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INSIDE

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The Evolution of the Cervical Cancer Screening: HPV Testing

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *In a community-based, randomized controlled clinical trial comparing conventional Pap testing to HPV testing, the latter was associated with greater sensitivity for high grade cervical intraepithelial neoplasia.*

Source: Mayrand MH, et al. Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer. *New Engl J Med.* 2007; 357:1579-1588.

Human Papillomavirus (HPV) testing has proved efficacious in triaging minimally abnormal cytology to further investigation or surveillance. However, despite its high sensitivity for cervix pathology, its value as a primary screening technology has been formally evaluated in only a limited way. To address the hypothesis that HPV screening is superior to conventional Pap testing, a randomized clinical trial was conducted in 10154 women in 30 clinics from Montreal and St. John's, Canada. Eligible participants included women aged 30 to 69 years, who otherwise were not being followed up for a cervical lesion, lacked a cervix, were pregnant, had a history of cervical cancer or had undergone Pap testing in the previous year. Patients were randomized 1:1 to either a "focus on Pap" or "focus on HPV" screening group. Since the hypothesis consideration was two-tailed, double sampling occurred in all patients; however, the first test performed was directed by randomization. High-grade (grade 2 or higher) cervical intraepithelial neoplasia in tissue was the primary endpoint. The endpoint could be reached by biopsy (liberal-definition) or excision (conservative-definition). The sensitivity for HPV testing for this endpoint was 94.6% compared to 55.4% for conventional Pap testing ($p = 0.01$); the specificity was 94.1% for HPV testing com-

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pared to 96.8% for conventional Pap (p <0.001). Performance was unaffected by sequence. All patients with significant pathology were identified when both tests were used, however, specificity dropped to 92.5%. Combining tests improved specificity but at the cost of sensitivity. As compared to Pap testing, HPV-based screening has greater sensitivity for cervical intraepithelial neoplasia.

COMMENTARY

Since the introduction of the Pap smear, deaths from cervix cancer in the US, as well as other resource-rich countries, have steadily dropped; the screening test is the most successful ever introduced for a solid malignancy. Its success is dependent on several factors, not the least of which is an index disease that is well suited for screening. However, outside the available, accepted and cheap sampling method, resources required to make this screening effort successful are vast and include not only specialized personnel to interpret the cytology but also an availability to evaluate (colposcopy) and to exact treatment (excision/destruction) for pre-invasive lesions that are suggested or confirmed. The costs are prohibitive for resource-poor situations and the system doesn't address the highest risk groups now facing the medical community—the never- and under-screened population. Since nearly 100% of cervix cancer is associated with HPV infection, testing returns and unambiguous result, and the sampling for HPV in the general population can be accomplished with little medical intervention, attention has turned to evaluation of the next iteration of screening in an effort to break the stalemate of mortality still observed in this and other countries.

The primary objective of this provocative randomized clinical study was to address the potential impact of a screening program based solely on the identification of HPV DNA as compared to conventional cytology. It was performed in a population of average risk women seeking care in the community setting. Given the previously suggested improved sensitivity of HPV testing for high-grade CIN, it was expected that molecular testing would do a better job in representing patients with disease. However, as was also expected, the potential for false positive results would necessarily lead to greater secondary referral. Nevertheless, this front-end "disease" focus over the long run could translate into the need for less repeat testing—this has been suggested by others but was untested in the current study. Additionally, it may be inferred from the current study that secondary cytologic evaluation of HPV positive screens could improve overall screening performance. This is a viable health care question and should be a primary focus of future clinical trials. Other recent efforts to raise the bar on screening performance have focused on the processing, interpretation and automation of cytology-based screening. While these objectives are of great importance, an avenue to address mortality from this preventable cancer where it is of greatest burden is a persistent and formidable challenge. ■

Other Reading:

Belinson JL, et al. Shanxi Province Cervical Cancer Screening Study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. *Int J Gynecol Cancer.* 2003;13:819.

