

TOBACCO USE, A PUBLIC HEALTH PROBLEM OF EPIDEMIC PROPORTION

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Background: Tobacco smoking is increasing day by day. One of every three persons who start smoking falls ill and dies prematurely. The UN Health Agency says 4.9 million deaths attributable to smoking in a year now, are likely to exceed 10 millions in a year in next 20 years. At the present billions of dollars are being spent to support antismoking campaign all over the world. The efforts are being focused on different aspects like: creation of public awareness about hazards of smoking, introduction about the measures regarding prevention, importance of putting ban on advertisement and promotion of smoking, restriction on smokers activities, protection of non smokers from second-hand smoke, provision of free consultations and required supplements to those who wants to quit smoking and many more. The reported success rates of antismoking campaigns vary from country to country. The highest reported by the State of California Department of Health and National Cancer Institute; which includes, 20% lowering of adults smoking prevalence, 50% lowering of per Capita cigarette consumption. The California's TCP (Tobacco control programe) has saved an estimated \$3.62 for every dollar spent on program, is an other encouraging aspect.

Materials and methods: This is a review article, literature survey was carried out from various available sources.

Conclusion: In Pakistan, Federal Government had already enforced an Ordinance regarding the prohibition of Smoking and protection of Non-smokers Health since 30 June 2003. Moreover, through a notification "No Smoke and No Tobacco Use Places" had been identified very clearly. At the moment we need to implement it with full force and vigor.

Key Words: Smoking, Anti smoking campaigns and tobacco control programes.

Introduction

Tobacco smoking, particularly of cigarettes, is increasing day by day. It is one of the major causes of disease and death both in developed and developing world. The number of smokers found worldwide today, are more than "1.2 billion". Based on the current patterns, it is estimated that smoking related diseases will kill about 500 million out of these current smokers.

Cigarette smoke is a heterogeneous aerosol produced by incomplete combustion of tobacco leaf. It is composed of gases, particles and uncondensed vapors. More than 4000 substances have been identified in cigarette smoke, including some that are pharmacologically active, antigenic, cytotoxic, mutagenic and carcinogenic. International Agency for Research on Cancer has identified "55 carcinogens" in tobacco smoke.¹

The particulate matter in tobacco smoke, known as "tar" contains a long list of chemicals, primarily polynuclear aromatic hydrocarbons, aromatic amines and miscellaneous organic compounds. Metabolic activation of tobacco component can incite DNA adduct formation, gene mutations and sequence of

events that can lead to cancer. Cytochrome P-450 hydroxylates compounds such as debrisoquine and tobacco specific N-nitrosamines.²

Smokers, capable to metabolize debrisoquine rapidly, have eight fold higher risk^{3,4} of developing lung cancer, risk increases 18-35 fold in occupationally exposed to asbestos or polycyclic aromatic hydrocarbons.

Nicotine, the most characteristic of tobacco, is a highly toxic alkaloid that is both a ganglionic stimulant and depressant.

Acute cardiovascular responses to nicotine include increases in systolic and diastolic blood pressure, heart rate, myocardial oxygen consumption, myocardial excitability and peripheral vasoconstriction. Nicotine plays important role in maintaining smoking habit.⁵

Cigarette smoke contains 2-6% carbon monoxide, a highly toxic gas, known to interfere with oxygen transport and utilization. It is responsible for 2 to 15 times elevated carboxy-hemoglobin level in smoker's blood as compared to non-smokers.

Potent pulmonary irritant and ciliotoxins, present in smoke adds to its toxicity.

Tobacco Use a Major Health Hazard:

One of every three persons who start smoking falls ill and dies prematurely because He or She smoked.⁶ Smoking has been casually linked to heart disease, cancer and respiratory diseases. About 60,000 studies have confirmed the devastating impact of tobacco use on human health. A strong dose response relationship exists between tobacco exposure and excess mortality, as measured by age at onset of smoking, cigarette consumption and depth of smoke inhalation. While the prevalence of smoking has been slowly declining in USA and most other high income countries over past 10 years, smoking prevalence rates have been steadily rising in developing nations at the rate of about 3.4% per year. The UN Health Agency says, if the current trends continue, the tobacco caused-deaths are expected to increase from 4.9 million per year today to about 10 million per year in next 20 to 25 years, with **70% victims in the developing world.**⁷ The said tobacco annual death toll will be higher than the combined mortality due to malaria, pneumonia, tuberculosis, and diarrheal diseases.

