategy appears to not work as intended.

Further, the data herein fail to show a protective effect of prophylactic oophorectomy before menopause even when estrogen is instituted and continued until the anticipated time of menopause. It would appear that the only women who might benefit from a prophylactic oophorectomy are BRCA carriers. Bilateral oophorectomy with hysterectomy might be rarely needed for women with endometriosis, but this point remains more controversial. The present data do not directly address this group, although the authors noted that "survival was improved for women who underwent unilateral oophorectomy for endometriosis." The authors also pointed out that the Women's Health Initiative seems to have led some patients and physicians to conclude that women under age 50 who have hypoestrogenism due to ovarian removal or failure should not use hormones and thus these women may be unwisely exposed to considerable durations of hypoestrogenism. They finished by noting that "estrogen might be protective before menopause, fairly protective during and soon after menopause, and have no or negative effects if introduced 10-15 years after menopause." Thus, the hormone controversy rages and the wise practitioner is advised to avoid dogmatism. If future studies support the notion that estrogen

is neuroprotective when begun at the time of menopause, it will tip the balance for many in favor of longer-term use. ■

Depot Medroxyprogesterone Acetate and Weight Gain

ABSTRACT & COMMENTARY

By Leon Speroff, MD

Synopsis: *Depot medroxyprogesterone acetate causes obese adolescents to gain more weight.*

Source: Bonny A, et al. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Arch Pediatr Adolesc Med*. 2006;160:40-45.

BONNY AND COLLEAGUES REPORT THE EFFECT OF depot medroxyprogesterone on weight changes in obese and nonobese adolescent girls.[1] This was a prospective study of 450 adolescents, aged 12 to 18 years. The objective was to compare body weight changes over 18 months in adolescents according to baseline body weight. Adolescent girls obese at the time of initiation of treatment with depot medroxyprogesterone acetate gained more weight (mean, 9.4 kg gain) compared to obese girls who started oral contraceptives (mean, 0.2 kg) or to a group not using hormonal contraception (mean, 3.1 kg). Weight in obese adolescents using depot medroxyprogesterone increased at a greater rate with increasing duration of use. Obese adolescents using depot medroxyprogesterone gained more weight than nonobese users. Among subjects who were not obese at baseline, there were no differences in weight gain according to methods of hormonal contraception. The authors conclude that depot medroxyprogesterone use may contribute to adolescent obesity.

■ COMMENTARY

By now it is conventional wisdom that the use of depot medroxyprogesterone acetate for contraception causes weight gain. Indeed, many users of this method discontinue its use because of weight gain. However, it has been difficult to know whether the drug causes weight gain or whether the weight gain is simply the consequence of lifestyle and diet. Attempts to document a greater weight gain have had mixed results.

It is worth emphasizing the negative studies. A placebo-controlled experiment concluded that depot medroxyprogesterone had no effects on food intake, energy expenditure, or body weight.[2] With the newer subcutaneous method, an average gain of only 1.5 kg occurred after one year.[3] On the other hand, specific individuals or ethnic groups may be more susceptible to weight gain. For example, an excellent study in Navajo women documented significant weight gain.[4]

So where does that leave us? Is weight gain a general reaction to depot medroxyprogesterone acetate or does it occur only in vulnerable individuals? Answers to these questions are hindered by limitations in the available studies. The evidence is not derived from randomized trials (something that is probably impossible to do). Therefore, results can be influenced by those reasons for which subjects choose a certain method and responses that affect continuation with methods. The individuals who choose to use depot medroxyprogesterone differ in their socioeconomic status, contraceptive practices, and sexual histories; thus the difficulty in matching users and nonusers.