Ratnam S, et al. Human papillomavirus testing for primary screening of cervical cancer precursors. *Cancer Epidemiol Biomarkers Prev.* 2000;945-951.

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Please call **Iris Young**, Managing Editor at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Ideal Weight Gain in Pregnancy

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: *Evaluation of gestational weight gain guidelines for women with normal prepregnancy body mass index.*

Source: DeVader S, et al. Evaluation of gestational weight gain guidelines for women with normal pre-pregnancy body mass index. *Obstet Gynecol.* 2007;110:745-751.

LAST MONTH AN ARTICLE WAS FEATURED IN THE *OB/GYN Clinical Alert* from the October issue of *Obstetrics & Gynecology*. Since the issue was rich in good material, I will go back to it to review information pertaining to one of the most common questions asked of providers—"How much weight should I gain in my pregnancy?"

Although I will focus on the first of three papers dealing with an answer to this question, material from the other two will be folded in.

De Vader et al reviewed Missouri birth certificate data from 1999-2001. Using only those women with a normal body mass index (BMI) who delivered term infants, the patients were broken up into 3 groups: 1) those who gained less than 25 lbs.; 2) those whose weight gain was within recommended guidelines; 25-35 lbs. (37,292); and 3) those who exceeded 35 lbs. (40,552).

Those in the lower weight gain category had significantly lower rates of preeclampsia (OR=0.56), cephalopelvic disproportion (OR=0.64), failed induction (OR=.68), cesarean section (OR=.82), and large-for-gestation (LGA) babies (OR=0.4) than those gaining the recommended weight. The downside was that they had a higher rate of small-for-gestation (SGA) babies (OR=2.14). Those in the upper weight gain category had a significantly lower rate of SGA (OR=0.48), but increased odds for preeclampsia (OR=1.88), LGA (OR=2.43), failed induction (OR=1.5), and cesarean section (OR=1.35) compared with those in the "normal" weight gain category.

This study indicated that with those with normal BMIs, gaining more than or less than recommended weight had higher rates of adverse outcome, as well as some interesting trade-offs. However, all in all, the recommendation of 25-35 lbs seemed to be a reasonable guideline. I did find it interesting that more (42%) Missouri women gained more than 35 lbs than those falling into the "recommended" category (37%).

The second article dealt with Missouri patients who were in the high BMI category (>30). As classified by the NIH definition, these obese patients were further broken down into Class I (30-35), Class II 35-40, and Class III (>40). The perinatal outcomes were assessed according to weight gain. The most important finding was that for every class of obesity, if the patient gained less than 15 lbs., the risk of LGA infants, preeclampsia and cesarean section was significantly lower than for those gaining more than 15 lbs. However, the incidence of SGA infants was higher in this group.

In the last article from Sweden, Cedergren analyzed perinatal outcome data from almost 300,000 pregnancies and came up with ideal weight gains for women with various body types. The results are laid out in the table below.

BMI	Ideal Weight Gain
<20	9-22 LBS
20-24.9	5-22 LBS
25-29.9	<20 LBS
≥30	<13 LBS

COMMENTARY

In so many aspects of medicine, the pendulum swings back and forth, sometimes very quickly. In the 1950's and 1960's, it was in vogue to recommend that patients restrict their weight gain since it seemed to make sense (without real proof at the time), that this would decrease the risk of preeclampsia and make it easier to attain their pre-pregnant weight after delivery. Then there was a major swing during the "I'm OK, You're OK" era toward a laissez-faire approach to weight gain (backed again by lack of data to support restrictive measures, but with no real evidence that extra weight gain was good for the fetus and mother). Now, we do have data to indicate that if one has a "normal" pre-pregnant weight, gaining more than 35 lbs (something that was done in 40% of Missouri gravidas) increased the risk of adverse outcome. Also, if patients were categorized as obese (BMI >30), their best outcomes came with some weight gain restriction (less than the lowest previously recommended level of 25 lbs).