In Europe more than 500,000 deaths per year are attributed to tobacco use. Tobacco products killing more than 800,000 people in China in the year now and will cause 2 million deaths in a year by 2025. It has been estimated that 450,000 Americans die each year due to tobacco use, are more than all of the deaths from AIDS, Alcohol, Cocaine, Heroin, Homicide, Suicide, Automobile crashes and Fire combined. Another 50,000 or even more Americans “who never smoked” also die each year because of exposure to Second Hand Smoke.

One can realize that tobacco use is an ever growing, global Public Health Problem of “Epidemic proportion”.

Table-1 Death attributable to tobacco use per year (n = 5million)

Sr. #	Disease	Percentage
1.	Cardiovascular including stroke	35-45%
2.	Cancer Lung	23-31%
3.	Chronic Lung disease stroke	19-24%
4.	Other Cancers	07-12%
5.	Other Diagonis	06-14%

N.B. Percentage varies from region to region

Cigarette smoking is the single most important cause of cancer mortality, accounting for more than 30% of all cancer deaths⁸ Data from large prospective studies

of populations in several countries show that cigarette-smoking men have 70% higher death rate than non-smokers, in all groups over the age of 35.

Well documented cause-and-effect relationship exist between cigarette smoking and lung cancer. Smoking is believed to be responsible for 85% of lung cancer. Men who smoke one pack a day has ten fold higher risk and it increases 25 time higher if cigarette consumption a day is two pack or more. Deaths from only Lung cancer are expected to exceed 30,00,000.^{9,10} Tobacco smoking is casually associated in men and women with higher rates of cancer of larynx, oral cavity, esophagus; alcohol consumption acts synergistically with cigarette smoking to increase the risk for these neoplasm. 75%-increased risk of breast cancer has been found among women who smoke heavily and who began smoking at young age.¹¹ Carcinoma of urinary bladder, kidney, pancreas, stomach and uterine cervix is also associated with cigarette smoking. 40% of bladder and kidney cancers are believed to be smoking related. The kidney and bladder are subject to the longest duration of direct exposure to carcinogens and radioactive substances in tobacco smoke.¹² Currently, 20% to 30% cases of leukemia attributable to tobacco smoking are¹³ due to presence of benzene and ionizing radiation (Polonium²¹⁰) in smoke.

Cigarette smoking is a primary risk factor for coronary heart disease (CHD). Overall, persons who smoke have 70% greater CHD death rate, a twofold to fourfold greater risk for sudden death than non-smokers.¹⁴ The risk of fatal cerebro-vascular disease is three times higher in smokers than non- smokers. It is also associated with aortic athero-sclerosis. The risk for myocardial infarction is proportional to number of cigarette smoked.

Cigarette smoking is the major causative-factor of chronic obstructive pulmonary disease (COPD), the leading cause of disability.¹⁴ The inhibitory action of tobacco smoke on ciliary activity and phagocytic activity in alveoli is major cause of increased infection, tissue destruction, and decreased lung function.

Smoking may delay conception in female smokers. Maternal smoking during pregnancy affects the fetus adversely including higher risk of having low birth weight baby, spontaneous abortion, fetal death, neonatal death and sudden infant death syndrome. This also includes the long-term adverse effects on physical growth and intellectual development of a child.

