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Review Article

PHARMACOEPIDEMIOLOGY: A COMPLEMENT TO THERAPEUTIC TRIALS

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Abstract

Pharmacoepidemiology as a discipline goes beyond epidemiologic studies of drug-related topics. Some topics receiving much attention in Pharmacoepidemiology get little in traditional epidemiology, whereas others included in traditional epidemiology without question involve some controversy about whether they should be part of Pharmacoepidemiology. Much of this occurs because Pharmacoepidemiology is what may be called a bridge science bringing together pharmacology and pharmacy, clinical specialties, epidemiology, biostatistics, demography and social sciences. Epidemiology and clinical pharmacology are the two main bridgeheads. That a significant part of the early development of Pharmacoepidemiology was within a clinical pharmacology context would account for a somewhat different perspective from traditional epidemiology. The development of more and more potent but also increasingly expensive medicines will accentuate the need for skilled practitioners of drug administration and drug safety, of which Pharmacoepidemiology is the basic science. Strategies in education have to be developed to meet such needs. One of the most challenging areas of research in Pharmacoepidemiology is to understand why individuals respond differently to drug therapy, both in terms of beneficial and adverse effects.

Keywords: Pharmacoepidemiology, Drug research, Drug safety; Adverse drug reaction, Pharmacotherapy

INTRODUCTION

Pharmacoepidemiology is a branch of science that investigates the use and effects (beneficial and deleterious) of medications ("*pharmaco*") in large populations ("*epidemiology*").[1] The need for pharmacoepidemiological studies became obvious in the 1960s when the introduction of the hypnotic agent thalidomide produced an epidemic of severe birth defects.[2] Further work done over the next few years established the ability of pharmacoepidemiological studies to identify associations between a drug (or drug class) and one or more clinical events that had been missed under the strictly controlled conditions of therapeutic trials. Side effects detected by pharmacoepidemiological studies include thromboembolism associated with combination oral contraceptives,[3] the outbreak of myalgia–eosinophilia related to tryptophan use,[4,5] pulmonary fibrosis induced by appetite suppressants,[6] and an increased risk of motor vehicle accidents in patients taking benzodiazepines.[7] In addition, data from pharmacoepidemiological studies are valuable in the area of public health, since they have implications for organizing the healthcare system. For instance, a rise in acute coronary events was detected in Canada in the wake of a decision to decrease reimbursement rates for a number of drugs.[8] Large high-quality databases constitute the basis for reliable pharmacoepidemiological studies.[9,10] Several countries or districts with public health insurance programs have large databases that contain information on diseases, healthcare system utilization, and prescription–medication use for nearly every resident of the country, in a single file or several compatible files. Examples include Quebec and Saskatchewan in Canada and the United Kingdom with its well-known general practitioner database. In countries where health insurance is private, such as in the United States, no information is available on uninsured individuals, and data on insured individuals are fragmented among many health insurance companies and health maintenance organizations. Nevertheless, the available databases

provide valuable information on events that are not dependent on the socioeconomic status of the patients. In France, although a public health insurance program covers all residents, it does not routinely record information into an integrated database, an endeavor that requires considerable energy, time, and money. In addition, French physicians are not accustomed to providing continuous information on their management practices. These characteristics have hampered the development of pharmacoepidemiological studies in France. Studies such as the Thales Observatory Study provide useful information, however.[11]

Pharmacoepidemiology came into its own sometime in the late seventies, as a specialty which linked clinical pharmacology to epidemiology, at a time when it became increasingly evident, that factors affecting drug use by the community played a critical role in the success or failure of drug therapy. Hailed as a "research tool" of global importance, the World Health Organization too promoted research into this key area by conducting workshops, publishing manuals, training investigators and encouraging research by funding projects. In India, this sub-specialty has found a niche among pharmacologists who are happy to embrace it as "pencil and paper" research, more for reasons of convenience rather than that of genuine interest. Dwindling financial support for research from the administration of many medical colleges, along with the difficulty faced in procuring and maintaining laboratory animals or recruiting patients/healthy volunteers, as well as the problems faced in conducting experiments - ranging from poor quality of reagents to maintenance and upkeep of equipment have literally pushed many researchers to choose pharmacoepidemiology as their area of research.[12]

Pharmacoepidemiology, by its very definition, lends itself to large variety of study designs, but for reasons unknown, Indian researchers seem to be interested in conducting only quantitative drug

utilization studies,[13] while these studies are necessary for hypothesis generation. Almost all papers in this area consist of analyzing a specific number of prescriptions and looking at the different classes of drugs prescribed, the number of drugs per prescription, the number of fixed dose drug formulations, injectibles and so on.[14] Most of the studies do not take it even one step further to assess whether each prescription was rational or not; probably out of fear of rubbing the clinicians on the wrong side and also out of the lack of standard treatment guidelines in many facilities. Even quantifying the drug use by using internationally accepted measures such as 'Defined Daily Dose' is not done. Two decades ago, studies which compared the drug utilization patterns of various departments in health care facilities by looking at “N” prescriptions were “publishable” material.[15,16] It is no longer so. The rapid studies in both quantitative and qualitative research methodology as well as sophisticated statistical analytical methods make it imperative that the “proper tools of epidemiological research” are used. Pharmacologists seeking to do research in pharmacoepidemiology should take the time and make the effort to learn the basic concepts of epidemiological research and ensure that the basic principles are satisfactorily addressed during planning. Any study describing factors which affect drug use in the community-be it compliance to therapy or drug metabolizing enzymes, must use the appropriate sampling techniques and methods to draw valid conclusions. “Pharmacoepidemiology is a powerful tool that can benefit patients and public health, but only if used appropriately.”[17]

