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INSIDE

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Management of Ovarian Torsion

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: *Adnexa-sparing laparoscopic procedures for ovarian torsion might predispose to recurrence of torsion.*

Source: Pansky M, et al. Torsion of Normal Adnexa in Postmenarchal Women and Risk of Recurrence. *Obstet Gynecol.* 2007;109:355-359.

In this retrospective study, the authors gleaned hospital records to identify cases of adnexal torsion at their hospital in Israel between 2002 and 2006. Sixty-two cases were found appropriate for the study. These were classified as having pathologic adnexa or normal adnexa. The patients were then followed via telephone interview to determine whether or not there was recurrence of adnexal torsion.

Twelve patients were found to have normal adnexa at the time of torsion. Fifty-seven patients were able to provide reliable follow-up information. Of the 11 patients who originally had normal adnexa, 7 had a recurrent episode of torsion (63.3%) while 8.7% (4 of 46) of patients with abnormal adnexa had recurrent torsion. Among the 7 women with recurrent torsion of normal adnexa, 4 were ipsilateral with a mean interval between the events of 2 years.

Of the patients with abnormal adnexa, recurrence was higher if minimal surgery was performed for the first event (detorsion with/without cyst aspiration). There was less likelihood that torsion would recur if resection of the pathology or the entire adnexa had been undertaken.

COMMENTARY

Hmmmmmm. So the pendulum continues to swing back and forth. Historically, adnexal torsion was managed by removal of

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the adnexa due to a fear of thrombus formation in the ovarian vein, which could lead to a thromboembolic event. Subsequently, due to the minimal risk of thromboembolism, conservation of the adnexa and untwisting of the adnexa became the standard management. These authors now challenge us to reconsider once again, particularly with regard to ovarian fixation, ie, ovariopexy. Hmmm again. What to do? First, it appears that the results here do not warrant returning to the old days of removing adnexa. Conservation of the adnexa in the absence of obvious pathology makes sense. With regards to ovariopexy, the authors acknowledge that neither the literature in general nor their data give us any guidance. There are no data that tell us that ovariopexy would have prevented any of these cases of retorsion.

Although the paper focuses on the postmenarchal patient, the authors do review the arguments for and against fixation of the normal ovaries in that population. Factors in favor of doing so include avoiding the devastating significance of losing the ovary if torsion were to reoccur, whereas negative factors include interference with adnexal blood supply and risk of tubal function. Despite an admitted lack of data, they conclude by suggesting that bilateral ovariopexy in cases of normal adnexal torsion in premenarchal patients is warranted.

Data on postmenarchal patients is even more scarce. I believe that they are objective in their suggestion that surgeons should at least raise the possibility of ovariopexy in patients who have had one adnexal torsion, with the possibility of even doing so bilaterally. So I say again: Hmmmmm. ■

Does Cervical Conization Predispose a Patient to Preterm Birth?

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

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

Synopsis: *To estimate whether the time interval between cervical conization and subsequent pregnancy is associated with risk of preterm birth.*

Source: Hines K, Simhan HN. Time from cervical conization to pregnancy and preterm birth. *Obstet Gynecol.* 2007; 109:314-319.

It has not been clear as to whether a cervical conization truly predisposes a patient to preterm birth (PTB). The authors of this enlightening paper set out to see if the interval between the procedure and subsequent conception had any effect on the incidence of PTB.

Hines and Simhan analyzed data over a three-year period on patients having had treatment for cervical dysplasia at Magee Women's Hospital in Pittsburgh. They compared pregnancy outcomes from 114 patients having had LEEP, large loop excisions or cold knife conizations, with a control group of 962 patients who were worked up with colposcopic directed biopsies, but received no treatment. Their endpoint was simple—a subsequent birth occurring between 20 and 36 weeks of gestation. The authors were particularly interested in the interval between conization and conception, the size of the cervical specimen at the time of conization, and the incidence of premature rupture of membranes (PROM).