Tobacco smoke is a ubiquitous personal as well as

environmental pollutant. Human inhalation of second hand smoke or environmental tobacco smoke (ETS) is also responsible for the preventable diseases, disability, and premature death. Most of the people spend 90% of their time in the two microenvironments, home and work place. Where, exposure to second hand smoke usually occurs. It is reported that side stream smoke has double the amount of nicotine than in the main stream. The concentration of carcinogens is also notably high.¹⁵ Case control studies have shown increased risk of lung cancer in non-smoker wives of husbands who smoke. ETS causes estimated deaths of 35,000-40,000 due to heart diseases and 3,000 deaths due to lung cancer in America.

Tobacco smoking qualifies as pediatric disease too. Second hand smoke is known to impair respiratory system of children. The Environmental protection agency (EPA) report and other studies¹⁶ attribute exacerbation of existing child hood asthma in 200,000 to one million children, development 26,000 new cases of asthma, 3,00,000 cases of pneumonia and bronchitis, and 2,700 sudden infant deaths due to second hand smoke in a year.

!The sphere of grave effects of tobacco smoking is not only injurious to health of an individual but also associated with multi-dimensional financial loss including:-

- ! The cost of cigarette itself
- ! Medical treatment of resulting ailments of smoker and his family
- ! Lack of earning during said ailments.

These, in most of instances, leads to repeated upsets in the tight economic schedule of most of families in third world with serious consequences including:-

- ! Los of buying power to provide proper food and shelter for children
- ! Inability to continue education of children

An ultimate out come is sending the children on various jobs to support expenditures rather than to school. Tobacco smoking is certainly a contributory factor towards “ill literacy and child-labor”. The associated psychological disturbances in members of such families may lead to anti-social activities and criminality. On the whole, the higher magnitude of such occurrences in a society or country may provide both seed and soil for the growth of law-less-ness inducing feeling of in-security and instability. The domain of devastating effects of “tobacco smoke polluted atmosphere” are not limited to human health but the intellectual, social, educational, scientific, and economic development of a country, specially the third world country, is at risk. The Americans are

spending almost 157 billion dollars per year¹⁷ including 75.5 billion dollars annually on direct medical care of smoking related illnesses and 81.9 billion dollars due to lost productivity and fortified earning as a result of smoking related disability. For each pack of cigarette sold in 1999, \$3.45 was spent on medical care due to smoking, with \$3.73 in lost productivity. The economy of any third world country is least likely to with stand a burden of 150 billion dollar per year just for the sake of smoking only.

Tobacco Smoking is The Beginning of Endless Chain of Psycho-Socio-Economic Disturbances.

Developing a welfare state in third world and smoking can not go to-gather.

Antismoking Activities

The concern about smoking had long been raised in scientific community. Cancer has been linked to tobacco use for more than two centuries. In 1761, John Hill¹⁸, a London physician, reported an association between use of snuff and cancer nose. Lombard¹⁹ reported high incidence of smoking among patient with cancer than among controls in 1928. Perle²⁰ reported a shorter life expectancy in smokers in 1938. The Epidemiological studies published by Doll²¹ in UK and Horn²² in USA alarm the medical professionals to take ***Smoking as Serious Health Problem***. In 1958, The First solid step taken in this connection was ***“Putting ban on cigarette advertisement”*** in the Journal of American Medical Association, a regular feature for last many years. In 1970, the antismoking movement all over the world focused on the issue to create “smoke- free public places”. The implementation of law to ban smoking in Aircraft was an effort to restrict smoking. The American Cancer Society has made several contributions, including the adoption of the annual stop-smoking day, sponsorship of world conferences on smoking and health, etc. “Tobacco Control Program” longed to restrict smoking, and “Tobacco News” published to create awareness are examples of such activities in Pakistan. At the moment antismoking campaign is continuous all over the world, both at the governmental level (in almost every country) as well as the NGOS (hundreds of antismoking associations). The efforts are being focused on different aspects like: creation of public awareness about hazards of smoking, introduction about the measures regarding prevention, importance of putting ban on advertisement and promotion of smoking, restriction on smokers

activities, protection of non smokers from second-hand smoke, provision of free consultations and required supplements to those who want to quit smoking and many more.