BENEFITS AND RISK OF MODERN PHARMACOTHERAPY

An amazing number of new pharmaceutical products and pharmaceutical principles have been developed in the past decades. They probably amount to us much progress in the healing sciences as all other therapeutic and preventive advances in the same period and perhaps as much as all the progress in medicine since the dawn of history. HZ-receptor antagonists, the physiologically targeted

cardiovascular drugs or particularly antihypertensive, vaccines and antibiotics are some examples.[18,19] But effective medicines used to treat and prevent disease also have the capacity to do harm. There is no such thing as an absolutely safe drug, as a knife is either blunt or sharp. Both individuals and whole groups of patients are vulnerable to adverse consequences of pharmacological therapy, both to expect and not expected undesirable effects. This includes major events as serious disease, permanent disability or even death. Questions are raised: "is the benefit of a newly developed product worth the cost of the patient and group society? ", "how distinct have advantages of a new drug or a biological to be in order to justify its disadvantages in risk or in cost? ". Patients, physicians, public health authorities and the general public are challenged to pursue a balance of benefit and harm that does not neglect the need neither of the patients or the legitimated needs of the society.

Pharmacoepidemiology is the study of the use and effect of drug in large numbers of people or the study of the use of drugs in society. The process of identifying and responding to safety issues about drugs. Pharmaco-epidemiology has been called pharmaco-vigilance. For example, the diabetes drug called Rezulin was found associated with a risk of liver damage.[20] The FDA and manufacturer sent 4 separate warning letters to doctors, asking them to watch out for the problem and order liver tests for their patients on Rezulin. Less than half of patients got the recommended liver tests and, though liver monitoring was to be done monthly, only 5% of doctors were regularly testing the liver function of patients on the drug 5 months after the warnings. Rezulin was withdrawn from the market in March of 2001 by the FDA.[21]

It is used to gain efficacy and especially the safety of new drugs once they have passed from limited exposure in controlled therapeutic preregistration trails to the looser conditions of their use in the community.[22] It is observational in that the groups to be compared have been assembled from subjects

who are or who are not (the controls), taking the treatment in the ordinary way of medical care. If they show adverse effect products are recalled soon after they are marketed. Examples: Guillain- Barre Syndrome from influenza vaccine, Diethylstilbestrol from endometrial[23] cancer, Cardiac valve disorders from Fen-Phen (fenfluramine and phentermine).[24] A major reason for these drug product recalls is that premarketing studies treat too few patients (especially 3000 to 4000). Because adverse effects of drug products are more commonly observed after marketing, the Food and Drug Administration (FDA) created the *Med Watch Medical Product reporting program* in the US. A similar program is operated by the WHO. The overall effect of this program will be reduce the time required to approved New Drug Application. Doing so would enhance the need for post marketing (Phase IV) studies, wherein pharmacoepidemiological methods are needed.[25, 26]

MED WATCH PROGRAM

The MedWatch program is an important part of FDA's mission to ensure that medical products are safe and effective. It is essential that this program be preserved and strengthened. The MedWatch program logged approximately 85,000 voluntary reports, mostly from health professionals, in the first five years of its current form.(1993-1998).

This statistic suggests an underutilized reporting system, given the billions of doses and products used each year, and that concern is supported by recent reports and studies. For example, a recent report from the Office of the Inspector General of the U.S. Department of Health and Human Services concluded that current surveillance systems for identifying adverse reactions from dietary supplements probably detected less than one percent of adverse reactions.[27] A recent article in *The British Journal of Clinical Pharmacology* reported that 515 face-to-face interviews with individuals taking herbal remedies revealed that a substantial proportion of individuals would not consult their general

practitioners or pharmacists following serious adverse drug reactions to conventional over-the-counter medicines or herbal remedies. The MedWatch program is an important part of postmarketing surveillance, which is essential for providing additional safety information "that cannot realistically be collected before approval of a drug."Clinical trials cannot assess the effects of every new drug in combination with every other approved drug. Moreover, clinical trials are conducted on relatively small numbers of patients; adverse reactions are often more obvious when the product is used by thousands or millions of patients.[28] There are more rigorous models in other countries. For example, the European Network System for reporting adverse events, Eudranet, provides for the regulatory transfer of information between any company and any authority in Europe during the whole life cycle of a medical product. It is unfortunate that the FDA's MedWatch program discourages the reporting of unusual and unanticipated adverse events unless the adverse event qualifies as "serious". The FDA defines serious adverse event in terms of outcomes such as death, life- threatening event, hospitalization, disability, congenital anomaly or requiring intervention to prevent permanent impairment/damage. Much important information is lost as a result. In contrast, the Canadian Adverse Drug Reaction Monitoring Program Guidelines define an adverse drug reaction as a "noxious and unintended response to a drug which occurs with use or testing for the diagnosis, treatment or prevention of a disease or the modification of an organ function. This includes any undesirable patient effect suspected to be associated with drug use. A temporal or possible association is sufficient for a report to be made Adverse Drug Reactions that should be reported include all suspected adverse drug reactions which are: unexpected, regardless of their severity, i.e. not consistent with product information or labeling; or serious, whether expected or not; or reactions to recently marketed drugs (on the market for less than five years) regardless of their nature or severity. A successful surveillance