Interestingly, there was no difference in the incidence of PTB between the two groups, suggesting

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that conization, in general, did not predispose patients to early delivery. Also, the incidence of PROM was essentially the same in both groups (1.8%), and, although it is unclear from the paper whether the size of the excised tissue made a difference, the average size of the excised tissue was 1.9 cm. This does suggest that conization, at least soon after the procedure, has a significant effect on cervical length.

The major finding was that there was a significant difference in PTB in those with short excision to conception intervals. For example, those conization patients having a PTB had an average interval of 2.5 months, compared with an average 10.5 month interval in those conization patients who delivered at term.

COMMENTARY

First, as opposed to another recent study, there did not appear to be an overall difference in the rate of PTB in conization patients compared with controls. This is not surprising, since the most important structural portion of the cervix (regarding the job of containing the pregnancy) would be the area in the neighborhood of the endocervix, and not the one that was excised. However, the outer third is the first barrier that bacteria will encounter when attempting to move up the canal and, until the area is stabilized after excision, it may be vulnerable to infection while undergoing its own reparative processes. Some studies correlating cervical length, in general, with PROM have catalyzed the thinking that the decreased distance between vaginal bacteria and the membranes lends itself to weakening of these membranes over the cervix. However, the Hines study showed no difference in PROM between those who would undergo a conization and those who did not.

The take-home message here is that the cervical length is less of a problem than the time interval between treatment and initiation of pregnancy, and, therefore, patients should try to wait at least twelve months before contemplating pregnancy after any type of conization. ■

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Clomiphene, Metformin, or Both

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *The polycystic ovary syndrome is a common cause of infertility. Clomiphene and insulin sensitizers are used alone and in combination to induce ovulation, but clomiphene should be first-line treatment.*

Source: Legro RS, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *New Engl J Med.* 2007;356:551-566.

Legro and colleagues, reporting for the Cooperative Multicenter Reproductive Medicine Network, presented the results of a multicenter, randomized trial indicating that clomiphene is superior to metformin in achieving live births in women with the polycystic ovary (PCO) syndrome.[1] Two hundred and nine women with PCO were randomized to clomiphene (50 to 150 mg per day for 5 days), 208 women received the extended-release form of metformin (2000 mg per day), and 209 women were given both drugs; the treatment limit was 6 cycles.

	Clomiphene	Metformin	Both
Live-birth rate	22.5%	7.2%	26.8%
Multiple pregnancies	6.0%	0%	3.1%
Conception rate	29.7%	12.0%	38.3%
Average BMI	36.0	35.6	34.2

COMMENTARY

Small studies previously concluded that metformin administration to women with PCO who are resistant to clomiphene yielded an increase in pregnancy rates.[2,3] A randomized trial of 100 women with PCO in Italy observed similar ovulation rates comparing metformin with clomiphene treatment, but a greater live-birth rate

was recorded in the metformin group because of a higher spontaneous abortion rate associated with clomiphene.[4] The Italian study was noteworthy in that the subjects were not obese and likely had a low prevalence of insulin resistance, making the outcome even harder to explain when comparing it with the American trial.

In the American trial, the subjects were considerably overweight, and the rate of live births progressively decreased with increasing body weight. Nevertheless, the superiority of clomiphene treatment was observed in all weight groups. Of the metformin group, 45% failed to achieve a single ovulation compared with 24.9% in the clomiphene group. Although the average fasting insulin levels were elevated, the standard deviations were very high, consistent with the known variability in this measurement. More importantly, the calculated insulin resistance was similar in the 3 groups. Metformin treatment caused a small loss of weight and improved insulin sensitivity, but despite this beneficial change, there was no advantage in live births.

A possible explanation for the better outcome with clomiphene is that clomiphene treatment is associated with multiple follicle development as evidenced by the increase in multiple pregnancies. There still may be a role for metformin; an increased rate of pregnancy complications in the clomiphene group, especially gestational diabetes and preeclampsia, suggests a role for metformin treatment throughout pregnancy in overweight women with insulin resistance.

