



Health Matters August 2007; Volume 2, Issue 2

Give Me Your Sick, Your Poor, Your Depressed by Lorrie Chong

Is the United States slowly becoming a nation overwhelmed with poor physical and mental health or are people just becoming more health-conscious and further utilizing medical and prescription care? In the most recent Centers for Disease Control and Prevention Ambulatory Medical Care Utilization Estimates, Americans increased their visits to physicians' offices, hospital outpatient departments (OPDs), and hospital emergency departments (EDs) by approximately 36% over ten years (1995 to 2005)¹. In 2005, 1.2 billion ambulatory visits occurred, with almost half (49%) made to primary care physicians in office-based practices. These national annual estimates and others come from a sample of medical records compiled by the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). The main focus of these surveys is to provide the nation, its healthcare professionals, and the public with vital information concerning the utilization and provision of ambulatory care services.

For example, in 2005 visits made by patients 40 to 59 years of age comprised 28.5% of total ambulatory care visits, versus 23.9% in 1995¹. Half of all patients 50 or older made three or more visits to their provider in a year, and averaged two or more drug prescriptions at each visit. This indicates that the United States' quickly aging population is having huge effects on medical care and drug utilization as well as costs.

In contrast, statistics show that those without medical insurance consume far less healthcare in physician office-based settings and OPDs. Thus, this specific population of more than 42.4 million people must resort to seeking a majority of their healthcare in EDs instead². Uninsured patients visited the ED at a rate almost two times (45.9 visits per 100 persons) more than those with some form of private insurance (23.8 visits per 100 persons)¹. For many of these patients this lack of insurance translates into deferring needed medical care. Estimates from June 2006 reveal that 5.5% of the nation's population was unable to obtain needed medical care due to cost at some time during the past 12 months². The same study results also concluded that a majority of those who did not obtain medical care were Hispanic and non-Hispanic Black persons.

for non-Hispanics (417.4 visits per 100 persons). This informative data indicates that this nation still has many healthcare disparities when it comes to race as well as financial status.

Like the evident utilization differences amongst different populations, the cause for ambulatory care visits was also dominated by some distinct aspects. According to 2005 statistics, the leading reason for medical care was treatment of a chronic disease with a majority of these healthcare visits also medicinal in nature¹. 71.3% of all visits resulted in one or more medications being prescribed. Overall, this translated into more than 2.4 billion medications prescribed or administered at ambulatory visits. This exponential growth of drug utilization is also witnessed via the nation's spending. Prescription drugs alone make up one-tenth of the United States' total medical bill³. However, they still are the fastest growing expenditure. In just one year (2004-2005), overall prescription drug expenditures increased by 5.5%⁴. Topping the list of prescription drug expenses were antidepressants, antihypertensives, nonsteroidal anti-inflammatory drugs, hyperlipidemia drugs, and nonnarcotic analgesics¹.

Continued on page 2

Inside this issue:

Medical care utilization estimates	1
Extensive drug resistance TB (XDR TB)	2
Prescription drug cost sharing	3
SSRIs during first trimester	4
NSAIDs/Cox-2 inhibitors for prevention of colorectal cancer	6
Medical therapy with or without PCI for stable coronary disease	7

Also reflecting this difference in utilization of healthcare are the ambulatory care visit rates of non-white persons compared to white persons. The African-American population on average had visit rates to the OPDs and EDs almost double that of the white population¹. However when it came to visit rates to office-based primary care, surgical, and medical specialists, African-Americans only visited half as often as whites. Similar statistics were also seen with the Hispanic population. Hispanics' overall ambulatory care visit rate (308.4 visits per 100 persons) was lower than that



Sick, Poor, Depressed, cont from page 1

This high consumption of antidepressant medications creates a major discrepancy according to 2005 data. Statistics indicated only 7.6 percent of all ambulatory care visits concerned mental health treatment¹. However being the number one drug prescribed, more than 117 million of the year's 2.4 billion prescriptions were for antidepressants alone. As astounding as these figures may sound, though, this escalation in antidepressant use has been steadily developing. Between the periods of 1988-1994 and 1999-2000, antidepressant use tripled⁴. The most recent statistics available from the CDC also observed a rise of 48 percent in use between 1995 and 2002.