system must accommodate the urgent need for the detection of all unusual and unexpected phenomena resulting from the use of medical products, as well as any adverse reactions that may outweigh the benefits of the product. The FDA should do more to encourage reporting (including simplifying the MedWatch form), educate the public on quality reporting, and communicate suspected risks. Reporting should be taken seriously and the safety concerns of the public weighed favorably against the FDA's time management concerns. Rather than weaken or dismantling the Med Watch system, the FDA should borrow ideas from more rigorous systems in other countries. The FDA should provide ongoing education and incentives for quality reporting by both health professionals and consumers. Adverse event reporting forms should be easier to obtain, complete, and use. These changes would enable the FDA to better fulfill its mission to protect the public health.[29]

Goals of the FDA's Med Watch Program

(1) To increase awareness of drug- and device induced disease.

(2) To clarify what should (and should not) be reported to the agency.

(3) To make it easier to report by operating a single system for health care professionals to report adverse events and product problems to the agency.

(4) To provide regular feedback to the health care community concerning safety issues involving medical products.[30]

TYPE OF STUDIES

There are fundamental two types of studies- Experimental and Nonexperimental (Table 1 and Table 2)

Table 1. Experimental Studies

Study type	Description	Number Relative of cost patients	Example
Randomized clinical trials	Study patients with specific disease	50-5000 $$-$$$$	Efficacy of alteplase and reteplase in preventing death after myocardial infraction[31,32]
Field trials	Study subject to prevent disease	>5000 $$$$	Vaccination to prevent polio[33,34]
Community intervention trials	Study communities to prevent disease	>5000 $$$	Fluoridation of eater to prevent dental cavities[35,36,37]

Table 2. Nonexperimental Studies

Study type	Description	No. of patients	Relative cost	Example
Prospective cohort	Observed groups of patient treated with the same drug	>5000	$$$$	Nurses health study cohort[38,39,40]
Retrospective cohort	Extract data from an existing repository to look at outcomes of exposed groups	>5000	$	Risk of renal insufficiency from NSAIDS[41,42]
Case Control	Determine the association between a drug and rare event	20-1000	$$-$$$	Risk of Alzheimer's disease and vitamin use[43]
Cross sectional	Determine the prevalence of drug use in a patient population at a given time	50- million	$	Profile of calcium channel antagonists in a managed care organization[44]
Ecological	Determine the association between drug use of a population or group and an event	5-100	$	Deaths from asthma and the quantities of metered dose inhalers dispensed[45]
Case series	Reveal the common experiences of a number of patients following drug exposure	3-30	$	Valvular heart disease associated with fenfuramine-phentermine[46,47]
Case report	Revel the experience of a single patient following drug exposure	1	$	Toxic epidermal necrolysis from phenytoin[48]

Examples:

1. Objectives: To evaluate the use of two Canadian provincial databases by a systematic review of published studies that used them as a primary data source to answer epidemiologic and health services research questions.

Study Design and Setting: PubMed, EMBASE, BIOSIS, and CINAHL (keywords: ‘‘Manitoba’’ 1970e2004 and ‘‘Saskatchewan’’ 1969e2004) and the web sites of the provincial data custodians were searched to address objective. Broad screening of citations and data abstraction were performed using a predefined collection form. Information on study characteristics, therapeutic areas studied, databases used, authors’ affiliation, and issues related to data validity was recorded.

Results: Three thousand nine hundred and forty-nine citations were screened, 610 studies retrieved, and 325 included. In Saskatchewan, the principal research type was assessment of exposures and health outcomes (48.2%) with 50.4% using a cohort or case control design, whereas, in Manitoba, it was health services utilization (47.8%) and 86.6% were descriptive. Local investigators performed 83.3% of the Manitoba studies, compared with 35.5% of the Saskatchewan studies. Only 6.2% of the studies assessed the validity and reliability of the database for research purposes and few incorporated relevant information about the validity of their diagnostic data.

Conclusion: Important differences exist in the administration and use of these databases. Similar systematic evidence synthesis should be conducted on other databases.[49]

2. Objective: The case-crossover design was originally intended to study brief exposures with immediate and transient effects, and acute outcomes with abrupt onsets. We investigated whether case-crossover methods can be used to study prolonged exposures and insidious outcomes.

