

Health Matters September 2007; Volume 2, Issue 3

Direct-to-Consumer Advertising of Prescription Drugs by April Berry

A recent article in the New England Journal of Medicine (NEJM) reported on the use of direct-to-consumer advertising of prescription drugs over the past 10 years. The authors investigated both the promotion of drugs by pharmaceutical manufacturers and the regulation of those promotions by the Food and Drug Administration (FDA) and found that while spending increased, letters of citation sent by the FDA to manufacturers decreased.

Advertising spending data were collected from TNS Media, which tracks advertising campaigns, and Verispan, a medical information company. Annual spending was classified into three categories: direct-to-consumer advertising, professional promotion (including physician detailing and journal advertising) and free samples. In 1996, total spending on promotion of drugs was estimated to be \$11.4 billion, which amounts to 14.2% of total sales that year. Direct-to-consumer advertising represented \$985 million or 1.2% of total sales. In 2005, drug manufacturers spent \$29.9 billion on advertising, amounting to 18.2% of total sales. Of

total advertising, 2.6% or \$4.2 million was spent on ads aimed at consumers. These figures represent a 10.6% annual increase over 10 years in total spending on promotion, and 330% increase from 1996 to 2005 in spending on direct-to-consumer advertising.

The authors found that the amount spent on advertising a particular drug was likely influenced by its drug category, status as chronic or acute therapy, and time from FDA approval date. Money was more likely spent on new drugs to treat chronic conditions, and the proton pump inhibitors, HMG-CoA reductase inhibitors, and SSRIs/SNRIs consumed the most advertising dollars of the top 10 drug classes. For all 10 of the top drug classes, more money was spent on physician detailing than any other form of promotion. Spending on direct-to-consumer advertising ranged from 34% of all advertising dollars for the HMG CoA reductase inhibitors to 0% for the angiotensin II antagonists as a class.

The FDA is responsible for monitoring all forms of prescription drug advertising. The FDA monitors advertisements for compliance with federal regulations and sends letters of citation to manufacturers for violations such as false claims, minimizing risks, or exaggerating effectiveness. While spending on advertising has increased, the number of letters sent by the FDA has decreased in the past few years. Two possible reasons for the change presented in the article are better compliance with regulations by the manufacturers and decreasing oversight by the FDA. Based on increased internal review requirements and a disproportionate increase in FDA staffing with the increase in advertisements, the authors conclude that the decrease in citations is due to weakening FDA oversight.

This study in the NEJM presented a limited view of prescription drug advertising in the

United States. The authors attempted to include a representative sample of health care professionals and media outlets, but expenditures such as data from small drug manufacturers and information on the sale of biotechnology drugs were likely missed. However, based on the information reviewed, it is clear that spending on direct-to-consumer advertising has increased significantly since the FDA relaxed restrictions on this mechanism of prescription drug advertising.

Reference:
Donohue JM, Cevasco M, Rosenthal MB. A Decade of Direct-to-Consumer Advertising of Prescription Drugs. *N Engl J Med* 2007;357:673-681.

Inside this issue:

Direct to Consumer Advertising	1
PPIs and cardiovascular risk?	2
Genetic testing for warfarin dosing	2
New recommendations for HRT	3



Updated Prescribing Information for Warfarin by Kelly Dighton

The Food and Drug Administration (FDA) has recently approved changes to the prescribing information for warfarin. The updated information is based on research that suggests variants of two genes can affect how warfarin is metabolized by individuals. The FDA is proposing that genetic testing be done on those patients requiring warfarin therapy to achieve better efficacy and decrease the risk potentially of life threatening events associated with over- or under-coagulation.

Currently, there are no new guidelines based on how to dose warfarin once a patient's genetic profile is known, but the FDA is funding several studies to establish dosing guidelines based on genetic testing. The two genes under investigation are CYP2C9 and VKORC1. Patients with variants of one or both of these genes may require dosage decreases of almost 40% based on preliminary data. It is estimated that one third of patients receiving warfarin have a variant in one or both of these genes, which can lead to unexpected warfarin metabolism. Warfarin is second only to insulin in adverse drug events leading to emergency room visits¹. Because of these statistics, it is important that the dosing of warfarin be closely monitored and tailored to an individual as much as possible.

The dosing of warfarin is already individualized based on the patient's prothrombin time (PT) and international normalized ratio (INR). Genetic testing will allow practitioners to further individualize dosing to attain better efficacy and fewer adverse events. The changes in dosing of warfarin are in line with the FDA's new initiative to individualize patient dosing to achieve better outcomes and fewer adverse effects from drug therapy.

