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The Continuum of Postmarketing Drug Surveillance: From Early Signals to Action

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Clinical pharmacology and the practice of medicine are based on an understanding of the benefits and risks of pharmaceuticals in humans. Much of our what we know about the efficacy and the short-term safety of drugs arises from well-controlled studies conducted during the extensive drug development and approval process. Randomized controlled trials (RCT) provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs. However, the rigorous circumstances surrounding design and implementation of the RCT do not necessarily extrapolate to the "real world". Many additional risks and, to a lesser degree, additional benefits are only identified after the drug is widely used by the general population. In fact, there is a continuum of drug safety knowledge that begins with pre-marketing evaluations and extends into a drug's post-approval period.

Information learned following a drug's approval may range from relatively minor to clinically important effects that seriously alter an individual drug's benefit-to-risk ratio. For example, the relationship between certain widely-used appetite-suppressant drugs and primary pulmonary hypertension and valvular heart disease is an example where serious adverse effects were discovered only after these drugs were marketed and had come into widespread use.[1,2] This example highlights both the limitations of the drug development process and the need to study populations receiving medications obtained through usual clinical practice. The purpose of this presentation is to introduce you to the field of postmarketing drug surveillance and pharmacoepidemiology and to illustrate the continuum of its role drug development and good patient care: from early signals to action. This manuscript is adapted from a book chapter in preparation.[3]

Pharmacoepidemiology is the study of the use of and the effects of drugs in large numbers of people. The field as applied to the period after a drug enters the market is referred to as postmarketing drug surveillance (PMS). Pharmacoepidemiology bridges pharmacology with epidemiology to provide valuable clinical drug safety information for testing hypotheses (known as analytic studies) as well as determine the distribution or rates of drug utilization and/or diseases (known as descriptive studies).

Pharmacovigilance refers to the continual monitoring for unwanted effects or *signals* and other safety-related aspects of marketed drugs, primarily through the use of spontaneous reporting systems. As will be described later, health care professionals play an essential role in pharmacovigilance by reporting suspected adverse drug reactions to central agencies and/or manufacturers. Pharmacovigilance also depends upon systematic reviews of the literature to identify possible adverse effects of marketed drugs.

Central agencies, such as the U.S. Food and Drug Administration (FDA) and its Korean equivalent review and validate information resulting from pharmacovigilance activities.

Drug Approval and Drug Safety Knowledge The new drug approval process in the United States consists of three phases of clinical testing plus phase 4 studies and other post-approval surveillance activities.

Despite the rigorous process for drug approval and regulation, there have been many major adverse drug reactions over the past 30 years. Examples of serious but uncommon effects include acute flank syndrome associated with suprofen,[4] the gastrointestinal effects associated with nonsteroidal anti-inflammatory drugs in the elderly,[5] troglitazone and the risk of hepatotoxicity,[6] and the adverse effects of the contraindicated use of cisapride.[7] Partially in response to concerns about adverse drug effects, a number of epidemiology programs were developed, beginning in the 1970s. In the United Kingdom, the Drug Surveillance Research Unit established the Prescription Event Monitoring program in 1980, now called the Drug Safety Research Trust. Resources for pharmacoepidemiology also evolved from the use of Medicaid data and databases from health maintenance organizations (HMOs).[8] Advantages to conducting PMS in an HMO setting include the availability of an identifiable population base for the estimation of rates, presence of a relatively stable population base, and access to medical records and computerized databases.

Drug development should be viewed as a process that continues even after a drug is approved for marketing. As noted in the previous section, it is not possible to detect all potential risks and benefits during premarketing studies. The FDA' s postmarketing surveillance program provides important information on the clinical experience of medical products. Its involvement in postmarketing drug surveillanceincludes monitoring approved drug use, monitoring the serious adverse drug events associated with the use of approved drugs, and the initiation of selected epidemiologic studies to estimate the risk or test specific hypotheses. One of the primary uses of findings from PMS of drugs is modification of a drug' s labeling or package insert. Other methods used to communicate the results of PMS efforts involve requiring the manufacturer to mail out a "Dear Doctor" letter, publishing in the *FDA Medical Bulletin*, presentation of findings at professional meetings, and publication of findings in peer-reviewed journals.

Methodologies for Pharmacoepidemiologic StudiesEpidemiologic study designs are essential for evaluating drug safety and effectiveness in situations where it is either unfeasible or unethical to randomly assign patients to active treatment or placebo. While the randomized, controlled, blinded trial (RCT) is the standard against which other designs are measured, it is often not suitable for questions within the domain of pharmacoepidemiology. Randomized trials, for example, cannot contribute much to our understanding of the long-term or rare adverse effects associated with therapies. Clinical trials conducted prior to drug approval cannot uncover every important health effect of a pharmaceutical.