Methods: We conducted a case-crossover study of 8220 patients aged _ 65 years enrolled in several health benefits programs in New Jersey during the period between 1991 and 1995. All had episodes of

central nervous system (CNS) adverse events (e.g., delirium). Drug exposures were assessed during case time periods and control time periods lasting 1, 2, 3, or 4 months. Exposures included 3 active regimens with established deleterious CNS effects (corticosteroids, digoxin, and opiates) and 2 inactive regimens without such effects (multivitamins and statins).

Results: In conditional logistic regression models, significantly elevated risks were observed for all three active drugs, regardless of which time windows were used. The magnitude of these risks generally increased with longer time windows. No significantly increased risks were observed for the 2 inactive drugs, regardless of the window duration.

Conclusions: These results suggest that with lengthened exposure assessment windows, case-crossover methods may be useful for studying exposures with prolonged effects and outcomes with insidious onsets.[50]

3. Epidemiologists benefit greatly from having case-control study designs in their research armamentarium. Case-control studies can yield important scientific findings with relatively little time, money, and effort compared with other study designs. This seemingly quick road to research results entices many newly trained epidemiologists. Indeed, investigators implement case-control studies more frequently than any other analytical epidemiological study. Unfortunately, case-control designs also tend to be more susceptible to biases than other comparative studies. Although easier to do, they are also easier to do wrong. Five main notions guide investigators who do, or readers who assess, case-control studies. First, investigators must explicitly define the criteria for diagnosis of a case and any eligibility criteria used for selection. Second, controls should come from the same population as the cases, and their selection should be independent of the exposures of interest. Third, investigators should blind the data gatherers to the case or control status of participants or, if

impossible, at least blind them to the main hypothesis of the study. Fourth, data gatherers need to be thoroughly trained to elicit exposure in a similar manner from cases and controls; they should use memory aids to facilitate and balance recall between cases and controls. Finally, investigators should address confounding in case-control studies, either in the design stage or with analytical techniques. Devotion of meticulous attention to these points enhances the validity of the results and bolsters the reader's confidence in the findings.[51]

SELECTION OF CONTROLS IN DATABASE CASE-CONTROL STUDIES

In case-control studies conducted using computerized databases, controls are often selected as a random sample from the base population. This representative choice of controls is intended to guard against selection bias. We show, using data from a database case-control study, that such a definition of controls may also lead to selection bias under two conditions: (1) if the target disease has a prolonged asymptomatic clinical course with its detection depending on a specific physical examination and (2) if exposed patients have a higher likelihood of having the disease detected than unexposed patients. The extent of the bias that could result from the use of randomly selected controls was investigated in the context of a case-control study of the risk of ocular hypertension or glaucoma associated with the use of glucocorticoids, conducted using the Quebec universal health insurance computerized databases. This article also illustrates that a computerized database can be useful to empirically explore opportunities for bias.[52]

This study demonstrates that a randomly selected control population may not always present a valid strategy in case-control studies conducted from databases. Choosing a ran-dom sample of individuals from the same source as the cases has been described as the simplest way to satisfy the study base principle.[53] In database case-control research, the entire database usually serves as a source from

which con-trols are randomly selected, since cases are equally identified from the entire database. While this approach of control selection appears to be valid in most instances, caution is needed when investigating the risk of diseases with a pro-longed asymptomatic clinical course. Although cases are still identified among all subjects in the database, they no longer represent as base experience all subjects, but only subjects who had an opportunity of having the disease diag-nosed. Accordingly, controls will have to be drawn from this source population and can no longer be selected ran-domly among all subjects in the database. Serious selection bias may result if exposed patients are preferentially diag-nosed and controls are not selected from the appropriate study base. In our study example, we identified as the source population for cases and controls subjects with visits to oph-thalmologists, since ophthalmologist visits are usually a pre-requisite for the diagnosis of ocular hypertension and glau-coma. For glucocorticoids exposures that were not associated with increased ophthalmologic monitoring, the risk esti-mates were similar in both study samples, characterizing preferential surveillance of exposed subjects as a second necessary condition for the occurrence of selection bias in the study setting. Our example illustrates that a database may also serve to empirically explore concerns about biases.

MEASUREMENT OF PHARMACOEPIDEMIOLOGY

There are several fundamental matrices helpful to understand pharmacoepidemiology-

1. For descriptive studies includes frequencies, distributions, prevalence and incidence rates.

2. For analytic studies includes rate difference, rate ratio, relative risk and odd ratio.

Types of measurements

1. Prevalence: The term prevalence is used to indicate the frequency of cases at a given time or period. LAST has given a broader definition of prevalence as "the total number of all individuals who have an attribute or disease at a particular time (or during a particular time period) divided by the population at risk of having the attribute or disease at this point in time or midway through the period". It is generally expressed as a percentage of the population and can range from 0% to 100%.[54] Prevalence is of two types:

i) Point Prevalence: The point prevalence of a disease is a census type of measure. It is frequency of cases at an instant. It can be defined as "the number of all current cases (both old and new) of a specific disease at one point in time in relation to a defined population". The 'point in time' in point prevalence can be either a day or few days or even few weeks, depending upon the time taken to examine the sample of the population. Point prevalence can be represented by the formula;