New dosing guidelines are expected at the end of the FDA's funded studies, so additional information on this topic is forthcoming.

Reference

1. FDA Approves Updated Warfarin (Coumadin) Prescribing Information. U.S. Food and Drug Information. <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html>. Last accessed Sept. 10, 2007.

Proton Pump Inhibitors and Cardiovascular Risk? by Sarah Gacke

The heart risk scare brought on by proton pump inhibitors (PPIs) began on March 29, 2007 when AstraZeneca, manufacturer of Prilosec® (omeprazole) and Nexium® (esomeprazole) reported preliminary study data to the U.S. Food and Drug Administration (FDA). Two small long-term clinical studies, in patients with severe gastroesophageal reflux disease (GERD), suggested an increased risk of cardiovascular effects in patients being treated with Prilosec® or Nexium®. In both studies, patients were randomly assigned to receive treatment with a drug (Prilosec® or Nexium®) or to have surgery to control their GERD. Both studies were developed to evaluate the long-term clinical efficacy of the treatments and not to assess the outcome of cardiac safety.

Within the first year of the fourteen year Prilosec® study, also known as SOPRAN, the group treated with Prilosec® had a higher incidence of adverse cardiac events than the surgery treatment group. During a closer evaluation of the study, a few problems were discovered that potentially skewed the incidence of adverse events. Seventeen patients in the Prilosec® treatment group compared to eight patients in the surgery group experienced serious adverse cardiac events. However, six of those 17 patients receiving Prilosec® came into the study with histories of previous myocardial infarctions (MI).² The surgery treatment group contained no patients with history of MI, and the population in general was younger than in the Prilosec® group. Another concern of the study involved the expected rates of cardiac events. Compared to epidemiologic data antici-

pated for the general population, cardiac events reported in the surgery group were five fold lower than expected, whereas patients receiving Prilosec® reported cardiac events within 10% of what would be expected in the general population.³ This would lead one to believe that the difference seen between treatment groups was not an accurate difference, but one potentially brought on by a poorly stratified study population.

The Nexium® study, LOTUS, is still ongoing and does not have study details available for the public at this point in time. Although initial data suggested a difference between treatment groups in the rate of cardiovascular events, an analysis was performed on the five-year follow-up data, demonstrating that there was no difference in reported cardiac events between the drug treatment and surgery option.⁴

AstraZeneca supplied the FDA with pooled analyses of safety data collected from 83 randomized, placebo-controlled Prilosec® and Nexium® trials.³ The Prilosec® trials, lasting anywhere from six months to two years, included over 14,000 patients. The pooled Nexium® trials included over 16,000 patients. Based on the pooled data, cardiac event rates in patients treated with Prilosec® or Nexium® were either similar to, or lower than, the event rates seen in patients receiving the placebo.³ The post-marketing safety data, looking at 1.3 billion patients treated with either product, has not shown an association between PPIs and cardiac events.⁴

On August 9, 2007, the FDA issued a statement concluding that at this time the data did not suggest an increased risk of cardiovascular events with the use of the PPIs - Prilosec® and Nexium®.¹ A continued safety review by the FDA for both products is still underway and is predicted to conclude by early to mid-November 2007. At this time, the FDA recommends healthcare providers not change their prescribing practices for either Prilosec® or Nexium® with regard to concerns of the potential risk for cardiovascular-associated adverse effects.

References:

1. Transcript of FDA Press Conference of FDA's review of Prilosec and Nexium. Available from: <http://www.fda.gov/bbs/transcripts/transcript080907.pdf>. Accessed date: August 20, 2007.
2. AstraZeneca. SOPRAN Trial Summary. Available at <http://www.astrazenecaclinicaltrials.com/Article/526660.aspx>. Accessed date: August 21, 2007.
3. AstraZeneca. Evaluation of controlled clinical trial data of esomeprazole and omeprazole. 2007 August. Available at http://www.omeprazole-esomeprazoleinformation.com/sites/277/imagebank/typearticleparam525961/evaluation_of_studies.pdf. Accessed date August 21, 2007.
4. AstraZeneca letter to Healthcare Professionals. Available from: <http://www.omeprazole-esomeprazoleinformation.com/article/525931.aspx>. Access date: August 21, 2007.