What do these shocking numbers say about healthcare prescribing habits and patients' welfare? Dr. Kelly Posner, an assistant professor at Columbia University College of Physicians and Surgeons in New York City, claims that, "depression is a major public health issue" with almost 25% of adults and 8% of adolescents having a major depressive episode sometime in their life⁵. Thus, high rates of genuine depression diagnoses are driving the number of antidepressant prescriptions upward. According to the CDC's most recent mental health data, 2.9% of adults aged 18 years and over have experienced serious psychological distress during the past 30 days⁶. The high numbers of reported psychological distress events and increasing antidepressant utilization rates may indicate that the public is becoming less concerned with the social stigma associated with psychiatric health and more comfortable asking for help. Conversely, many physicians including Dr. Ronald Dworkin, a Maryland anesthesiologist and senior fellow at Washington's Hudson Institute, argue that too many doctors are "medicating unhappiness"⁵. These pressures to prescribe are further worsened by pharmaceutical marketing; marketing to the doctors as well as directly to consumers. Therefore, what is left is a battle between providing an appropriate amount of medical care and unnecessarily treating a life of discontent.

References

1. Burt CW, McCaig LF, Rechtsteiner EA. Advance data from vital and health statistics: Ambulatory medical care utilization estimates for 2005. Hyattsville, MD: Centers for Disease Control and Prevention National Center for Health Statistics; June 29, 2007;388:1-16.
2. Cohen RA, Martinez ME. Health insurance coverage: Early release of estimates from the national health interview survey, january-june 2006. Hyattsville, MD: Centers for Disease Control and Prevention National Center for Health Statistics; December 2006:1-3. Available from: <http://www.cdc.gov/nchs/about/major/nhis/released200612.htm#11>. Accessed July 20, 2007.
3. CDC: Almost Half of Americans Use at Least One Prescription Drug Annual Report on Nation's Health Shows. Available at: <http://www.cdc.gov/nchs/pressroom/04news/hus04.htm>. Accessed July 13, 2007.
4. Hoffman JM, Nilay DS, et al. Projecting Future Drug Expenditures. *Am J Health-Syst Pharm.* 2007;64(3):298-314.
5. Cohen E. CDC: Antidepressants most prescribed drugs in U.S. Available at: <http://www.cnn.com/2007/HEALTH/07/09/antidepressants/index.html?iref=newssearch>. Accessed July 12, 2007.
6. National Health Interview Survey. Early Release of Selected Estimates Based on Data From the January-June 2006 National Health Interview Survey. Available at: <http://www.cdc.gov/nchs/about/major/nhis/released200612.htm#11>. Accessed July 19, 2007.

Extensive Drug-Resistant Tuberculosis (XDR TB) by Tizita Sahleyesus

Tuberculosis is a communicable infectious disease caused by *Mycobacterium tuberculosis*, and is a leading cause of death in the world. It is currently estimated that one-third of the world's population is infected and that 2 to 3 million people die from TB each year. The United States had over 15,000 new cases of active TB in 2002 and about 1500 deaths. *M. tuberculosis* is transmitted from person-to-person by coughing or sneezing. Approximately 90% of infected patients have no clinical manifestations. About 10% of infected patients develop active disease whereby the inflammatory response to the bacterial infection results in the formation of cavitory lesions in the lungs. The symptoms of TB include feelings of malaise, weight loss, fever, night sweats, coughing, chest pain, and hemoptysis. If left untreated, TB continues to destroy the lung, resulting in difficulty breathing and eventually death.

Resistance to tuberculosis drugs may develop due to a patient missing doses or failing to complete a course of treatment. There are two types of drug resistant tuberculosis; Multi- Drug-Resistant Tuberculosis (MDR

TB) and Extensive Drug-Resistant Tuberculosis (XDR TB). MDR TB is resistant to first-line TB drugs (i.e., rifampicin and isoniazid). On the other hand, XDR TB is not only resistant to the first-line TB drugs, but also to second line drugs (i.e., fluoroquinolones, kanamycin, capreomycin, or amikacin). XDR TB is a serious health condition because patients are left with few treatment options that are effective and safe. A March 2006 report by the CDC and WHO documented the presence of XDR TB in at least 17 countries. In the United States, 49 cases of XDR TB have been reported between 1993 and 2006. It is clearly an emerging public health issue that needs to be addressed effectively. The following link identifies the location of XDR TB cases. <http://www.hhs.gov/asl/testify/2007/03/070321fig1.JPG>

Treatment for XDR TB is complex and varies according to the extent of drug resistance, severity of the disease and whether the patient's immune system is compromised. Early detection through rapid drug susceptibility testing is critical to ensure quick diagnosis and effective treatment. A combination of three or four second-line drugs (i.e., ethionamide, cyc

loserine, fluoroquinolones, para-aminosalicylic acid), and one injectable agent (i.e., kanamycin, capreomycin, or amikacin) is required for effective treatment. Treatment duration of 24 months is recommended. It is absolutely critical for a patient to take these medications as prescribed to avoid developing resistance to the few drug combinations still effective. To ensure compliance, XDR TB patients are required to comply with directly observed therapy (DOT).