$$\text{Point prevalence} = \frac{\text{total number of all current cases (old and new) of a specific disease at a given point in time}}{\text{Estimated total population at the same point in time}} \times 100$$

$$\text{Period prevalence} = \frac{\text{Total number of existing cases of a specific disease during a given period of time interval}}{\text{Estimated mid-interval population at risk}} \times 100$$

ii) Period Prevalence: Period prevalence is a measure that expresses the frequency of cases within a period such as one year. It is the sum of the point prevalence (the number of cases existent at the beginning of the period) and the incidence (the number of cases coming into existence during the period). It can be represented by the formula:

$$\text{Incidence} = \frac{\text{Number of new cases of a specific disease during a given time period}}{\text{The population at risk}} \times 100$$

Uses:

a) Prevalence are useful in estimating the magnitude of disease or health problems in community.[55]

b) In identifying the potential high-risk populations.

c) Useful in administrative and planning purposes like, assessing manpower needs in health services, delivery of health services etc.[56]

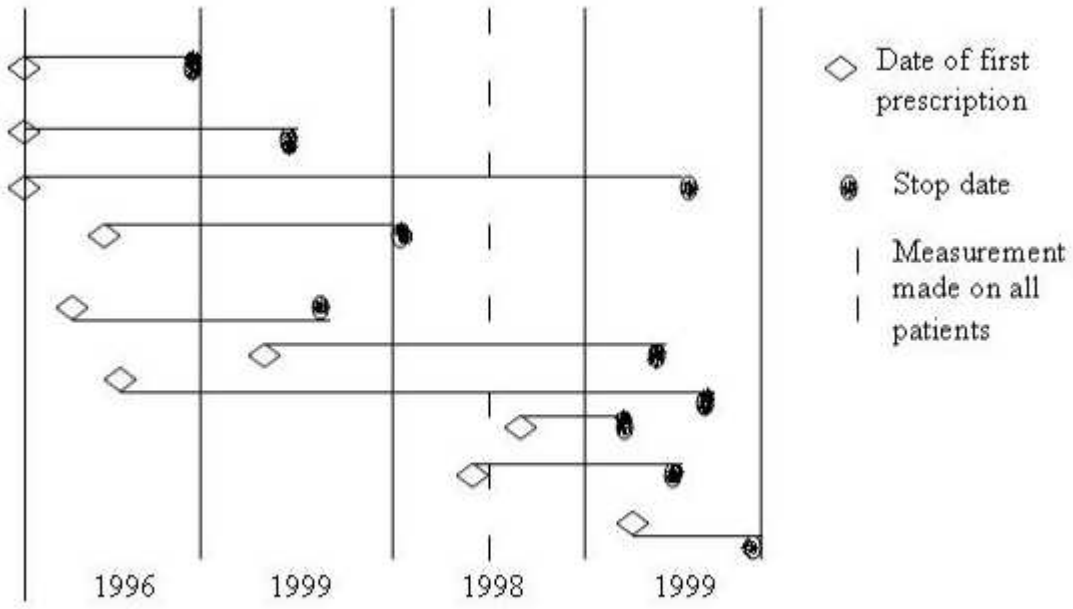
2. Incidence: Incidence can be defined as frequency of new cases in a population over a period. In other words, the incidence of a disease is the number of cases of the disease, which come into being during a specified period of time.[57] It can range from zero to infinity. Incidence can be represented by the formula;

Relationship between Prevalence and Incidence: In epidemiology, the prevalence and incidence of events are the most commonly used and also the most commonly confused. The primary issue that distinguishes prevalence from incidence is the types of patents counted per unit time.[58] The prevalence of an event is equal to the number of patients with the outcome of interest at a single point in time, referred to as a point prevalence. If the measurement is made on all patients during a specific time

interval called period prevalence, Incidence is measured as counts of patients with the outcome per unit time (Figure I).

Figure I.

Distribution of experiences of 12 patients prescribed a medication over 4 year's period to illustrate difference between prevalence and incidence



Prevalence is dependent on two factors, the incidence and duration of the disease. Assuming that the population is stable, the incidence value and the duration is unchanging, a relationship can be brought out as;