Two other recent randomized trials agree with the American results. A 6-month, multicenter study of 228 women in the Netherlands compared the effect of adding metformin or placebo to clomiphene treatment.[5] There were no differences in ovulation rates, ongoing pregnancy rates, or spontaneous abortion rates; in other words, metformin did not improve the response to clomiphene. A Canadian study of 154 women reported higher ovulation rates with first-line metformin treatment, but the pregnancy rates were similar comparing metformin-alone, clomiphene-alone, and both drugs in combination.[6]

Two small randomized trials, only 21 women in Turkey and 26 women in the U.K., also did not find any improvement in ovulation and pregnancy rates when metformin was added to clomiphene treatment.[7, 8]

The bottom line is that metformin treatment improves insulin sensitivity and lowers androgen levels, important achievements in terms of reducing the risk of the long-term consequences of diabetes mellitus and cardiovascular disease in anovulatory women with insulin resistance. But the evidence from recent clinical trials of respectable size fails to demonstrate any live-birth advantage of metformin treatment for infertility. It seems to me that it remains reasonable to add metformin when women with insulin resistance are unable to achieve pregnancy with multiple cycles of clomiphene treatment. Based on the new evidence, first-line treatment should be clomiphene. ■

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EVRA and Venous Thrombosis — Part II

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Insurance company statistics indicate that the risk of venous thromboembolism is greater with transdermal contraception compared with oral contraception.*

Source: Cole, JA, et al. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive users. *Obstet Gynecol.* 2007;109:339-346.

Cole and colleagues from I3 Drug Safety reported that the use of the transdermal contraceptive system was associated with a 2.4-fold increase in the risk of venous thromboembolism compared with users of a 35 µg ethinyl estradiol and norgestimate oral contraceptive.[1] i3 Drug Safety is a unit of Ingenix, a medical information company owned by United Health Group. United Health Group also owns UnitedHealthcare, a major national provider of health insurance. The study used insurance claims data from UnitedHealthcare to identify women using transdermal or oral contraception. There were 20 cases of venous thromboembolism with the transdermal method for a rate of 40.8 per 100,000 woman-years, compared with 37 cases with oral contraception for a rate of 18.3 per 100,000 woman-years. This difference yielded a higher rate ratio among transdermal users in the cohort analysis of 2.2 (CI = 1.2-3.8). A nested case-control study was performed in order to control for high risk factors, producing an odds ratio for transdermal users of 2.4 (CI = 1.1-5.5). Myocardial infarction and stroke occurred too rarely to allow risk estimates.

COMMENTARY

This is the second report on the risk of venous thromboembolism comparing transdermal and oral contraception. Both studies were funded by Johnson & Johnson, the parent company for the EVRA contraceptive patch. The first report was a case-control study of nonfatal venous thrombosis using information derived from a very large database that records prescriptions and diagnoses longitudinally in managed health care plans.[2] The study over a 3-year time period compared new users of the contraceptive patch with new users of an oral contraceptive containing 35 µg ethinyl estradiol and norgestimate. Sixty-eight cases of venous thrombosis and 266 controls were identified and matched for year of birth and for the date of the thrombotic episode (thus providing comparable dates for exposure). A comparison of the patch to the oral contraceptive indicated no difference in the risk of venous thrombosis:

		Comparison to OCs
Contraceptive patch	31 cases	127 controls OR=0.9 (0.5-1.6)

The U.S. Food and Drug Administration (FDA) issued a press release on November 10, 2005 calling attention to the fact that women using the oral contraceptive patch are exposed over time to a greater amount of estrogen. Subsequently, the patch labeling was updated to include a warning about this higher exposure. Here are the facts:

1. The contraceptive patch delivers daily 20 µg ethinyl estradiol and 150 mg norelgestromin (the primary active metabolite of orally administered norgestimate).
2. The serum ethinyl estradiol concentration averages 50 pg/mL, with a range of 25 to 75 pg/mL.[3, 4]
3. The peak estrogen blood levels with the contraceptive patch are about 25% to 35% lower compared with oral products containing 30 µg or 35 µg ethinyl estradiol.[5, package label]
4. Over time, patch users are exposed to about 60% more estrogen compared with an oral product containing 35 µg ethinyl estradiol.