Last, although it is clear from the Swedish study that we may be dealing with "apples and oranges" regarding body habitus, life styles and diet, it is clear that when it comes to food "some" is good but "more" is not necessarily better and "less" in some cases may not be necessarily bad. ■

Oral Contraceptives and Cervical Cancer

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr Edelman reports no financial relationship to this field of study

Synopsis: *The risk of cervical cancer is minimally increased (less than 1 additional case per 1,000 women) among current users of oral contraceptives but declines after cessation of use. This study does not provide evidence that oral contraceptives cause cervical cancer.*

Source: International Collaboration of Epidemiological Studies of Cervical Cancer. *Lancet.* 2007;370:1609-1621.

The Collaborative Group on Epidemiological Studies of Cervical Cancer has combined and reanalyzed any relevant data from all epidemiological studies on the association between cervical carcinoma and the pattern of oral contraceptive use.[1] The risk of cervical cancer was increased in current oral contraceptive (OC) users with increasing duration of use [relative risk for 5 or more years' use vs never use 1.90 (95% CI 1.69-2.13)]. After OC cessation, the risk declines and is equal to that of never users at 10 years. When adjusting for potential confounders, in particular age at first intercourse and number of sexual partners, the relative risk of invasive cervical cancer in current OC users decreased to 1.05 (95% CI 1.04-1.07). Although based on limited numbers, high-risk HPV infection was not significantly associated with ever-use of OCs or use for 5 years or greater [RR 1.19 (95% CI 0.92-1.52)].

COMMENTARY

Unfortunately, the most important implication of a study like this (birth control is incredibly safe) is not the one that is publicized by the media (birth control causes cancer). This study *did not* demonstrate that OCs cause cervical cancer and is not a study that can establish causation. This study found a very small risk of cervical cancer associated with OC use.[1] The findings in this study are no surprise given that several previous articles have found a similarly small risk of cervical cancer associated with OC use.[2,3]

Now, what kind of risk are we talking about? A relative risk of 1.0 translates to no difference in risk between two groups being studied.[4] This study found a small but statistically significant risk of cervical cancer associated with OC use (RR = 1.9) but after adjusting for confounders (ie, age, age at first partner, number of partners, smoking status) this risk decreased to 1.05.[1] Just because something is statistically significant doesn't mean that it's clinically significant! To put these numbers in perspective, a relative risk of 1.9 translates to less than one additional case of cervical cancer per 1,000 women. To really put this in perspective, the relative risk of lung cancer with tobacco use is 10.7 and has been shown to be the cause of about 87% of lung cancers.[5]

Thus, the findings of this study should, overall, be reassuring to you in its confirmation of a weak and non-persistent association of OCs and cervical cancer. Instead, we can use this as an opportunity with patients to discuss cervical cancer prevention and early detection. HPV infection is a known cause of cervical cancer. We have two very effective tools to prevent HPV infection— the HPV vaccine and condoms. In addition, regular PAP screening can detect and allow treatment of precancerous lesions.

Finally, remember to focus on the forest rather than the trees. Not to diminish the seriousness of cervical cancer, but unintended pregnancy rates are at epidemic levels in the United States (approximately 50%) and internationally, pregnancy is a major cause of maternal morbidity and mortality.[6,7] Misinterpretation and exaggeration of scientific results by the media in regard to birth control have been shown to directly influence rates of unintended pregnancy by scaring women to discontinue their birth control ("Pill Scare of 1995") when in reality, OCs have been well-studied and are extremely safe.[8,9] OCs provide women with a multitude of health benefits beyond contraception including prevention of ovarian and endometrial cancer.[10-13] ■

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Special Feature

Biological Determinism: Time for a Paradigm Shift in Cancer Therapeutics?