The level of achievements against tobacco smoking through various programs and legislation vary from country to country. Recently, the State of California Department of Health and National Cancer Institute²³ have published their achievements, rated as best among various States of America. They include:

- ! 20% lowering of adults smoking prevalence, “now they have 10,00,000 fewer smokers than was expected
- ! Overall per Capita cigarette consumption has fallen by more than 50%.
- ! The lung cancer incidence is decreasing significantly.
- ! Youth smoking rate is also on decline. It is down from 12.1% in 1995 to 6.9% in 1999.
- ! Saving from California's TCP between 1990 and 1998 amounted to an estimated \$8.4 Billion in smoking attributable direct and indirect cost. In avoided direct Medical Cost alone, the program saved an estimated \$3.62 for every dollar spent on program.

Tobacco Smoking is “Forbidden” in Islam

*Allah's Messenger MOHAMMAD said: Whoever eats garlic or onion, let him avoid us and our masjid, and stay in his home. The angels are surely hurt by things that hurt the human beings. MOHAMMAD did not like smoke. Tobacco smoking / spitting not allowed in mosque while “Halal Food” can be taken. Tobacco can't be kept / stored in mosque. Smoking spoils a person's acts of worship and reduces their rewards. For instance, it spoils the prayer, which is the pillar of Deen. It also spoils Fasting. Fasting is very hard for smoker and he is reluctant to fast on next day

*Mufti of Egypt, Dr. Farid Wasil, declared smoking as “Haram” (forbidden) in Islam because of its damaging effects to human health. (Islamic Republic News Agency, IRNA 20 May 2000)

*According to large number of Muslim scholars, including Sheikh Gadul Haq Ali Gadul (Imam of Al-Azhar, Cairo), Dr. Hamid Jamie (former secretary of Al-Azhar, Cairo), Dr. Abdul Gali Shalabi (member of Islamic Research Academy), smoking is “forbidden” on account of its extensive health and financial damages to smoker and society.

**The council of Islamic Ideology Pakistan has declared the use of tobacco as an*

“un-Islamic” act. Dawn Newspaper (Pakistan), 26 May

2000

The Framework Convention on Tobacco Control (FCTC) is the first treaty initiated by the World Health Assembly, the governing body of the World Health Organization (WHO). Negotiations began in October 1999 and concluded on March 1st 2003. The FCTC was adopted at the World Health Assembly on May 23, 2003 and kept open for signature and ratification.

In the Annual Meeting of World Health Organization, in which 192 countries participated including Pakistan, unanimously adopted. The Framework Convention on Tobacco Control (FCTC), committing them-selves to fighting the devastating consequences to tobacco consumption and exposure. All these countries approved the first ever, “International Treaty Against Smoking, including an Advertising Ban”. In Pakistan, Federal Government had already enforced an Ordinance regarding the *prohibition of Smoking and protection of Non-smokers Health* since 30 June 2003.

No Smoke and No Tobacco Use Places

Those are; Hospitals, Dispensaries and other health care establishments, Educational Institutions, Offices, Conference Rooms, All domestic flights, Restaurants, Buses, Wagons, Trains, Indoor Stadiums, Gymnasiums, Clubs, Lounges of Airports, Waiting Rooms at railways stations and places of public work.

Penalties: Any person, who contravenes the provisions of said Act shall be punishable with fine, which may extend to one thousand rupees and in case of second or subsequent offence, shall be punishable with a fine which shall not be less than one thousand rupees, may extend to one hundred thousand rupees.

Now more than one and a half Year has Passed, there is no noticeable Change in society regarding behavior of smokers, prohibition of smoking in the declared smoke free places. The law enforcing agencies seems to be least interested, they have registered least activity in respect of implementation of the said Ordinance.

Most recently, on February 27, 2005 the world's public health treaty, the Frame Work Convention on Tobacco Control, became **International Law**. 167 nations signed it and more than 55 countries including **Pakistan ratified it**. The objective of FTFC is to protect present and future generation from devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke. This legally binding treaty gives nations powerful new tools to protect the

health of their citizen from the tobacco industry's deceptions and silk marketing.