Which is more important, a higher peak level or greater exposure over time? Or maybe it doesn't make a difference.

A weakness of the current report was the inability to confirm diagnoses in 100% of the cases through review of medical records (completed for 83% of the cases). A strength of the study is the thorough attempt to control for factors that influence venous thrombosis in the case-control study. A strong point of both studies was a focus on new users, eliminating the problem known as attrition of susceptibles (comparing new users, who are more likely to experience venous thrombosis, to old users would be comparing two different groups of subjects).

Comparing the two studies, it is worth noting that the negative report had a little more than 3 times as many cases as the positive report, giving it more statistical power. This is reflected in the wider confi-

dence intervals of the current study indicating an increase in risk, an indication of a less precise conclusion. Indeed, in the overall case-control analysis there were only 20 cases among transdermal users and 37 cases among oral contraceptive users, and the odds ratio of 2.0 was close, but it did not reach statistical significance (CI = 1.0-4.1). After excluding cases and controls with high-risk factors, the odds ratio with 16 transdermal cases and 26 oral contraceptive cases achieved 2.4 with statistical significance, but a relatively very wide confidence interval, 1.1-5.5.

So where does that leave clinicians and patients? These are the first epidemiologic data on this important issue. One study is reassuring, one is disturbing. But note that the confidence interval in the second study is relatively wide, indicating imprecision of the conclusion. Because the confidence intervals of the two studies are within the same range (ie, they overlap), it is not certain that the different results do not reflect a chance finding.

The authors of the transdermal report raise a criticism of the earlier, negative report. They point out that the first report compared only first-time users of each method, and they conclude that prior users of norgestimate oral contraceptives were thus excluded from the oral contraceptive group, but could not be excluded from the transdermal group because of its recent introduction to the market.

This confusion underscores the inappropriate strategy of the FDA in issuing press releases and making conclusions public before the publications are available for assessment by clinicians. At this point in time, it seems to me, that if there is a difference in the risk of venous thrombosis comparing transdermal and oral contraception, the difference has to be very small. Certainly the available evidence does not indicate a major difference. ■

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Using Gabapentin for Vulvodynia

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Synopsis: *Gabapentin appears to be effective in the treatment of generalized vulvodynia with a low incidence of side effects. Longer-standing cases may be less likely to respond to this therapy.*

Source: Harris, G, et al. Evaluation of Gabapentin in the Treatment of Generalized Vulvodynia, Unprovoked. *J Reprod Med.* 207;52:103.

This retrospective chart review covered all patients with vulvodynia treated with gabapentin at a single facility between January of 2002 and September of 2004. Among 601 charts, 152 fulfilled the criteria of having patients with generalized vulvodynia, being treated with gabapentin as a single agent, having 30 months of follow-up, and having adequate documentation of outcome. Sixty-four percent had at least 80% relief from symptoms. The time needed to achieve this level of therapeutic response varied among the responders. Resolution in less than 6 months occurred in 21% of patients. Seventeen percent responded during the 6-9 month interval and the 9-12 month time period. Seven percent responded during the 12-15 and 15-18 month intervals. Response took longer than 18 months in 29% of patients. Thirty-two percent (N = 49) had no resolution or showed no effect from the medication within 6 months of starting therapy.

The dosing range was from 100 to 3000 mg daily. The most common starting dose was 300 mg in divided doses with titration up to 900 mg daily over 3 weeks. Twenty-eight percent of patients remained at that dose. Thirty-two percent required 1200 mg a day with smaller percentages of response seen at

higher doses. Among co-morbidities, sleep disturbance was the only one that negatively impacted drug efficacy. Chronic headache was the most common, occurring in 44% of patients with vulvodynia. Other co-morbidities included: sleep disturbance (43%), irritable bowel syndrome (38%), anxiety (36%), chronic fatigue (23%), and interstitial cystitis (17%). Among the 40 patients with side effects (26%), fatigue was the most common (10%) and was also the most common side effect given as a reason for discontinuation of the medication.