This problem also applies to another problem assigned by conventional wisdom to depot medroxyprogesterone users: mood changes and depression. When studied closely, it has been difficult to find an increase in depressive symptoms in depot medroxyprogesterone users.[5,6]

Because low-dose estrogen-progestin contraceptive methods do not cause weight gain, it would seem appropriate to promote the use of these methods in overweight individuals, especially obese adolescents. However, the small increase in failure rates reported with oral contraceptive use in obese women combined with lower continuation rates (and higher pregnancy rates) with oral contraceptives stand out in contrast to better compliance and efficacy rates with depot medroxyprogesterone acetate. Thus it is important to promote the consideration of the transdermal and vaginal ring methods for this population. Perhaps the most attractive choice will prove to be the new subcutaneous rod, Implanon, known to be highly effective even in heavy women. ■

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CME Questions

17. Which of the following statements best captures the results of the mortality outcomes in the current study of women who underwent oophorectomy?
a. Bilateral oophorectomy prolongs survival while unilateral oophorectomy does not.
b. Bilateral oophorectomy saves lives only when it is done before age 50 years.
c. Women who have a bilateral oophorectomy and take hormones until age 45 have improved survival over women who do not have surgery.
d. Bilateral and unilateral oophorectomy before age 45 increases mortality.
e. Bilateral oophorectomy before age 45 have increased mortality.

18. The following statements are true regarding body weight and steroid contraception *except*:
a. All methods of hormonal contraception have an increase in failure rates with increasing body weight.
b. Body weight does not increase significantly in all users of depot medroxyprogesterone acetate.
c. Oral contraceptives do not increase body weight.
d. Transdermal hormonal contraception and vaginal ring contraception do not cause weight gain.

19. Which surgical stage cohort was found to *not* benefit (survival) from the performance of an extensive lymphadenectomy (> 20 nodes)?
a. Stage IB, G2
b. Stage IC, G1
c. Stage IIA, G2
d. Stage IV

20. The following statements are true regarding estrogen doses in postmenopausal women *except*:
a. Many women respond to low doses of estrogen with a gain in bone density.
b. Low doses of estrogen may lower the risk of coronary heart disease in early postmenopausal women.
c. All women respond favorably to low doses of estrogen.
d. Some women lose bone on low doses of estrogen.

Answers: 17 (e); 18 (a); 19 (a); 20 (c)

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Sweeping Changes Needed for US Drug Safety System

In response to several high-profile drug misadventures including the rofecoxib (Vioxx®) withdrawal from the market, the FDA's Center for Drug Evaluation and Research (CDER) asked the Institute of Medicine (IOM) to assess the drug safety system in the United States. The recommendations, published in the October 26 *New England Journal of Medicine*, call for sweeping changes, especially in the post-marketing surveillance of new drugs.

The report suggests that the FDA has acted to accelerate drug approvals without ensuring the safety of these drugs once they are approved and on the market. Direct-to-consumer advertising is also partially to blame, especially when aggressive marketing campaigns lead to sudden widespread use of a new drug. Chronic under funding and a poor work environment at the FDA are also partially to blame. But the biggest culprit is the lack of an effective mechanism of continued evaluation of new drugs once they're on the market, which currently amounts to little more than reports of adverse events from practitioners. The IOM's report recommends changes in the FDA's committee structure, which strengthens conflict-of-interest restrictions and recommends that the FDA commissioner be appointed for a fixed term of 6 years. They also recommend labeling new drugs with a symbol such as a black triangle for up to 2 years to signify "the uncertainty associated with new drugs" and a moratorium on direct to consumer advertising during that period. Five years after a drug's launch, the FDA should perform a review of the risk/benefit status of all approved drugs (*N Engl J Med*. 2006;355:1753–1755).

An accompanying editorial points out that much of the money provided to the CDER is for drug approval, and much of it derives from industry, whereas little funding is earmarked for monitoring of the safety of drugs after they've been approved and introduced onto the marketplace. The editorialists recommend that all clinical trials beyond phase I must be registered in the public database, as has been recommended previously. The editorial also endorses the black triangle indication in the first 2 years after the drug's approval in a moratorium on direct-to-consumer advertising during that time. Most importantly, the editorialists ask for better funding and more transparency in the FDA, and urges Congress to implement the recommendations (*N Engl J Med.* 2006;355:1821).