Tobacco Industry Motives:

Tobacco industry may be the one of few industries in the world with largest daily clientage of one billion people using their product repeatedly day and night. While billions of dollars are being spent each year on antismoking campaign on one hand, the “Tobacco Industry” is spending more and more on advertisement and promotion on the other hand. During last two decades, tobacco industry has nearly quadrupled its advertisement and marketing budget.²⁴

Cigarette smoking

promotion & Advertisements opens Gateway to drug addiction

Tobacco use in children is linked to higher likelihood of drug indulgence and alcohol abuse. It is noted that children, who smoke, are 3 times more likely to drink alcohol, 8 time more likely to smoke marijuana, 22 time more likely to use cocaine. It is also associated, among boys especially, aggressive or disruptive classroom behavior leading to antisocial behavior and criminality.

Young people constitute a highly strategic market for tobacco industry. Therefore they are continuously exposed to cigarette messages through print media and promotional activities. Cigarette advertisements are prepared with the objective to attract young people selectively. The sponsorship of sporting events and public entertainment programs by tobacco industry is to attract youth. As a result, the trend of smoking is rapidly increasing among teenagers. In USA, 3 million teen-agers smoke regularly. Its current prevalence among adolescents²⁵ is astonishingly high 42.7%. It is estimated that 3000 young people start smoking each day.²⁶ In Pakistan, one can see large number of teen-age or even younger smokers all around. The boundaries of Colleges and Schools are no more a barrier for smokers. Cigarettes are available on Tuck-shops and Canteens in school and colleges. Promotion of “less hazardous” cigarettes, including filtered, low tar, and low nicotine cigarettes, are just creating the illusion that risk had been diminished. Such cigarettes, offer few if any safety advantages, increased total cigarette sale²⁷ from 17% to 59%.

Tobacco industry is investing millions of dollars as “contributions” in Election Campaigns of leading political parties all over the world²⁷. They successfully solicit allies to help (lobby or advance arguments that oppose regulation against them). This way they

generally escape the strong Government legislation.

Recommendations:

In this alarming situation the Governmental Agencies, Public Health organizations and Academic Institutions have to exert much Leadership than ever before on this issue.

The dawn of the twenty-first century offers us a new opportunity to create a smoke free society. Anti-tobacco program needs to be implemented with full force and vigor in such a way that it must touch each and every individual in the country whether smoker or non-smoker.

The health care professional should raise awareness and promote cessation with every clinical opportunity. Anti-smoke clinics may be opened in OPD of all the hospitals with the provision of free consultations and required supplements to those who wants to quit smoking. Workshops and seminars on related topics must be included as a permanent feature in the curriculum and routine activities of all the Educational and Health institutions.

Children learn to say “No Thanks” to cigarettes

A comprehensive counter-advertising program to deglamorize tobacco use is immediate requirement. School-based campaigns to engender ridicule toward tobacco companies and cigarette advertising will be helpful.

At the societal level, communities can commit to changing permanently to a nonsmoking social norm. Such efforts include:

Restricting tobacco advertising and promotion to all especially to teenagers and children, cigarette advertisements may be eliminated from all youth mag. Prohibiting tobacco access by youth, complete ban on sale and smoke in canteens in the premises of schools and colleges, atleast.

A complete ban on free sampling of cigarettes and other promotional offers (lucky draws, gift schemes, etc)also required.

Enhancing public education

Raising tobacco excise taxes

Control in tobacco exports.

Smoking Cessation Benefits should be displayed at least in Schools & Colleges

Smoking cessation produces immediate and long-term physical, psychological, and economic benefits. Within days of quitting the sense of smell and taste improve. One year after quitting there is substantial decrease in risk of myocardial infarction. After five years diminished risk for lung cancer is experienced. 15 years after quitting total mortality among former smokers decreases almost to that of nonsmoker's. Former smokers live, on

average, longer than continuing smokers. Women, who quit smoking before pregnancy, or in first trimester, eliminate the risk of delivering low birth weight baby.