North American Menopause Society Releases New HRT Guidelines by Alisha Eggers

In March 2007, the North American Menopause Society (NAMS) released new guideline recommendations for treating peri- and post-menopausal women with hormone replacement therapy (HRT). The NAMS recommendations offers disease state-specific recommendations for women experiencing peri- or post-menopause based on evidence that was reviewed by the society. (Table 1) NAMS reminds health care providers that women with an intact uterus should be prescribed estrogen and progestogen combination therapy (EPT) because of the increased risk of endometrial cancer in patients taking unopposed ET. Progestogen is not necessary in women without a uterus or women using low dose estrogen therapy locally.

The NAMS states that all women should have a complete health evaluation before any HRT is initiated. This health evaluation should include a physical examination, a complete medical history, and a mammogram within 12 months of starting HRT. Bone density evaluations may also be deemed appropriate on a case-by-case basis.

When implementing ET or EPT, individual treatment goals, risks, and benefits should be considered. Risks to consider are: underlying cardiovascular disease, stroke, venous thromboembolism, and diabetes. Lower ET and EPT doses are better tolerated and may provide a better risk to benefit ratio. The society recommends using local, vaginal ET and EPT in women only experiencing vaginal symptoms such as vaginal dryness, dyspareunia, and atrophic vaginitis. Long term, low dose HRT therapy should be considered in women who determine that the benefit of symptom relief outweighs the risks associated with HRT use. Long-term, low dose HRT should also be considered in women who are at high risk for osteoporosis fractures and experience menopause symptoms, as well as women who have a reduction in bone mass and other therapies preventing bone mass reduction are not appropriate.

Table 1.

Disease State	NAMS Recommendation
Coronary Heart Disease	The use of ET/EPT in patients for primary or secondary prevention of coronary heart disease is not recommended in peri- or post-menopausal women at this time due to conflicting data.
Stroke	HRT should not be used for the primary and secondary prevention of stroke. HRT should be avoided in women with an increased risk of stroke.
Venous Thromboembolism	Low dose estrogen may be safer than higher doses of oral estrogen due to the increased risk of venous thromboembolism associated with systemic ET/EPT.
Diabetes	HRT is not recommended at this time for the prevention of diabetes in perimenopausal women.
Breast Cancer	Breast cancer risk has been shown to increase in patients receiving EPT for more than five years. Although evidence suggests that ET for less than five years has little impact on breast cancer risk, ET should not be used for the prevention of breast cancer.
Depression	HRT is not recommended to be used strictly for the treatment of patients experiencing depression.
Osteoporosis	ET/EPT should be considered in women who have a high risk for developing osteoporosis. The risks and benefits of using ET/EPT in these women should be weighed with the risks and benefits of using other FDA approved agents for the prevention of osteoporosis.
Dementia & Cognitive Decline	Beginning EPT treatment after the age of 65 years is not recommended for the primary prevention of dementia or cognitive decline. There is evidence to suggest a possible increased risk of dementia within five years of initiating therapy in these women.
Premature Menopause	There is no clear data available to determine whether ET/EPT affects the morbidity and mortality in these patients who have an increased risk of osteoporosis and coronary heart disease.
Premature Ovarian Failure	There is no clear data available to determine whether ET/EPT affects the morbidity and mortality in these patients who have an increased risk of osteoporosis and coronary heart disease.

In summary, HRT should not be ruled out in all patients as the benefits may outweigh the risk in some patients. The decision of whether or not to use HRT should be made after a full history and physical evaluation and should be a decision made by both the physician and the patient, after education on the possible risks of using HRT. Up-to-date information with new research on HRT is needed to make informed, evidence-based decisions for patients.

Reference:

North American Menopause Society. Estrogen and progestogen use in peri- and postmenopausal women: March 2007 position statement of The North American Menopause Society. *Menopause* 2007; 14(2): 168-182.

Health Matters September 2007; Volume 2, Issue 3

Our Mission...

To serve the health care professional community by providing evidence-based, timely and unbiased information in an effort to contribute to comprehensive patient-based care. We also strive to provide excellent training and foundational skills to prepare our students to competently meet the challenges of providing such information throughout their careers.

Creighton University Center for Drug Information & Evidence-Based Practice
2500 California Plaza
Omaha, NE 68178

Contact us:

Telephone: 402-280-5100
800-561-3728

Fax: 402-280-5149

Email: druginfo@creighton.edu

We're on the web!!
<http://druginformation.creighton.edu>



Editor:

Amy Friedman Wilson, PharmD.
Director, Center for Drug Information & Evidence-Based Practice