Antiaging Supplements Proven Ineffective

Dehydroepiandrosterone (DHEA) and testosterone are not effective antiaging supplements, according to 2 new studies. Both compounds have been widely marketed as antiaging supplements. The first study from the *New England*

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Journal of Medicine was a 2-year, placebo-controlled, randomized, double-blind study involving both women and men.

Among the men, 29 received DHEA, 27 received testosterone, and 31 received placebo. Among women, 27 received DHEA and 30 received placebo. After 24 months the men showed no significant effect of DHEA on body-composition measurements. Neither DHEA nor testosterone affected oxygen consumed per minute, muscle strength, or insulin sensitivity. Testosterone resulted in a slight increase in fat-free mass, and both DHEA and testosterone resulted in an increase in bone mineral density at the femoral neck. Women who received DHEA had an increase in bone mineral density at the ultradistal radius. There was no difference in quality-of-life issues in either group with any intervention. The authors conclude that neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life (*N Engl J Med*. 2006; 355:1647–1659).

The second study was also a double-blind, randomized, controlled trial that included a hundred men age 70 and over. Subjects were randomized to receive DHEA 50 mg/d, the anti-estrogen atamestane 100 mg/d, the combination of the 2, or placebo for 36 weeks. No differences were found in either treatment arm compared with placebo on a battery of tests, which included isometric grip strength, leg extensor power, and physical performance (*J Clin Endocrinol Metab*. 2006;91:3988–3991).

The Three Most Common Culprits of ADE

Three drugs are responsible for a third of the estimated 700,000 outpatient adverse drug events per year in this country, according to a new study. A collaborative effort of the FDA, CDC, and US Consumer Chronic Safety Commission developed the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project several years ago to assess the risk of adverse drug events (ADEs) in the outpatient setting. During the 2-year study period, 21,298 ADEs were reported that resulted in patients presenting to the emergency departments of the 63 reporting hospitals. This extrapolates to over 700,000 cases annually in this country. Individuals age 65 or older were more likely than younger individuals to suffer an ADE. Drugs for which regular outpatient monitoring is used to prevent toxicity accounted for 41.5% of hospitalizations, and 50% of hospitalizations were in people age 65 and older. Of those drugs, insulin, warfarin, and digoxin were responsible for one in 3 estimated ADEs treated in emergency departments. The authors conclude that adverse drug events are an important cause of morbidity in the United States, especially among the elderly, and that ongoing population-based surveillance may help target prevention strategies (*JAMA*. 2006; 296:1858–1866).

New Guidelines for Lyme Disease Prevention

The Infectious Disease Society of America has issued new guidelines for Lyme disease (LD) prevention. Of note, guidelines state that routine use of antimicrobial prophylaxis or serologic testing is not recommended after a recognized tick bite; however, a single dose of doxycycline 200 mg may be given to adults and children over the age of 8 if 1) the attached tick is recognized as a potential carrier of LD and has been attached for least 36 hours; 2) the dose can be given within 72 hours of tick removal; 3) the patient is in an endemic area; 4) doxycycline is not contraindicated. Testing of ticks is not recommended. Even if patients have been prophylaxed, they should be monitored for signs and symptoms of tick-borne illness for up to one month (*Clin Infect Dis*. 2006:43—published online October 2, 2006).

FDA Actions

The FDA has approved a new agent for the treatment of hepatitis B infections. Telbivudine (Tyzeka™), from Novartis, has been approved for the treatment of adults with chronic hepatitis B infections. In clinical trials, the drug was shown to suppress replication of hepatitis B virus and reduce liver inflammation.

The FDA has approved Merck's sitagliptin (Januvia™), a new oral antidiabetic for the treatment of type 2 diabetes. The drug is a DPP-4 inhibitor, a new class of medications that prolongs the action of incretin hormones, resulting in improved glycemic control. The drug is approved for monotherapy or as add-on with metformin or a thiazoldinedione. Sitagliptin has the theoretical advantages of not causing weight gain or increasing the risk of hypoglycemia. It is supplied as a 100 mg tablet that is given once a day. ■