Epidemiologic studies of the patterns of drug prescribing and use are also essential to assess a drug' s usefulness. As a discipline, pharmacoepidemiology has traditionally concerned itself with the study of adverse drug effects. Epidemiologic study designs, such as case control and cohort studies, are also used to identify beneficial effects of drugs in populations. For example, to determine the relationship between patterns of use of inhaled corticosteroids and the risk of fatal or near fatal asthma, Suissa and colleagues conductd an epidemiologic study of 30,569 residents of Saskatchewan who were dispensed 3 or more

asthma drugs in any one year from September 1975 through December 1991.[4] They found the death rate to be 21% lower among inhaled corticosteroid users for each additional canister used in the previous year and an increased death rate in patients who had discontinued inhaled corticosteroid use. These findings support practice guidelines that recommend the use of inhaled anti-inflammatories in moderate to severe asthmatics.

Epidemiologic studies typically do not use randomization to determine who will receive a particular drug exposure. Rather, associations between exposure(s) and disease(s) under study are determined through the use of observational study designs and statistical analyses. Observational methods are used in most situations as ethics and cost limit the use of experimentation. A variety of methods are used to study health events associated with drug exposures. The usual approach to studying adverse drug reactions begins with the collection of spontaneous reports of drug-related morbidity or mortality.

Signal Generation Through Case Reports. Case reports describe a single patient who was exposed to a drug and experienced a particular, usually adverse, outcome. For example, within the first 3 months of marketing, hemolytic anemia and acute renal failure following use of the antibiotic temafloxacin were reported to the Spontaneous Report System, the predecessor of the MEDWATCH System. Case reports are useful for raising hypotheses about drug effects to be tested with more rigorous study designs. It is uncommon for a case report or a series of case reports to be used to make a statement about causation.

As a condition of approval for marketing, drug manufacturers are required to notify the FDA of all adverse events of which they are aware. It is important for clinicians to report ADEs. In the U.S., the MEDWATCH program depends on health care professionals and the lay public to report serious adverse events observed in the course of their practice as part of their professional responsibility. In 1999 alone, 258,125 reports of adverse drug reactions were filed with the FDA by health professionals, drug manufacturers, and consumers - an 89% increase from 1993.

Case Series. Case series are collections of patients, all of who have a single exposure, whose clinical outcomes are then evaluated and described. They are useful for quantifying the incidence of an adverse reaction, particularly for a newly approved drug. Further, case series can be useful for being certain that the incidence rate of any particular adverse effect of concern does not occur in a population, which is larger than that studied prior to drug' s marketing. If the event is rare and the exposure combination is very specific, the cause of the adverse health event may be inferred from a case series study. In most situations, however, it is necessary to compare cases with a group of controls to identify risk factors. Thus, the major disadvantage of a case series study is the lack of a comparison group.

Case-Control Studies. A case-control study assembles a group of cases (people who have the disease of interest) and controls (people who do not). The exposure histories of the cases and the controls are determined to establish the extent of association between exposure(s) of interest and disease. Case control studies compare patients with a specific disease to a control group composed of similar people but without the disease. Case-control studies attempt to identify risk factors for a disease by examining differences in antecedent exposure variables between cases and controls. For example, one can select cases of women of child-bearing age with ovarian cysts and compare them to controls, looking for differences in prior use of oral contraceptives. Such a study was performed to determine if the then newly introduced triphasic oral

contraceptives were associated with functional ovarian cysts.[9]

Case-control studies have been extensively used to assess the safety of pharmaceuticals. There are many examples of case control studies that have identified important associations between drugs and adverse health events: vaginal cancer and diethylstilbestrol (DES), Reye's syndrome and aspirin, peptic ulcer disease and nonsteroidal anti-inflammatory drugs, and venous thromboembolism and oral contraceptives. Data from case control studies are used to calculate an odds ratio, which is the ratio of the odds of developing the disease for exposed patients to the odds of developing the disease for the unexposed patients.

An advantage of the case control design for the study of drug-outcome relationships is its efficiency for the study of rare or delayed outcomes. Compared with other strategies, the case control study is relatively inexpensive. One potential problem with case control studies is their susceptibility to certain types of bias, including selection bias and information bias. Selection bias refers to systematic differences between those selected for study and those that are not while information bias is systematic differences in the quality of information gathered for study and comparison groups.