Prevalence = Incidence X Mean duration

3. Relative risk or odd ratio: It is incidence in the exposed group divided by the incidence in the unexposed group.

4. Odd ratio: It is probability of an outcome happening divided by the probability of the event not happening.[59]

5. Attributable risk or risk difference: It is incidence in the exposed group minus incidence in the unexposed group.

Relative risks (RR) and odds ratios (OR) estimate the strength of association between diseases and risk factors; whereas attributable risk (AR) estimates the amount of disease attributable to a certain factor.[60] A risk factor may be strongly related to a disease, but may contribute less to the problem of that disease in the population if its prevalence is low (low AR). Conversely, a risk factor with a weak association may contribute more if its prevalence is high (high AR).3 Control of the latter factor would reduce burden of disease in the population more effectively than control of the former. AR can link causality with public health action. AR can be best derived from cohort studies; its estimation from case-control studies is also possible if controls represent the general population.[61] Despite repeated advocacy of its importance for public health, AR has received less attention than RR. We counted the number of papers reporting RR with AR which appeared on MEDLINE from January, 1966, to January, 1998. The "Textword" procedure was used in searching for: "relative risk" or "odds ratio" for retrieving articles with RR or OR, and "attributable risk", "attributable fraction", or "aetiological fraction" for articles with AR. There was one report with AR for 31 with RR irrespective of publication type (619 versus 18 955, **table 3**). Although the proportion of reports with either RR or AR increased throughout the period (partially because of increase in articles with abstracts included in the database), the AR:RR ratio decreased. Although cohort studies are the most suitable to estimate AR, AR:RR ratio reported from them remained lower (0·017) than case control studies (0·021), and clinical trials (0·019). One of the reasons for under-reporting of AR relative to RR may be the drive to search for new risk factors for a disease rather than examining the extent or attribution of known risk factors.

Another may be that it is cumbersome to calculate AR because many statistical packages cannot yield adjusted ARs and their confidence intervals. Our analysis may have overlooked articles reporting RR or AR in the text but mentioning them neither in the title nor in the abstract. Public health recommendations relying on epidemiological findings with the stress on RR are not sufficient; for policy makers, more attention to AR is essential.[62]

AR indicates attributable risk; RR, relative risk. Subject of study is classified according to the MeSH category. Total includes all reports irrespective of area of study by "docz.dz" command. The number of articles included in "1993-January 1998" is less than in "1987-1992" because registration for indicated period is now processing. The five periods are categorized on the basis of duration covered by the latest CD-ROM supplied by the Ovid Co.[63]

Table 3. Relationship between Attributable risk and Relative risk on the basis of study type and number of articles

Subject of study	Number of articles					
	1966-75	1976-80	1981-86	1987-92	1993-98	1966-
Cancers						
No	18259	12915	19558	22410	20026	93168
AR	0	1	3	7	9	20
RR	2	22	78	208	284	594
AR:RR	0	0-045	0-038	0-034	0-032	0-034
Coronary heart disease and myocardial infarction						
No	29767	20146	29574	34431	24124	138 042
AR	0	2	4	19	17	42
RR	3	32	129	448	892	1504
AR:RR	0	0-063	0-031	0-042	0-019	0-028
Cerebrovascular disorders						
No	8080	3987	5215	6764	7097	31143
AR	0	1	1	5	10	17
RR	2	2	18	115	299	436
AR:RR	0	0-500	0-056	0-043	0-033	0-039
Geriatrics and aged						
No	173 426	113 155	194 485	239 938	229 830	950 834
AR	1	8	25	59	106	199
RR	10	99	538	1840	4421	6908
AR:RR	0-100	0-081	0-046	0-032	0-024	0-029
Diabetes mellitus						
No	15726	8327	9463	7331	5883	46730
AR	0	1	1	4	13	19
RR	2	15	45	80	198	340
AR:RR	0	0-067	0-022	0-050	0-066	0-056
Total						
No	2 231 188	1 297 647	1 753 717	2 190 264	1 843 262	9316078
AR	4	21	75	220	299	619
RR	40	353	1642	5744	11176	18955
AR:RR	0-100	0-059	0-046	0-038	0-027	0-033

CASE STUDIES

Oral anticoagulants like the coumarin derivatives are characterised by a particularly narrow therapeutic range. Concurrently taken drugs such as alcohol, barbiturates, and anti-inflammatory agents potentially interact with coumarin derivatives and can seriously affect anticoagulant activity. Any interfering comedication can pose a challenge to establishing a stable anticoagulant dosage regimen and thus present a serious risk for the patient.[64,65] Here we describe two cases of possible drug interactions between phenprocoumon and the proton pump inhibitor omeprazole, requiring adjustment of the anticoagulant dose.

Case 1

A 68-year-old woman (height: 160 cm; body weight: 60 kg) with a history of recurring tachyarrhythmia, hypertension and severe hyperlipaemia was treated with phenprocoumon (Marcumar, Roche) since December 1998. After an initial phasing-in period of about 5 month, the required dosage for maintaining the patient's International Normalised Ratio (INR) between 2.1 and 2.7 had stabilised at 5½ to 6½ tablets of phenprocoumon (3 mg/tablet) per week. At this stage, the INR was determined every 3 to 4 weeks to monitor anticoagulation therapy. Concurrently the patient was treated with β-acetyldigoxin (Novodigal 0.2: 1 × 1/day), sotalol hydrochloride (Sotalex 80: 2 × 1/day), piretanide (Arelix mite: 1 × 1/day), hydrochlorothiazide (Esidrix: 1 × 1/day), irbesartan (Aprovel 150: 1 × 1/day), potassium chloride (Rekawan: 1 × 1/day), and simethicone (Enzym-Lefax: 3 × 1/day). On October 15th 1999, a gastroscopy was performed to investigate the patient's persistent upper abdominal complaints. This revealed the presence of a large hiatus hernia as well as histological evidence of reflux esophagitis. After commencing (October 15th) treatment with omeprazole (Antra MUPS 1 × 20 mg/day), the patient's INR increased from initially 2.15 (determined on October 6th) to 3.34 (November 3rd), although the phenprocoumon dosing regimen and all other medication had been

continued without changes. For the following weeks, the phenprocoumon dose was therefore reduced to 5½ tablets per week, compared to 6 tablets per week just prior to omeprazole treatment. At the next check-up (November 17th), the INR had returned to 2.28, a value well within the targeted range.