References:

1. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach Sixth Edition*. Sixth ed. New York: McGraw-Hill; 2005
2. Dennis L, Kasper, Eugene Braunwald, Anthony S. Fauci, Stephen L. Hauser, Dan L. Longo, J. Larry Jameson, and Kurt J. Isselbacher, Eds. *Harrison's Principles of Internal Medicine*. 16th ed; 2004.
3. CDC. Extensively Drug-Resistant Tuberculosis (XDR TB). Available at: www.cdc.gov/tb. Accessed July, 2007.
4. Raviglione MC, Smith IM. XDR tuberculosis--implications for global public health. *N Engl J Med.* 2007;356:656-659.
5. WHO. Frequently asked questions: XDR-TB. Available at: <http://www.who.int/tb/xdr/faqs>. Accessed July 19, 2007.

Prescription Drug Cost Sharing: Associations with Medication, Utilization, Spending and Health by Anna Sample

A recent article pooling 132 studies from a variety of sources looked at prescription drug plan cost-saving measures, and what effect those measures are having on medical and pharmaceutical utilization and spending, as well as health outcomes. These studies focused on different prescription plan payment options and restrictions including co-payments, coinsurance, tiering, monthly prescription limits, and benefit capitations.

Sixty-five studies examined one of the most important concepts of drug benefit plans: cost-sharing, or out-of-pocket expenses. Cost-sharing can be categorized into three main groups: co-payments, tiering, and coinsurance. These studies compared cost-sharing to pharmacy utilization—patient use of pharmacies.¹ Overall results showed a decrease in pharmacy utilization when the patient's cost-sharing was increased. The relationship of cost-sharing and utilization of pharmacies seems to be directly proportional. If the patient's out of pocket expense increased by a minute amount (ex. \$0.50), it was associated with a lesser decline in utilization of pharmacy services; as opposed to drastic increases in cost-sharing (ex. \$15), which resulted in a more significant decline in utilization.

Several studies suggest that 1) consumer sensitivity to cost sharing depends on a drug's therapeutic class and 2) that increased cost may decrease "non-essential" drug use more than "essential" drug use.¹ Results from these studies were mixed and did not show an overall decrease in non-essential medication utilization.

Eleven studies evaluated how benefit limitations correlate with drug use and drug costs.¹ Benefit limitations included limits on the number of prescriptions monthly. When a 3-drug per month limit was introduced, studies showed a decrease in use of medications in the Medicaid population from 15-49%, depending on the class or indication of the medication. When looking at the Medicare population and benefit capitations of \$1000, patients had 31% lower pharmacy costs than those that were not subject to a cap. Patients who exceeded their benefit cap were more likely to disenroll in a plan or discontinue medications.¹



Another group, comprised of 41 studies, investigated the effect of prior authorizations and formulary restrictions on drug and medical utilization and cost. These programs require use of older or less expensive medications before covering newer therapies. Studies that examined Medicaid patients taking a restricted statin medication showed fewer prescriptions filled, and also that patients were more likely to be nonadherent than patients without formulary restrictions.¹ Other studies found that prior authorization may indeed decrease pharmacy spending on that drug class but may not affect pharmacy spending in general.

Instead of prior authorizations, some drug benefit plans have a closed formulary or generic-only formulary. According to one study, plans that operated on a closed formulary were associated with decreased rates of drug continuation in patients with chronic disorders. Another study found that the degree of formulary restriction was positively correlated with higher drug costs, more office visits, and high likelihood of hospitalization among patients with certain diseases.¹

Many points have been raised in this article about prescription drug plan benefits and their effects on medical services and health outcomes. The evidence suggests that for each 10% increase in cost sharing, overall prescription drug spending decreases by 2-6%, depending on the class of medications and the patient's condition. Therefore, the consequence of benefit changes may be a greater use of expensive medical services.¹

References:

1. Goldman DP, Joyce GF, Zheng Y. Prescription Drug Cost Sharing: Associations with Medication and Medical Utilization and Spending and Health. JAMA 2007;298:61-69.