Cohort Studies. A cohort study assembles a group of persons without the disease(s) of interest at the onset of the study, ascertains the exposure status of each person, and then follows the cohort over time to determine the development of disease in exposed and nonexposed persons. Cohort studies involve the comparison of the incidence of one or more outcome events among those who received a drug or some other exposure of interest compared with the incidence of the event(s) for a comparison group. For example, much information about the risk of fatal cardiovascular diseases among oral contraceptive users has come from the Royal College of General Practitioners Oral Contraception Study, in which 23,000 oral contraceptive users were compared with 23,000 nonusers chosen from the same British general practices.[10]

Cohort studies can be prospective, as the RCGP study illustrates, or retrospective. Prospective cohort studies are one of the most valid types of observational study designs, because exposure is measured and recorded prior to the development of the health outcome(s) of interest. Using a prospective cohort study design, Hooton and colleagues determined the association between contraceptive methods and symptomatic urinary tract infections in young women.[11] The investigators recruited sexually active young women who were starting a new method of contraception and followed them for 6 months to determine the incidence of symptomatic urinary tract infections by contraceptive method.

An alternative to the prospective cohort design is the retrospective cohort study.

Retrospective cohort studies are useful when comparison cohorts of persons exposed and not exposed to drugs of interest can be identified at some time in the past from large preexisting databases and followed from that time to the present with regard to the incidence of a given outcome. Soumerai and associates used a retrospective cohort design to study the determinants and adverse health outcomes of beta-blocker underuse in elderly patients with myocardial infarction.[12] Controlling for other predictors of survival, the mortality rate among beta-blocker recipients was 43% less than that for the comparison group, suggesting that use of beta blockers reduces the risk of death among elderly patients with myocardial infarction.

Prospective cohort studies can provide strong evidence of associations between drugs and diseases because the exposure is assessed before the outcome occurs.

However, because many cohort studies require large numbers of people followed for long periods of time, they can be expensive and, in some instances, infeasible.

Retrospective or historical cohort studies can overcome these limitations if high quality data have already been collected.

Illustration of the Continuum: From Early Signal to Action

Through its cooperative agreements program, the FDA has encouraged the utilization of large databases for use in pharmacoepidemiology. These agreements provide the FDA with access to data on the safety of pharmaceuticals. The objectives of these programs include the rapid and efficient conduct of pharmacoepidemiologic research designed to test hypotheses, particularly those arising from the MEDWATCH program. Of particular interest is the ability to determine incidence rates and test hypotheses based on signals of possible drug safety problems. Current programs receiving funding for postmarketing drug surveillance from the FDA include United HealthCare (UHC).

UHC' s databases have been used on several occasions to investigate suspected associations between specific drug exposures and specific adverse events and estimate both adverse event rates and estimation of risk in the ambulatory care setting.

13 Examples include the estimation of prevalence of Clostridium difficile diarrhea and the risk for CDD associated with different oral antibiotics,[14] estimation of incidence of adverse gastrointestinal events in alendronate users,[15] tramadol use and the risk of seizures,[16] the risk of hepatotoxicity associated with the use of troglitazone, and the contraindicated use of cisapride.[17] The last two evaluations are of medications which were subsequently removed from the U.S. market by the manufacturer. Of interest to clinicians is the manner in which one online pharmacy, drugstore.com, communicated these and other important safety warnings to its customers. drugstore.com' s eMedAlert program notifies its customers of important product information and FDA recalls in a proactive, rapid,secure, targeted manner. For example, within 48 hours drugstore.com notified more than 12,000 customers who purchased products containing phenylpropanolamine (PPA), alerting them to the FDA announement.[18]

Pharmacoepidemiologic studies conducted during the postapproval period provide important information to assist in optimizing therapeutic responses to drugs. These studies can provide valuable information about the relationship between therapeutic agents and adverse and beneficial health outcomes. One of the noteworthy developments in the field has been the use of automated, linked databases that permit efficient and rapid studies of drug effects. Information from pharmacoepidemiologic studies also contributes to improved patient care and drug regulatory decisions. A combination of medical and epidemiologic knowledge leads to the choice to use a particular medication. Moreover, patient monitoring to optimize the therapeutic response to drugs also involves epidemiologic data and logic to balance likely benefits against potential risks. Epidemiologic information can provide vital information regarding safety, patterns of drug use, and effectiveness to assist in the provision of evidence-based health care.

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