Case 2

The second case concerns a 72-year-old diabetic woman with advanced arthropathy which had immobilised her for a considerable period of time. Her condition led to a bilateral pulmonary embolism which was scintigraphically confirmed on April 9th 1999. A thrombosis in her left leg was phlebographically confirmed six days later and on April 16th the patient was put on a loading schedule of phenprocoumon commencing with 4 tablets on day 1, 3 on day 2, 1 on day 3, and further as required. At the same time, the patient was given omeprazole (1 × 20 mg before bedtime) to treat a minimal antrum gastritis. Other co-medications were enalapril (Xanef: 1 × 1/day), glyburide (Euglucon: 1 × 1/day), and dipyrone (Novalgin: 3 × 20 drops/day).

Before anticoagulation was initiated, the patient's INR value was 1.02. On the third and fourth day of anticoagulation therapy it had increased to 2.02 and 3.28, respectively. Because the patient responded so strongly, she received no further phenprocoumon during the following days. However, surprisingly the INR value remained at the high level throughout the following 9 days. It was suspected that this unusually long persistence of anticoagulant activity was caused by interference of omeprazole[66,67] with the metabolism (and thus elimination) of phenprocoumon. Consequently, omeprazole was discontinued on April 29th. Four days later the INR value had decreased to 1.5 and anticoagulation therapy with phenprocoumon was successfully resumed using initially 5½ tablets per week. By mid July, the required dose for maintaining the INR within the therapeutic range had stabilised at 3 to 3½ tablets/week.

In December 1999, the patient had to undergo minor surgery and, thus, phenprocoumon was withheld for three weeks. Within 7 days the INR value had dropped to below 1.5, and no problems were encountered when anticoagulation therapy was resumed with a loading schedule similar to the one used in April. This observation lent further support to the notion that indeed omeprazole may have been responsible for the problems with the anticoagulation regimen encountered in April.

Discussion: In both patients the INR increased beyond the therapeutic range in correlation with omeprazole treatment. In case 1, the INR returned to therapeutic levels after reducing the dosage of phenprocoumon. In case 2, even after phenprocoumon was discontinued the INR remained above therapeutic levels and decreased only after omeprazole was also discontinued; when phenprocoumon was subsequently resumed there were no difficulties in adjusting this patient's INR to the desired level. Nor were any such difficulties encountered at a later stage when phenprocoumon was first withheld from the same patient in preparation for surgery and then subsequently reintroduced with the usual loading schedule. In neither case were any of the other co-medications adjusted. Throughout the observation period both patients continued with the routine of their other co-medications. Collectively, above observations suggest that our difficulties in adjusting the anticoagulation level may be due to some interference from omeprazole. Unfortunately, neither phenprocoumon nor omeprazole levels were measured in the two patients and on the basis of the available evidence any suggestions about the possible mechanism(s) of interference remain speculative.[68,69,70,71,72]

Case 3.

Potentially lethal arrhythmia, occurring in association with terfenadine (Seldane) use in a young woman.[1] This ECG is a classic example of torsades de pointes, which is French for "twisting of the

points." Torsades is a form of ventricular tachycardia that can most often be due to medications. The QRS complexes during this rhythm tend to show a series of "points up" followed by "points down" often with a narrow waist between. Recognition and reporting of this arrhythmia in association with terfenadine, astemizole (Hismanal), cisapride (Propulsid), grepafloxacin (Raxar), and mibefradil (Posicor) ultimately led to the removal of these medications from the market.[73, 74, 75,76]

Case 4.

Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study: The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. 1985 report in the Journal, based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results. METHODS: Followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study, and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes. RESULTS: After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking,

diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke. CONCLUSIONS. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.[77]

Case 5:

Relenza (zanamivir) Inhalation Powder

GlaxoSmithKline (GSK) and FDA notified healthcare professionals of a report of the death of a patient with influenza who received Relenza (zanamivir) Inhalation Powder which was solubilized and administered by mechanical ventilation. Relenza (zanamivir) Inhalation Powder is not intended to be reconstituted in any liquid formulation and is not recommended for use in any nebulizer or mechanical ventilator. GSK is aware that Relenza Inhalation Powder is being removed from its FDA-approved packaging and dissolved in various solutions for the purpose of nebulizing zanamivir for inhalation by patients with influenza who are unable to take oral medications or unable to inhale Relenza Inhalation Powder using the Diskhaler. Relenza or zanamivir for nebulization have not been approved by the FDA. The safety, effectiveness, and stability of zanamivir use by nebulization have not been established.