COMMENTARY

I know some of the readers will look down their noses at this study. It's a retrospective chart review so it doesn't pass the scrutiny of scientific rigor. The clinicians in the readership who see these patients in their practices will see some real clinical pearls buried in the article. First of all, the fact that it is a diagnosis of exclusion needs to be reinforced. Oncologic, dermatologic, and infectious etiologies are always in the differential diagnosis and should get first consideration. Another important finding, something that we commonly forget in the busy daily practices that we have, is that the significant incidence of co-morbidities is always muddying up the waters. It becomes more and more challenging to identify a specific gynecologic syndrome among the headaches, bowel issues, and other pain concerns. The third pearl to me is that patience is necessary, on the part of both clinician and patient. Notice that a large proportion of patients got better after many months of treatment. This raises the clinical question of whether the patient got better because of the gabapentin or because it ran through its own course and just resolved. A fourth pearl involves the dosing of the medication, with patients responding to various levels of medication. Once again, the patient and clinician, as a team, should determine together the efficacy of various doses.

As a final note, I find studies like this fascinating. In my own practice, I am loaded down with referrals for patients who turn out to have vestibulitis. Only a small proportion have vulvodynia. One of my additional messages to the reader is to look specifically for vestibulitis with a q-tip. It is extremely easy to overlook. The second add-on message from me is to look beyond gabapentin. The tricyclic antidepressants such as amitriptyline and nortriptyline are commonly used. Remember that other medication such as Lyrica, Gabitril, Keppra and Topamax can also provide some relief for these patients. There isn't very much in the peer-reviewed literature, but there is a lot of clinical experience that we can call on. ■

How Should the OB/GYN Doctor Dress for the Office?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Synopsis: *Physicians should dress according to personal preference because patients' perceptions of physician competence and professionalism is not affected by physician attire.*

Source: Fischer RL, et al. *Am J Obstet Gynecol.* Feb 2007:186.

These New Jersey authors hypothesized that attire and patient satisfaction would be unrelated. For 3 months, full-time faculty, both generalists and subspecialists, were randomly assigned to different attire, ie, business attire, casual clothing, or scrubs. The 3 attires had very specific definitions, and the randomization and compliance issues were very strict. The study included 1116 patients who had a visit of at least 10 minutes with a new obstetrician/gynecologist. The patients could not have had previous participation in the study. Immediately after the encounter, they were given an anonymous 1-page questionnaire by office staff. None of the questions made any reference to the attire of the physician.

The results of the survey were essentially identical for the 3 groups. When asked about their personal attire preference, the 8 attendings identified casual dress, 7 preferred business attire, and 5 preferred scrubs. The patient ratings of the physician did not differ according to physician preference of attire.

COMMENTARY

So how do you dress when you go to the office? For that matter, do you even think about it? I know that historically, some residencies insist on their trainees not wearing scrubs to the office/clinic. Even some private practices that I know mandate that physicians wear white coats without fail, going so far as to have physicians wear someone else's coat with the other person's name on it in order to comply with practice policy. Good idea or bad idea? I guess it depends on what you're trying to accomplish.

If the goal is to have a certain "look" in the office, that's one thing. If there is the perception that the patients will see the physician as more professional or

competent, this study should create some second guessing. It's reassuring that interpersonal skills, medical knowledge, and personal demeanor are more important than the clothes you wear. Even though the study was done in New Jersey, is there any reason to doubt that the findings are generalizeable to your practice?

If you spend a lot of time worrying about what you're wearing to the office, and you think it matters to your patients, perhaps the new theme for you ought to be "Don't worry, be happy!" Wear whatever makes you feel most professional and competent (and comfortable). ■

P.S. For the specific definitions of each of the attires, check out the article itself. Otherwise, you'll just have to imagine what the various definitions include.