Risk of Birth Defects after Antenatal Exposure to SSRIs During First-Trimester

by Thu-Van Doan

Approximately 10% of women are affected by the symptoms of clinical depression during pregnancy, and many of these women are treated with antidepressants.¹ In the late 1980s, a new class of antidepressant, Selective Serotonin Reuptake Inhibitors (SSRI), was developed and rapidly gained extensive acceptance due to its more favorable side effects and overdose/toxicity profiles compared to the older tricyclic antidepressants. Nonetheless, over the years, concerns have been raised regarding the potential harm to the fetus due to maternal use of SSRIs during pregnancy. Recently, the use of SSRIs has been reported to be associated with increased risks of birth defects including omphalocele, craniosynostosis, and congenital heart defects.¹ Omphalocele is a condition where part of the intestine protrudes outside of the abdomen at the umbilicus. Craniosynostosis is defined as premature fusion of the cranial sutures preventing the normal growth of the baby's head.² An analysis was conducted utilizing the data provided from the Slone Epidemiology Center Birth Defects Study, (an ongoing program of case-control surveillance of medications in relation to birth defects), to evaluate the impact of first-trimester use of SSRIs on the risk of birth defects.¹

Briefly, since 1976 the Birth Defects Study has been identifying infants with malformations associated with medications in five study centers: Boston, Philadelphia, Toronto, San Diego, and New York State. Infants with minor birth defects, such as accessory nipples, dislocated hips, or low-set ears are excluded. Mothers of identified infants are interviewed within six months after delivery. The interview extracts demographic, reproductive, cigarette smoking, and alcohol/caffeine consumption information. Also collected is all medication usage (including prescriptions, over-the-counter, vitamins, minerals, and herbal products), any time from two months before conception to the end of pregnancy. The main focus of this study is on medications for the indications of anxiety, depression, and other psychological conditions. More specifically, mothers are asked about their use of the following medications: Prozac, Zoloft, Paxil, Effexor, Elavil, Celexa, Luvox, Lexapro, and Wellbutrin.¹

The analysis evaluated the previously reported associations of SSRIs with omphalocele, craniosynostosis, and congenital heart defects, as well as other specific birth defects (exploratory analyses). To qualify for the exploratory analyses, the defects needed to be observed in at least 100 subjects overall, and at least 5 SSRI-exposed subjects. First-trimester exposure included any use of SSRIs from 28 days prior to the last menstrual cycle through 112 days after the last day of cycle (fourth lunar month). To prevent the potential of "confounding by indication," where the outcome is due to the condition for which the SSRI is used, non-SSRI antidepressants were also included in the analysis. The study group was individuals exposed to any antidepressant during the first-trimester. The control group was individuals with no exposure to antidepressants at any time from 56 days prior to the last menstrual cycle through the end of pregnancy. In the evaluation of potential confounders, the authors assessed factors that may be associated with exposure to SSRIs and to the risk of birth defects overall. The factors included maternal age, maternal ethnic group, maternal education, study center, first-trimester smoking, seizures, diabetes, infertility, obesity, and hypertension.¹

A total of 9849 infants with and 5860 without birth defects were assessed. Infants were excluded if they had chromosomal defects, metabolic disorders, and defects of known cause. Of all the cases of birth defects, there were 127 cases of omphalocele, 115 cases of craniosynostosis, and 3724 cases of congenital heart defects. For the exploratory analyses, defects were excluded from further investigation if exhibited in less than 5 SSRI-exposed patients: esophageal atresia (189 subjects, 4 exposed), absent kidney (178 subjects, 4 exposed), horseshoe or accessory kidney (127 subjects, 4 exposed), abnormal intestinal rotation (149 subjects, 3 exposed), cystic kidney (179 subjects, 2 exposed), and small intestinal atresia (129 subjects, 2 exposed). Table 1 depicts the outcomes and rates of exposure to any SSRI, specific SSRIs, and non-SSRI antidepressants. Due to minimal exposures to fluvoxamine (5 subjects) and escitalopram (8 subjects), these medications were not further evaluated, and therefore, not included in the statistical data. Table 2 demonstrates the adjusted odd ratios and 95% confidence intervals for the use of SSRIs and their outcomes. There were no significant increases in the risk of omphalocele, craniosynostosis, or congenital heart defects associated with the overall use of SSRIs. Only 3 of 127, 2 of 115, and 100 of 3724 infants with omphalocele, craniosynostosis, and congenital heart defects, respectively, were associated with exposure to an SSRI during the first-trimester.¹