At the individual level, one must maximize access to cessation services for all smokers and donate generously. We must promote further research into improving nicotine replacement therapies and other pharmacological approaches in this respect.

At the Mosque level: Imam can deliver message against tobacco use daily or at least weekly in speech before Jumma prayer. Message to “avoid tobacco” can be displayed in the mosques all over the country.

Agricultural changes: Replacement of tobacco by another crop through legislation and to end “tobacco subsidies & World Bank support” for growing tobacco are required.

On the legal front, multiple individual and class action suits ultimately may change the tobacco industry's ability to conduct business as usual. Implementation of existing law with full force is need of the day. Enforcement of existing penalties for violations may also be considered.

Conclusion

“Smoking is Number One Preventable Cause of Morbidity and Mortality” is still an un-challenged, strong and continues believe. All the health-care professionals, and indeed all the citizens, can work to achieve the goal to prevent associated morbidity and mortality. This up-hill task is not an impossible mission. The Success like Californian's have achieved is only possible if we Allocate Enough Resources, Political Will and Social Capital in right direction like they have done.

It is hoped that all these combined efforts will cause the decline and prevention of tobacco-related cancers in new millennium and there will be beginning of a new “smoke-free” chapter in public health.

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MEDICAL NEWS

The Rosiglitazone Story

On July 30, 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) convened to discuss the myocardial ischemic risk associated with rosiglitazone treatment in patients with type 2 diabetes mellitus. The joint committee, consisted of 24 experts in cardiovascular disease, epidemiology, biostatistics, and endocrinology. After lengthy discussions, it was concluded that the use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischemic events than placebo, metformin, or sulfonylureas.

That conclusion was based primarily on three independently conducted meta-analyses demonstrating an increase in the relative risk of myocardial infarction, angina, or sudden death among patients taking rosiglitazone. Presentations by FDA staff members suggested that a subgroup of patients with type 2 diabetes who are at higher risk for these events includes those with long-term nitrate use and those receiving concomitant insulin therapy. Still, there were several caveats inherent in the meta-analyses, including the facts that most of the clinical trials lasted only 6 months (although the two largest trials, which contributed most of the end points, were longer), that there were relatively few myocardial events overall, and that differences existed in adjudication of ischemic events. Ultimately, the committee voted to recommend not that rosiglitazone be removed from the market but rather that label warnings and extensive educational efforts be instituted immediately. The committee also requested further studies, but disconcertingly, none of the several proposed analyses of the ongoing clinical trials is likely to define an absolute risk for myocardial ischemic events in patients with diabetes who are taking this drug. The basic plot of the rosiglitazone story quickly became obvious to the advisory committee: a new "wonder drug," approved prematurely and for the wrong reasons by a weakened

and underfunded government agency subjected to pressure from industry, had caused undue harm to patients. Notwithstanding this characterization, as well as the emotional nature of the hearing and the media distractions, the committee meeting attempted to demonstrate the dispassionate application of scientific evidence to public health decision making. In fact, several basic tenets emerged at this meeting that might ideally be used as guiding principles for improving the process of approving new drugs: first, the pathogenesis of disorders that require intervention must be fully understood; second, treatment options for these diseases should be clarified through an evidence-based system; and third, a uniform approach should be used to determine the societal benefits and risks associated with a given intervention.

It has been 80 years since insulin was discovered and 50 years since sulfonylureas were introduced. Since those developments occurred, tremendous strides have been made in understanding the origins and sequelae of diabetes mellitus. For example, because it accelerates atherosclerosis, type 2 diabetes quadruples the risk of macrovascular disease. And ischemic heart disease continues to be a major cause of death among patients with diabetes. Yet the results of our current therapies fall short of our high expectations for chronic disease management.