CME Questions

9. The following statements are true regarding metformin treatment of women with PCO except:
a. metformin is effective in lowering insulin resistance in many women with PCO.
b. clomiphene may be superior to metformin in achieving live births.
c. clomiphene and metformin both increase the rate of multiple births.
d. clomiphene has no impact on insulin resistance.

10. In the above study the average diameter of the cervical conization specimen was:
a. about 1 cm
b. about 2 cm
c. about 3 cm
d. more than 3 cm

11. Which of the following is a valid interpretation of the study:
a. Conization increased the risk of PTB (over controls).
b. Conization increased the risk of PROM.
c. The time interval between conization and conception was the only significant finding in this study.
d. Cervical length was a factor in the rate of PTB

Answers: 9 (c); 10 (b); 11 (c)

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:
- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
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- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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CUMULATIVE INDEX

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PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Which Inhaler Combination is Best for COPD Treatment?

Two recent large studies have looked at the effects of various inhaler combinations on outcomes in patients with COPD. In the first, published in the February 22 issue of the *New England Journal of Medicine*, researchers from the United Kingdom looked at over 6,000 patients with COPD in a randomized, double-blind trial comparing salmeterol plus fluticasone inhaler twice daily (in a single inhaler) vs salmeterol alone, fluticasone alone, or placebo for 3 years. The primary outcome was death from any cause, the frequency of exacerbations, health status, and spirometry values. The all-cause mortality was 12.6% in the combination therapy group, 13.5% in the salmeterol group, 16.0% in the fluticasone group and 15.2% in the placebo group. The hazard ratio for death in the combination therapy group was 0.825 vs placebo ($P = 0.052$), a level that did not reach statistical significance, but was associated with a 17.5% relative reduction in mortality. The mortality rate for salmeterol alone or fluticasone alone did not differ from placebo. Combination therapy was associated with a statistically significant lower rate of exacerbations ($P < 0.001$). The probability of having pneumonia was higher among patients receiving fluticasone alone or medications containing fluticasone (*N Engl J Med*. 2007;356:775-789). An accompanying editorial suggests that the findings show that monotherapy with fluticasone should not be recommended, monotherapy with a bronchodilator may be an option, and that combination therapy "offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids... and protection against a decline in lung function" (*N Engl J Med*. 2007;356:851-854).

In the second study, 449 patients with moderate or severe COPD were treated with the anticholinergic inhaler tiotropium plus placebo, tiotropium plus salmeterol, or tiotropium plus fluticasone/salmeterol. The primary endpoint was COPD exacerbation that required treatment with systemic steroids or antibiotics. After one year there was no difference in the rate of exacerbation between tiotropium alone (62.8%), tiotropium plus salmeterol (64.8%), or tiotropium plus fluticasone/salmeterol (60.0%). Tiotropium plus fluticasone/salmeterol improved lung function ($P = 0.049$), disease-specific quality of life ($P = 0.01$), and reduced the number of hospitalizations for COPD exacerbation and all-cause hospitalization compared with tiotropium plus placebo. The authors conclude that adding fluticasone/salmeterol to treatment with tiotropium did not influence rates of COPD exacerbation but did improve lung function, quality of life, and hospitalization rates (early release *Annals of Internal Medicine* 2/20/2007, print date 4/17/2007). So, what is the upshot of these papers? Combination inhalation therapy in patients with COPD works best, bronchodilator plus steroid inhalation therapy should continue to be the recommended regimen perhaps along with an anticholinergic inhaler.

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First Antihypertensive Drug Approved in Last 10 Years: Aliskiren

The FDA has approved the first of new class of antihypertensive drugs, and the first new antihypertensive medication to be approved in more than 10 years. Aliskiren is an oral renin inhibitor, inhibiting the renin-angiotensin system earlier in the cascade than angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The drug is a once-a-day oral agent that is approved for use as monotherapy or in combination with other antihypertensives.