In summary, the results of the analysis did not confirm the previously reported associations of omphalocele, craniosynostosis, or heart defects with the maternal use of SSRIs during the first-trimester. However, the analysis suggests that specific SSRIs individually may contribute to the increased risk of specific birth defects. More studies are needed to investigate these important clinical findings. Meanwhile, it is important to understand that the absolute risks of these rare birth defects are small with the overall use of SSRIs during the first-trimester.¹

References:

1. Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007; 356:2675-2683.
2. Medical Dictionary Web site. Available at: <http://www.medterms.com/script/main/hp.asp>. Accessed July 20, 2007

See page 5 for tables

SSRIs continued from page 4

Table 1. Rates of Exposure to Antidepressants within Outcome Groups.¹

Outcome	Total No. of Subjects	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Anti-depressant
		Number of subjects (%)					
Craniosynostosis	115	2 (1.7)	0	1 (0.9)	1 (0.9)	0	0
Omphalocele	127	3 (2.4)	0	3 (2.4)	0	0	1 (0.8)
Any cardiac defect	3724	100 (2.7)	31 (0.8)	32 (0.9)	25 (0.7)	5 (0.1)	23 (0.6)
Cleft lip with or without cleft palate	704	22 (3.1)	11 (1.6)	3 (0.4)	4 (0.6)	4 (0.6)	6 (0.9)
Pyloric stenosis	688	18 (2.6)	6 (0.9)	7 (1.0)	3 (0.4)	2 (0.3)	6 (0.9)
Renal-collecting-system defects	644	17 (2.6)	5 (0.8)	6 (0.9)	4 (0.6)	2 (0.3)	4 (0.6)
Hypospadias	497	14 (2.8)	3 (0.6)	3 (0.6)	3 (0.6)	4 (0.8)	5 (1.0)
Clubfoot	413	20 (4.8)	3 (0.7)	5 (1.2)	10 (2.4)	2 (0.5)	4 (1.0)
Cleft palate alone	377	7 (1.9)	3 (0.8)	0	3 (0.8)	1 (0.3)	3 (0.8)
Undescended testis	349	11 (3.2)	1 (0.3)	0	6 (1.7)	2 (0.6)	2 (0.6)
Neural-tube defects	320	5 (1.6)	0	1 (0.3)	4 (1.2)	0	1 (0.3)
Anal atresia	215	7 (3.3)	2 (0.9)	3 (1.4)	1 (0.5)	1 (0.5)	3 (1.4)
Diaphragmatic hernia	192	6 (3.1)	3 (1.6)	1 (0.5)	1 (0.5)	0	2 (1.0)
Limb-reduction defects	193	9 (4.7)	3 (1.6)	3 (1.6)	1 (0.5)	1 (0.5)	1 (0.5)
No malformations	5860	160 (2.7)	61 (1.0)	46 (0.8)	30 (0.5)	15 (0.3)	49 (0.8)

Table 2. Adjusted Odd-Ratios and 95% Confidence Intervals for Specific SSRIs in Relation to Outcomes Previously Reported to Be Associated with SSRI use.*¹

Outcome	Any SSRI	Fluoxetine	Sertraline	Paroxetine	Citalopram	Non-SSRI Anti-depressant
		Odds ratio (95% Confidence Interval)				
Craniosynostosis	0.8 (0.2-3.5)	---	1.8 (0.2-14.9)	1.7 (0.2-14.4)	---	---
Omphalocele	1.4 (0.4-4.5)	---	5.7 (1.6-20.7)	---	---	1.2 (0.2-9.3)
Any Cardiac defect	1.2 (0.9-1.6)	0.9 (0.6-1.5)	1.5 (0.9-2.6)	1.4 (0.8-2.5)	0.7 (0.2-2.1)	0.8 (0.5-1.5)

*Odds ratios are adjusted for maternal age, maternal race or ethnic group (self-reported), maternal education, year of last menstrual period, study center, first-trimester smoking status, first-trimester alcohol consumption, history of birth defect in a first-degree relative, pre-pregnancy body-mass index, presence/absence of seizures, diabetes mellitus, hypertension, infertility, first-trimester use of folic acid. The reference group was all women not exposed to any antidepressant. Dashes indicate no exposed subjects.