By Robert L. Coleman, MD

In the November 20th issue of the *Journal of Clinical Oncology*, two important articles appear, demonstrating the clinical impact of a novel therapeutic, bevacizumab, in women with recurrent ovarian cancer.[1,2] Bevacizumab is a fully humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF)—a principle compound secreted by tissues (tumors) to gain access to new endogenous vasculature. The drug, often referred to as a "biologic" because of its primary focus on functional interruption of the tumor microenvironment, has been shown to be of significant merit in combination with chemotherapy in several solid tumors, such as colon, lung and breast cancer—each with substantive improvement in progression-free and, in the former two, in overall survival.[3] The current articles represent seminal events for ovarian cancer therapeutics because they are the first two completed Phase II clinical studies in this disease site and demonstrate clinical efficacy as single agents. A summary of the two trials is presented in the Table below.

Table. Comparison of GOG170-D and AVF2949

Trial	GOG 170-D[1]	Genentech[2]
Agent	**Bevacizumab**	**Bevacizumab**
Primary Endpoint	OR + 6 Mo PFS	OR Rate
Eligibility		
Measurable Disease	Yes — RECIST	Yes — RECIST
Platinum DFI	Unrestricted	1° or 2° < 6 mo
Prior Regimens	1-2	2-3
PS	0-1	0-1
Target Sample Size	60	53
Dose/Schedule	15 mg/kg q 21 d	15 mg/kg q 21 d
Enrollment	**62**	**44**
1° Platinum DFI < 6 mo	36%	84%
% Prior Regimens (1/2/3/4)	34/66/0/0	0/52/48/0
% GOG/ECOG PS (0/1/2)	73/27/0	59/41/0
≥ G3 Toxicity		
GI Perforation	0	5
Arterial TE	0	3 (8%)
HTN	6 (10%)	6 (14%)
CNS	0	1
Proteinuria	1	1
RR	13 (21%)	7 (16%)
6 mo PFS	40%	27%

PFS: Progression-free survival; OR: Overall response

In the study conducted by the Gynecologic Oncology Group, 62 evaluable women with recurrent ovarian cancer (no more than 2 prior regimens) were given bevacizumab every three weeks until progression. Since it was anticipated that patients may experience "non-progression" as a reflection of the targeted therapy's effect, the design uniquely incorporated consideration of both objective response (traditional measures—RECIST) and percentage of patients being progression-free at 6 months in its statistical decision algorithm for efficacy. In all, clinical response was seen in 21%, including 2 patients remarkably achieving complete response; 40% were progression-free at 6 months. Severe treatment-related toxicity was uncommon. In contrast, the second

trial, initiated by the pharmaceutical sponsor was conducted in a more heavily pretreated population (up to 3 prior regimens) and demonstrated sufficient toxicity, predominately gastrointestinal perforation, to warrant early termination. Overall response (primary endpoint) was 16%—all partial responses. While the same dose and schedule of bevacizumab was used in this study, the unanticipated toxicity and lack of easily identifiable risk factors reminds one of the importance of using investigational agents in the clinical trial setting. Currently, randomized clinical studies in the setting of primary and recurrent disease are underway and represent mature clinical development of this novel compound.

On the whole, validation of efficacy for this "noncytotoxic" agent has encouraged discovery, and has ushered in an explosion of new compounds with new targets and/or combinations of targets. Many of these have or are now poised to enter the clinic. The expansion of targets and "targetables" also raise speculation (and optimism) of the next evolutionary iteration in cancer therapy: "biological determinism." While the term may assume various interpretations (eg, intrinsic biology defining outcome), what piques our imagination is the ability to accurately describe an individual patient's specific tumor biology and concocting a tumor-directed lethal cocktail for treatment. Customized or individualized therapy is not a new clinical concept; yet, the ubiquitous prevalence of "standard therapy" studies highlights how far the body of mature literature is from this endpoint. A comical surrogate marker of our progress could be prevalence of such treatment depicted in science fiction features; if customized therapy was commonplace, we wouldn't see it in Hollywood. Nonetheless, the catalogue of relevant targets is expanding and with it an arsenal of new compounds that may be of relevance for therapy. Our difficulty is matching the two.