Relenza Inhalation Powder should only be used as directed in the prescribing information by using the Diskhaler device provided with the drug product. Relenza Inhalation Powder is a mixture of zanamivir active drug substance and lactose drug carrier. This formulation is not designed or intended to be

administered by nebulization. There is a risk that the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment.[78]

Case 6:

Pharmacoepidemiology of Antidepressant Use: Between 1988 and 1994, data from 3 large sites revealeda 3–5 fold increase in the prevalence of antidepressant (ATD) treatment for U.S. youths aged 2–19 years. In 1994, the ATD prevalence for youths of this age ranged from 13 per 1000 (in the HMO) to 18 per 1000 (in 2 state Medicaid systems). Males predominated in the 10–14-year-olds treated with ATDs, whereas females predominated among 15–19-year-olds. Caucasians were more than twice as likely to receive ATD therapy than their African-American counterparts. Primary care providers were the major source of ATD prescriptions for youths. The leading diagnoses in primary care were ADHD followed by depression, whereas the diagnostic order was reversed for youths who received psychiatric services. This review provides details concerning these patterns and trends in ATD treatment of youths from community-based clinical data sources. In addition, the role of these data in an expanded, comprehensive psychotropic knowledge base is discussed. Finally, the implications of an expanded knowledge base for ATD treatments are discussed in regard to generating research questions on effectiveness and safety and to improve treatment consensus within a public-health perspective.[79]

Case 7:

Are COX-2 inhibitors used appropriately in everyday practice?

That COX-2 inhibitors can provide safety benefits as compared to conventional NSAIDs is a reasonable assumption. However, a legitimate concern is whether these benefits might be canceled out if COX-2 inhibitors are used inappropriately, by the physician or the patient. The real-life data supplied by pharmacoepidemiological studies can help to clarify this issue. Whereas safety data can be readily generalized, data on physician practices and patient behaviors vary widely from one country to

another. The present issue of *Joint, Bone, Spine* reports valuable data collected in France by the Thales Observatory.[80] This database is less exhaustive than the public health insurance databases available in Canada and the United Kingdom, as it is maintained by a sample of general practitioners involved in the study on a volunteer basis and therefore committed to the goals of the observatory. Thus, these physicians may not be representative of the entire population of general practitioners in France. However, the Thales Observatory data provide material of interest. As in other countries, the NSAID market expanded in France with the introduction of COX-2 inhibitors. COX-2 inhibitors are being prescribed both as substitutes for previously used conventional NSAIDs and de novo in patients previously been kept off NSAID therapy because of a high risk for gastrointestinal toxicity. Thus, drug channeling is occurring. Another change consists in greater use of proton pump inhibitors and other gastro-protective agents in combination with conventional NSAIDs, reflecting heightened awareness among physicians of the gastro toxicity of NSAIDs, a byproduct of campaigns aimed at promoting COX-2 inhibitors. Whether this change in practices indicates improved protection of patients against gastrointestinal side effects or an effort on the part of physicians to protect them against malpractice litigation is unclear. Occasionally, COX-2 inhibitors are prescribed in combination with gastro-protective agents, such as proton pump inhibitors, a practice that may be questionable. However, the lack of information on the reasons for prescribing gastro-protective therapy hinders the interpretation of this finding. Further studies are needed in this area. In the next few years, pharmacoepidemiological studies will have an increasing impact on the everyday work of physicians, who will be able to compare their practices to those reported in the studies. In addition, some physicians will participate directly in these studies by collecting data. This new information on practice patterns among physicians will help us to evaluate and adjust our own behaviors, keeping the best and correcting the

rest. Ultimately, pharmacoepidemiological studies will produce valid data for maintaining or eliminating existing treatments or for introducing new treatments.

Conditions that place patients at high risk for drug interactions

1. High risk associated with the severity of disease state being treated

Aplastic anemia

Asthma

Cardiac arrhythmia

Critical care/intensive care patients

Diabetes

Epilepsy

Hepatic disease

Hypothyroid

2. High risk associated with drug interaction potential of related therapy

Autoimmune disorders

Cardiovascular disease

Gastrointestinal disease

Infection

Psychiatric disorders

Respiratory disorders

Seizure disorders[81]

CONCLUSION

Most new drugs are approved with an average of 1,500 patient exposures and usually for only relatively short periods of time. However, some drugs cause serious ADRs at very low frequencies and would require many more exposures to detect the reaction. For example, bromfenac (Duract) was a non-steroidal anti-inflammatory agent (NSAID) that was removed from the market in 1998, less than 1 year after it was introduced. Bromfenac caused serious hepatotoxicity in only 1 in 20,000 patients taking the drug for longer than 10 days.[1] To reliably detect the toxic effects of a drug with a 1 in 20,000 adverse drug reaction frequency, the new drug application database would have to include 100,000 patient exposures. A drug that is tested in a few thousand people 11 may have an excellent safety profile in those few thousand patients. However, within a short time after entering the market, the drug may be administered to several million patients. That means that for drugs that cause rare toxicity, their toxicity can only be detected after, not before, marketing.

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