NSAIDs and COX-2 Inhibitors for Primary Prevention of Colorectal Cancer: A Systematic Review by the US Preventive Services Task Force by Minh Nguyen

Colorectal cancer (CRC) is the second and third leading cause of cancer-related deaths in men and women, respectively, in the United States. In 2006, it was estimated that 148,610 new cases of CRC occurred and that 51,170 patients died of the disease. The U.S. Preventive Services Task Force (USPSTF) strongly recommends screening for men and women 50 years of age or older due to positive data suggesting that effective screening could decrease the incidence of CRC by up to 80 percent. Despite such evidence, adoption of routine CRC screening continues to be low in the United States. This has sparked interest in the use of CRC chemoprophylactic agents to complement, or replace a screening strategy.

At the request of the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), and the USPSTF, a systematic review to ascertain the effectiveness of non-aspirin (non-ASA), nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors in the chemoprevention of colorectal adenomas, CRC, and CRC-related deaths in average- to higher-risk individuals was conducted. A search strategy was developed and completed in MEDLINE (1966 to December 2006), EMBASE (1980 to the 14th week of 2005), Cochrane Central Register of Controlled Trials, Cochrane Library Issue 4, 2004, and PubMed Cancer subset. A total of 29 randomized controlled trials, cohort and case-control studies were included in the review to assess chemoprotection efficacy, and gastrointestinal and cardiovascular harms associated with the use of non-ASA NSAIDs and COX-2 inhibitors.

Three cohort studies showed a statistically significant dose-dependent protective effect of non-ASA NSAIDs on CRC. The relative risk reduction was up to 30% in colon cancer, but there was no observed benefit for rectal cancer alone. There was no significant protective effect of non-ASA NSAIDs on the incidence of CRC in patients who did not take the medication regularly or received less than 6 tablets per week. Similar results were observed with case-control studies. The relative risks were 0.70 and 0.57 for non-ASA NSAIDs and any NSAIDs, respectively. In randomized, controlled trials in patients with a history of colorectal adenomas, COX-2 inhibitors demonstrated statistically significant reduction in the incidence of all adenomas and advanced adenomas. The relative risk was 0.72. Similar results were observed in one cohort study with regular use of any NSAID.

Both cohort studies and case-control studies showed that higher doses of any NSAIDs were generally associated with a statistically significant reduction in relative risk in CRC frequency, whereas lower doses were not. However, low, medium and high doses were not clearly defined. Similarly, greater reduction in adenoma incidence was observed with celecoxib 800 mg daily, compared with celecoxib 400 mg daily (0.43 vs. 0.67). In addition, these studies demonstrated that longer duration of non-ASA NSAID use (beyond 2 to 5 years) generally resulted in statistically significant risk reduction for CRC, whereas shorter durations did not. However, the use of any NSAID had less consistent duration effects on adenoma prevention than on CRC prevention.

While no significant differences in death due to cardiovascular events with the use of COX-2 inhibitors compared with NSAIDs or placebo were observed, in some cases an excess risk for overall cardiovascular events (death, acute myocardial infarction, acute stroke, arterial hypertension, congestive heart failure, edema, and thrombotic events) with the use of COX-2 inhibitors compared with use of placebo was consistently demonstrated in others. The risk of developing cardiovascular events was greatest in patients already at highest risk for such events (those with an indication for aspirin). When considering acute stroke alone, there was no statistically significant increase in risk with COX-2 inhibitors compared with placebo or NSAIDs. In contrast, statistically significant increases in relative risk for acute myocardial infarction were observed with the use of COX-2 inhibitors or high dose non-ASA NSAIDs, particularly diclofenac and ibuprofen.