On a superficial level, customization of therapy is part of our current strategic practice. For example, patients can be identified with low or reasonable probability of response to certain agents through clinical evaluation (prior lack of response or lack of exposure to agents within a certain class) or through *in vitro* testing. Several companies now offer chemoresistance or sensitivity testing in sampled tissues where several agents and/or combination of agents are tested in cell cultures of an individual's tumor. Unfortunately, validation of these assays as a predictive test for choosing the optimal drug at a specific time in therapy is very difficult and requires many thousands of patients.[4] Prognostic scoring algorithms based on clinical and molecular data have now also become available and are currently being used to triage patients into different treatment programs (eg, chemotherapy vs hormonal therapy for breast cancer).

Much is known about the relevant biological pathways in human cancer. Certainly, that knowledge is only a fraction of what is truly needed for individualized cancer therapy. However, tumor biology has and is currently being leveraged in clinical trials. For example, P53, a housekeeping gene for many tumors, is frequently mutated in ovarian cancer. While the prognostic impact of P53 status on outcome is variably reported, the importance of functional P53 to cellular processing is substantial.[5] *In vitro* and *in vivo* preclinical studies demonstrated that insertion of a normal P53 gene could signal tumor cell death in ovarian cancer models.[5] These data paved the way for the development of a number of "gene therapy" trials where, among other strategies, normal P53 was inserted into cells by viral vector constructs delivered intraperitoneally.[6,7] In fact, at one point, a randomized clinical trial of P53 gene therapy in combination with chemotherapy was enrolling patients after surgery with primary ovarian cancer. The trial did not meet it accrual goals—largely due to toxicity concerns. Still of therapeutic interest, the strategy has been revisited now with extensive work being done in vector technology.[8]

Treatment directed at the epidermal growth factor receptor (EGFR) is another example of tumor-specific targeted therapy. EGFR, the first biological target selected for therapy, is overexpressed in most solid tumors including ovarian cancer. Activation of the growth receptor occurs when two individual like receptors or related receptors bind (dimerize), signalling a number of downstream functions including cellular proliferation, survival, adhesion and migration. The activation can be through ligand dependent and/or independent mechanisms and is the focus of several agents including monoclonal antibodies, dimerization inhibitors and tyrosine kinase small molecule inhibitors (TKIs).[9] Some of these have been very successful (trastuzumab, lapatinib) and others more variable. However, of great interest has been the recent recognition that certain individual characteristics of the target might actually predict in whom these agents may work. This was highlighted by the initial FDA accelerated approval and then retraction of approval of the agent gefitinib in patients with lung cancer. Initial work demonstrated

that selected patients had dramatic responses to single-agent gefitinib; however the agent did not reach its survival endpoints in mature phase III investigation. Subsequent studies demonstrated a candidate reason for the mixed observation was due the presence of certain mutations in the binding site of the receptor. Patients (and cell lines) with these mutations were substantially more likely to respond to gefitinib than those without.[10,11] Unfortunately, the presence of this factor is only a subset of the total lung cancer population but it draws light into how customization of therapy can be levied by understanding the key characteristics of a specific patient's tumor.