For example, we know that in type 1 diabetes, metabolic control can reduce the risk of microvascular complications. On the other hand, the two largest randomized, placebo-controlled trials in patients with type 2 diabetes, the United Kingdom Prospective Diabetes Study and the University Group Diabetes Program, failed to find a significant reduction in cardiovascular events even with excellent glucose control. Moreover, we are facing a troubling paradox: preliminary data that were presented at the meeting and published by Gerrits et al. suggest that among the thiazolidinediones—a class of drugs that has been shown to improve metabolic control—rosiglitazone may increase cardiovascular risk

whereas pioglitazone may reduce it. Until we have a better grasp of the pathogenesis of atherosclerosis in type 2 diabetes, it will be difficult to design therapies to prevent this complication or even to determine how the currently available agents that act at multiple sites may affect clinical outcomes in very different ways.

Not surprisingly, glycemic control has been the centerpiece of therapeutic interventions in type 2 diabetes for many years. Within the past decade, several new drugs that result in "glycemic durability" a reduction in the glycosylated hemoglobin level have been approved by the FDA. However, change in the glycosylated hemoglobin level is a relatively poor surrogate for cardiovascular outcomes in type 2 diabetes, accounting for only 5 to 15% of the variation in ischemic risk. This finding represents a major dilemma for practitioners, regulatory agencies, and patients who seek the newest and best treatments for this disease.

The controversy surrounding biochemical surrogates versus clinical outcomes was also highlighted at the FDA meeting when the advisory committee reviewed one of the largest randomized trials of rosiglitazone, A Diabetes Outcome Prevention Trial, or ADOPT. In that study, the percentage decrease in glycosylated hemoglobin was greater with rosiglitazone than with metformin or sulfonylureas, yet the risks of congestive heart failure and cardiovascular ischemia were higher. These data suggest that we urgently need to change the regulatory pathway for drugs for the treatment of type 2 diabetes to make clinical outcomes, not surrogates, the primary end points. This is not a radical proposal: 20 years ago, the FDA shifted its primary efficacy end point for osteoporosis drugs from bone mineral density (a reasonable surrogate for the risk of fracture) to fractures themselves.

Without a regulatory sea change with regard to diabetes drugs, we are certain to be in the same position 5 years from now that we are in now: we will again find ourselves in possession of a new wonder drug that is designed to treat a devastating chronic disease but that may do more harm than good.

Drugs are approved or removed from the market on the basis of evidence from randomized, controlled trials. In the FDA hearing on rosiglitazone, several meta-analyses revealed a significant increase in the risk of myocardial ischemic events among patients taking rosiglitazone. However, an interim analysis of the ongoing Rosiglitazone Evaluated for Cardiac

Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which was designed specifically to assess cardiovascular risk among patients receiving rosiglitazone, failed to demonstrate a similar risk. In addition, two large observational studies, one conducted by Tricare for the Department of Defense and one conducted by WellPoint (the largest health insurer in the United States), noted no appreciable signal of increased cardiovascular risk with either of the available thiazolidinediones.

The contrasts among the levels of evidence and the results regarding the safety of rosiglitazone raised new questions about relative and absolute risks but also highlighted the weaknesses of observational studies examining events that are common and whose rates are likely to be increased only slightly by a given drug, even in a large cohort (such as that used by WellPoint, which comprised 160,000 patient records). This issue led to an interesting sidelight at the meeting. Recently, there have been calls for the FDA to fund and oversee phase 4 postmarketing studies as a means of determining the safety of newly approved drugs. The two observational studies on thiazolidinediones whose results were presented at our meeting had been performed independently of the manufacturers and the FDA. The indeterminacy of their results, due to the inevitable effects of the many confounding variables inherent in such studies, illustrates why this approach alone will neither solve the overriding problems of drug safety nor ultimately help a chronically underfunded federal agency. There is no doubt that it will be costly to undertake true safety and efficacy studies of new drugs using clinical outcomes as primary measures, but in the long run, these efforts will save time, energy, and money.

The rosiglitazone story thus carries lessons for scientists, practitioners, and regulators alike. One can only hope that the energy generated by the advisory committee meeting will be channeled into improving the open hearing process to better serve all interested parties.

Source : [The New England Journal of Medicine](#)