All studies reported an increased risk for peptic ulceration and gastrointestinal hemorrhage with non-ASA NSAIDs use. A risk for perforation, obstruction, or bleeding of approximately 1.5% to 2% was observed in average-risk patients taking standard non-ASA NSAIDs. These same risks can reach 10% or more in higher-risk patients (those with a history of peptic ulcers or comorbid conditions and those who are older). In contrast, the use of a COX-2 inhibitors compared with a non-ASA NSAID resulted in statistically significant reduction in relative risk for gastroduodenal ulcers, clinically significant ulcer complication, and gastrointestinal symptoms. When compared with placebo, COX-2 inhibitors did not show statistically significant difference in the risk for gastrointestinal bleeding or ulceration, except for one study, which showed patients taking celecoxib 400mg daily were at increased risk. Furthermore, it has been demonstrated that the combination of ASA and celecoxib resulted in a four-fold increase in ulcer complications over celecoxib alone.

The results of this systematic review suggest that using non-ASA NSAIDs is effective at reducing the incidence of colorectal adenomas and CRC. COX-2 inhibitors seem to be effective as well for reducing the incidence of colorectal adenoma in patients with previous adenomatous polyps. Additionally, higher doses and longer durations of non-ASA NSAIDs use seem to be associated with greater protection from CRC and adenomas. However, the use of these agents is associated with gastrointestinal and cardiovascular risks. Currently, positive data on the reduction of death from the use of non-ASA NSAIDs and COX-2 inhibitors as chemoprophylactic agents are lacking to offset these added risks. Therefore, at this time the balance of benefits and risks does not appear to favor chemoprevention with these agents in average-risk patients or in those with a history of colorectal adenomas.

Medical Therapy With or Without PCI for Stable Coronary Disease by Karen Choi

Percutaneous coronary intervention (PCI) for the initial treatment of stable coronary artery disease (CAD) has been increasingly employed in the United States **despite** recommendations published in the American College of Cardiology/American Heart Association (ACC/AHA) 2002 Updated Guidelines. The guidelines recommend that patients with stable CAD be initially treated with medical therapy, which includes aspirin, beta blockers, ACE inhibitors, and lipid lowering agents, and lifestyle modifications such as exercise.¹

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (published in April 2007) analyzed whether PCI with optimal medical therapy was superior to optimal medical therapy alone in reducing the risk of cardiovascular events in patients with stable CAD.

The COURAGE trial was a prospective, multicenter, randomized study that lasted from 2.5-7 years with a median of 4.6 years. This study involved 2287 patients with evidence of myocardial infarction and CAD. 1149 patients were randomized to undergo PCI and receive optimal medical therapy (PCI group) and 1138 patients received optimal medical therapy alone (medical therapy group). Optimal medical therapy consisted of antiplatelet agents, anti-ischemic agents, lipid-lowering agents, ACE inhibitors/ARBs, and exercise.

The primary outcomes of the study were death from any cause and nonfatal myocardial infarctions. The secondary outcomes were a composite of death, myocardial infarction, and stroke; and hospitalization for unstable angina.

Results showed no significant differences in the primary outcome of the study. The event rate of death and nonfatal myocardial infarction at 4.6 years was 19% in the PCI group and 18.5% in the medical therapy group ($p=0.62$). There were also no significant differences in the secondary outcomes. The event rate of a composite of death, myocardial infarction, and stroke was 20% in the PCI group and 19.5% in the medical therapy group ($p=0.62$). The event rate of hospitalization for acute coronary syndromes was 12.4% in the PCI group and 11.8% in the medical therapy group ($p=0.56$). However, the rate of revascularization was significantly lower in the PCI group at 21.1% while the medical therapy group was at 32.6% ($p<0.001$). Also, based on the use of nitrates, there were significant reductions in the incidence of angina throughout the follow-up period seen with the PCI group.

In summary, the COURAGE trial shows that the addition of PCI to optimal medical therapy in patients with stable CAD does not significantly reduce the incidence of death and nonfatal myocardial infarctions or cardiovascular events when compared with optimal medical therapy alone. Although the rates of angina and revascularization were significantly reduced in the PCI group, the authors note that a definitive correlation is unclear. Several other limitations of the study include the decreased generalizability of the results due to fact that a majority of the patients were male and white. However, the authors conclude that the COURAGE trial further supports the current guidelines for patients with stable CAD to be initially treated with optimal medical therapy and PCI should be implemented when it is required for symptom control or for the development of an acute coronary syndrome.²

References:

1. Gibbons RJ, Abrams J, Chatterjee K, Daley J, Deedwania P, Douglas JS, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina – summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003; 41:159-168.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. *N Engl J Med* 2007; 356:1503-1516.





Health Matters August 2007; Volume 2, Issue 2

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