Globally, more than 360 biologically-based agents are in clinical development, many with specific biomarkers in the hopes of identifying in whom the agent works best. Putting these together in novel combinations and sequences is the true representation of biological determinism. However, tests to demonstrate which factors should be targeted (*in vitro* testing, tissue microarrays, gene profiling, etc) need validation, as does the pairing of identifiable targets with specific agents. In early September 2007, one "proof of concept" trial was presented, demonstrating "better than expected" outcomes in 4 of 7 refractory and heavily pretreated patients with solid tumors in which their individual tumors were profiled and matched with drugs targeting these pathways. The prospective allocation of agents (chemotherapeutics and biologics) was based on profiling computational analysis of the interaction of multiple targets and signalling pathways, and represents a first step in individualization of therapy. However, much more work in understanding which pathway/pathways is/are critical, can be targeted by specific-enough agents, can be administered with acceptable toxicity, and will genuinely identify the "Achilles heel" of an individual's tumor is needed before "biologic determinism" can be allocated more merit than just "pie in the sky." ■

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CME Questions

33. The authors looked at sequence of testing for the individual modalities as well as the value of using them in combination or simultaneously. Compared to HPV testing alone, specificity using a triage program using HPV first followed by conventional Pap:

a. increased
b. decreased
c. was unchanged
d. was not exactly evaluated

34. Which is true regarding excessive weight gain?

a. There is less preeclampsia
b. It has no effect on infant weight
c. There is a lower rate of CPD
d. There is a lower chance of SGA

35. Which of the following is untrue?

a. In the Swedish study, the ideal weight gain is less than 13 lbs for those with BMIs of >30
b. The only downside to weight restriction in non-obese patients is a somewhat higher rate of SGA
c. Preeclampsia is increased in those with low weight gain
d. CPD is increased with a weight gain of more than 35 lbs

36. After cessation of oral contraceptives, the risk of cervical cancer:

a. remains slightly increased as compared to never-users
b. is the same as never-users
c. is less than never-users
d. none of the above

Answers: 33 (a); 34 (d); 35 (c); 36 (b)

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;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

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.

FDA Warnings Dominate Pharmaceutical News

In this issue: *FDA warnings for existing drugs dominate pharmaceutical news this month. The FDA and its advisory committees have issued warnings on erythropoiesis-stimulating agents, oseltamivir (Tamiflu) and zanamivir (Relenza) for the treatment of influenza, rosiglitazone (Avandia) for the treatment of type 2 diabetes, varenicline (Chantix) to help stop smoking, the beta agonist salmeterol (Serevent), and modafinil (Provigil) for use in children. The FDA has also asked for marketing suspension of Bayer's aprotinin (Trasylol). These warnings represent a new push by the FDA to regulate existing drugs for safety after they have been approved for marketing. It also comes at a time when the FDA is cleaning up its advisory committee processes, especially with regard to limiting potential conflict of interest by advisory committee members. A summary of the new committee processes can be found at www.FDA.gov.*

Erythropoiesis-stimulating agents (ESAs) are the subject of new warnings from the FDA. The drugs, Aranesp, Epogen, and Procrit are used to treat anemia associated with cancer chemotherapy and chronic kidney failure. For cancer patients, several studies have shown that the drugs promote tumor growth and decrease survival rates in patients with advanced breast, head neck, lymphoid, and non-small cell lung cancer when given in doses that achieve a hemoglobin level of 12 g/dl or greater—the target in clinical practice. There is currently no evidence to know whether the ESA's promote tumor growth or shorten survival in patients who achieve hemoglobin levels less than 12 g/dl. The warning also specifically states that ESA's should only be used in cancer patients to treat chemotherapy-related anemia, not other causes of anemia associated with cancer and stress, and that the drug should be discontinued once chemotherapy is discontinued. For patients with chronic kidney failure, the new warnings states that ESA's should be used to maintain hemoglobin levels between 10 to 12g/dl. Higher hemoglobin levels increase risk for death and serious cardiovascular events such as stroke, heart attack, or heart failure. Finally, the new labeling emphasizes that there is no data that demonstrates that ESA's improve symptoms associated with anemia such as quality of life, fatigue, or patient well-being for patients with cancer or for patients with HIV undergoing AZT therapy.