Aliskiren's effect is additive with hydrochlorothiazide, and seems to be well-tolerated with other cardiovascular agents. It will be available in 150 and 300 mg doses. The FDA approval was based on 6 placebo-controlled trials in more than 2,000 patients in which the blood- pressure-lowering effect was maintained for up to one year. The drug seems be effective across all age ranges, but is slightly less effective in African-American patients as compared to Caucasians and Asians, as is the case with ACEI's and ARBs. The primary side effect is diarrhea, which was seen in 2% of patients, usually on higher doses. Angioedema was also rarely noted. As with other drugs that affect the renin-angiotensin system, aliskiren should not be used during pregnancy. Aliskiren will be marketed by Novartis Pharmaceuticals, and will be marketed under the trade name Tekturna.

Alternate Treatment for Osteoporosis

Antiresorptive agents are standard therapy for osteoporosis. These drugs, which include the bisphosphonates (alendronate, risedronate, etc.) prevent bone breakdown, but they do not stimulate production of new bone. A new study looks at recombinant human parathyroid hormone (1-84) (PTH), a bone forming agent, as an alternative treatment for osteoporosis. In an 18 month, randomized, double-blind, placebo-controlled, parallel group study, 2,532 postmenopausal women with low bone mineral density at the hip or lumbar spine were randomized to receive 100 µg of PTH or placebo daily by subcutaneous injection. All received additional calcium 700 mg/d and vitamin D 400 U/d. The main outcome was new or worsened vertebral fractures, changes in bone mineral density as well as safety of the medication. PTH significantly reduced the risk for new or worsened vertebral fractures. The relative risk varied depending on the assumptions about women who did not complete the trial, but there was improvement in all subgroups. PTH also resulted in increased bone mineral density compared to placebo of 6.9% at the spine and 2.1% at the hip compared to placebo, but decreased bmd at the forearm. PTH also resulted in increased percentage of participants with hypercalciuria, hypercalcemia, and nausea by 24%, 23%, and 14% respectively compared to placebo. The authors conclude that parathyroid hormone (1-84) reduced the overall risk for new or worsened vertebral fractures in postmenopausal women with osteoporosis, and suggest that PTH provides an alternative therapy option for fracture prevention (*Ann Int Med.* 2006;146:326-339). This study adds a second option for anabolic (bone-forming) agents along with teriparatide.

Roche's Oseltamivir: Scrutiny, Bird Flu, and New Drug Applications

Roche's oseltamivir (Tamiflu) has come under scrutiny in Japan after 2 students who took the drug fell to their deaths in February. The drug has been associated with abnormal behavior in anecdotal reports including a Japanese boy who ran in front of a truck after taking the drug in 2004. Roche counters that influenza can cause abnormal behavior and denies a link between the medication and psychiatric problems. The drug has previously been associated with delirium, and the FDA has required labeling urging close monitoring for abnormal behavior since November 2006. Countries worldwide are stockpiling oseltamivir in case of avian influenza outbreak. Meanwhile Roche has filed a new drug application with the FDA for pediatric doses of the drug for children one year and older. The new capsules and a 30 milligram and 45 mg capsule would join the 75 mg adult strength capsule.

FDA Actions

The FDA has approved duloxetine (Cymbalta) for the treatment of generalized anxiety disorder. The drug is currently approved for the treatment of major depressive disorder in the management of diabetic peripheral neuropathic pain. The FDA approved duloxetine 60 mg once daily for the treatment of anxiety based on three randomized, double-blind placebo-controlled trials in 800 patients.

The FDA has approved lisdexamfetamine dimesylate capsules for the treatment of attention deficit/hyperactivity disorder in children age 6-12. Lisdexamfetamine is a pro-drug of dextroamphetamine that may be associated with less drug abuse than dextroamphetamine. The once-a-day drug will be available in 30, 50, and 70 mg strengths. Lisdexamfetamine is marketed by New River Pharmaceuticals under the trade name Vyvanase. ■