An FDA panel is recommending new warnings on the flu drugs oseltamivir (Tamiflu-Roche) and zanamivir (Relenza-Glaxo) regarding abnormal psychiatric behavior associated with the drugs. This issue came up last year with a number of reports from Japan of erratic behavior including jumping from buildings resulting in deaths in patients taking the

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drugs. Many of the cases involved children. Japan has already taken the step of warning prescribers not to use the drugs in those aged 10 to 19. The panel reports 700 cases of psychiatric adverse events associated with both drugs, and 25 potential deaths in patients taking Tamiflu. No fatalities have been reported with Relenza. Both companies insist their drugs are safe and suggest that it is difficult to know if symptoms are caused by influenza or by medications. In the meantime Roche has agreed to stronger warnings for Tamiflu. Both medications reduce the symptoms of influenza and reduce the duration by approximately one-and-a-half days.

The manufacturers of rosiglitazone (Avandia-GlaxoSmithKline) have agreed to add new information to the existing black box warning regarding the potential increased risk of heart attacks associated with drug. The FDA's press release states that "People with type 2 diabetes who have underlying heart disease or who are at high risk of heart attack should talk with their health-care provider about the revised warning as they evaluate treatment options. FDA advises health-care providers to closely monitor patients who take Avandia for cardiovascular risks." Rosiglitazone is approved for treatment of type 2 diabetes as single therapy or in combination therapy with metformin, sulfonylureas or other oral anti-diabetes treatments. GSK has been asked by the FDA to conduct a long-term study to evaluate the potential cardiovascular risks of rosiglitazone.

The FDA has issued an "Early Communication" regarding varenicline (Chantix), Pfizer's prescription medication to help adults stop smoking. Pfizer has received reports describing suicidal ideation and erratic behavior in some patients taking the drug which have been submitted to the FDA. The Agency is soliciting any additional similar cases from Pfizer and will complete analysis when more data is available and then communicate conclusions and recommendations. In the meantime the FDA recommends health-care providers monitor patients taking Chantix for behavior and mood changes.

An expert panel of the FDA is also recommending a new warning for the long acting beta agonist salmeterol (Serevent-GlaxoSmithKline) regarding use in children. Nine new adverse event reports including five deaths in children using the drug had been reported in the last year as well as reports of increased hospitalizations and asthma-related deaths in children. Before a final recommendation is made by the FDA, review of other long-acting beta agonists will also be included, including formoterol (Foradil), Novartis' long-acting beta agonist and GlaxoSmithKline's Advair which is a combination inhaler of salmeterol and fluticasone. There is some evidence that steroid inhalers mitigate the risk of asthma-related deaths in patients taking long-acting beta agonists.

An FDA panel is recommending stronger warnings for use of modafinil (Provigil) in children. The drug is approved to treat certain sleep disorders in adults, and is not approved for use in children, but is occasionally used off label for the treatment of attention deficit hyperactivity disorder. The drug's labeling was recently updated to warn of serious skin reactions and psychological problems such as hallucinations and suicidal ideation.

Bayer Pharmaceuticals is complying with the FDA's request for a marketing suspension of aprotinin (Trasylol). The drug, which is used to control bleeding during heart surgery, is the subject of a large Canadian study, the preliminary results of which have shown an increased risk of death associate with the drug.

FDA Actions

The FDA has approved over-the-counter sales of cetirizine 5 mg plus pseudoephedrine HCL 120 mg (Zyrtec-D) for adults and children aged 12 years and older. The product has been available as a prescription drug since 2001 for the treatment of upper respiratory allergies.

The FDA has approved several new generics for marketing. Oxcarbazepine (Trileptal) will soon be available as a generic in 150, 300, and 600 mg strengths the treatment of partial seizures in adults and children. Hydrocodone/ibuprofen (Vicoprofen) is also approved as a new generic. The drug is approved for short-term treatment of acute pain. Rivastigmine (Exelon) will be available in generic 1.5, 3, 4 .5, and 6 mg strengths for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia assisted with Parkinson's disease. ■