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When Should One Perform Pharmacoepidemiologic Studies?

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As discussed in the previous chapters, pharmacoepidemiologic studies apply the techniques of epidemiology to the content area of clinical pharmacology. This chapter will review when pharmacoepidemiologic studies should be performed. It will begin with a discussion of the various reasons why one might perform pharmacoepidemiologic studies. Central to many of these is one's willingness to tolerate risk. Whether one's perspective is that of a manufacturer, regulator, academician, or clinician, one needs to consider the risk of adverse reactions that one considers tolerable. Thus, the chapter will continue with a discussion of the difference between safety and risk. It will conclude with a discussion of the determinants of one's tolerance of risk.

Reasons to Perform Pharmacoepidemiologic Studies

The decision to conduct a pharmacoepidemiologic study can be viewed as similar to the regulatory decision about whether to approve a drug for marketing or the clinical decision about whether to prescribe a drug. In each case, decision-making involves weighing the costs and risks of a therapy against its benefits.

The main costs of a pharmacoepidemiologic study are obviously the costs (monetary, effort, time) of conducting the study itself. These costs clearly will vary, depending on the questions posed and the approach chosen to answer them. Generally, the cost per patient in a postmarketing study, with the exception of postmarketing randomized clinical trials, is likely to be at least an order of magnitude less than the cost of a premarketing study. Other costs to consider are the opportunity costs of other research that might be left undone if this research is performed.

One risk of conducting a pharmacoepidemiologic study is the possibility that it could identify an adverse outcome as associated with the drug under investigation when in fact the drug does not cause this adverse outcome. Another risk is that it could provide false reassurances about a drug's safety. Both these risks can be minimized by appropriate study designs, skilled researchers, and appropriate and responsible interpretation of the results obtained.

The benefits of pharmacoepidemiologic studies could be conceptualized in four different categories: regulatory, marketing, clinical, and

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legal (see Table 5.1). Each will be of importance to different organizations and individuals involved in deciding whether to initiate a study. Any given study will usually be performed for several of these reasons, which will be discussed in turn.

Regulatory

Perhaps the most obvious and compelling reason to perform a postmarketing pharmacoepidemiologic study is regulatory: a plan for a postmarketing pharmacoepidemiologic study is required before the drug will be approved for marketing. Requirements for postmarketing research have become progressively more frequent in recent years. For example, in the 1970s the US Food and Drug Administration (FDA) required postmarketing research at the time of approval for about one third of drugs, a requirement which increased to over 70% in the 1990s [1]. Many of these required studies have been randomized clinical trials, designed to clarify residual questions about a drug's efficacy. Others focus on questions of drug toxicity. Often it is unclear whether the pharmacoepidemiologic study was undertaken in response to a regulatory requirement or in response to merely a "suggestion" by the regulator, but the effect is essentially the same. Early examples of studies conducted to address regulatory questions include the "Phase IV" cohort studies performed of cimetidine [2] and prazosin [3], discussed in Chapters 1 and 3. Now that the FDA has the authority to require such studies, such requirements are becoming more common.

Sometimes a manufacturer may offer to perform a pharmacoepidemiologic study with the hope that the regulatory agency might thereby expedite drug approval. If the agency believed that any new serious problem would be detected rapidly and reliably after marketing, it could feel more comfortable about releasing the drug sooner. Although it is difficult to assess the impact of volunteered postmarketing studies on regulatory decisions, the very large economic impact of an earlier approval has motivated some manufacturers to initiate such studies. In addition, in recent years regulatory authorities have occasionally released a particularly important drug after essentially only Phase II testing,

Table 5.1 Reasons to perform pharmacoepidemiologic studies.

- A) Regulatory
  - 1) Required
  - 2) To obtain earlier approval for marketing
  - 3) As a response to question by regulatory agency
  - 4) To assist application for approval for marketing elsewhere
- B) Marketing
  - 1) To assist market penetration by documenting the safety of the drug
  - 2) To increase name recognition
  - 3) To assist in repositioning the drug
    - a) Different outcomes, e.g., quality of life and economic
    - b) Different types of patients, e.g., the elderly
    - c) New indications
    - d) Less restrictive labeling
  - 4) To protect the drug from accusations about adverse effects
- C) Legal
  - 1) In anticipation of future product liability litigation
- D) Clinical
  - 1) Hypothesis testing
    - a) Problem hypothesized on the basis of drug structure
    - b) Problem suspected on the basis of preclinical or premarketing human data
    - c) Problem suspected on the basis of spontaneous reports
    - d) Need to better quantitate the frequency of adverse reactions
  - 2) Hypothesis generating – need depends on:
    - a) whether it is a new chemical entity
    - b) the safety profile of the class
    - c) the relative safety of the drug within its class
    - d) the formulation
    - e) the disease to be treated, including:
      - i) its duration
      - ii) its prevalence
      - iii) its severity
      - iv) whether alternative therapies are available

with the understanding that additional data would be gathered during postmarketing testing. For example, zidovudine was released for marketing after only limited testing, and not until later were additional data gathered on both safety and efficacy, data which indicated, among other things, that the doses initially recommended were too large [4].

Some postmarketing studies of drugs arise in response to case reports of adverse reactions reported to the regulatory agency. One response to such a report might be to suggest a labeling change. Often a more appropriate response, clinically and commercially, would be to propose a pharmacoepidemiologic study. This study would explore whether this adverse event in fact occurs more often in those exposed to the drug than would have been expected in the absence of the drug and, if so, how large is the increased risk of the disease. As an example, a Medicaid database was used to study hypersensitivity reactions to tolmetin [5], following reports about this problem to the FDA's Spontaneous Reporting System [6].

Finally, drugs are obviously marketed at different times in different countries. A postmarketing pharmacoepidemiologic study conducted in a country which marketed a drug relatively early could be useful in demonstrating the safety of the drug to regulatory agencies in countries which have not yet permitted its marketing. This is becoming increasingly feasible, as both the industry and the field of pharmacoepidemiology are becoming more international, and regulators are collaborating more.

Marketing

As will be discussed later in this chapter, pharmacoepidemiologic studies are performed primarily to obtain the answers to clinical questions. However, it is clear that a major underlying reason for some pharmacoepidemiologic studies is the potential marketing impact of those answers. In fact, some companies make the marketing branch of the company responsible for pharmacoepidemiology, rather than the medical branch.

Because of the known limitations in the information available about the effects of a drug at the time of its initial marketing, many physicians are appropriately hesitant to prescribe a drug until a substantial amount of experience in its use has been gathered. A formal postmarketing surveillance study can speed that process, as well as clarify advantages or disadvantages a drug has compared to its competitors.

A pharmacoepidemiologic study can also be useful to improve product name recognition. The fact that a study is underway will often be known to prescribers, as will its results once it is publicly presented and published. This increased name recognition will presumably help sales. An increase in a product's name recognition is likely to result particularly from pharmacoepidemiologic studies that recruit subjects for the study via prescribers. However, while this technique can be useful in selected situations, it is extremely expensive and less likely to be productive of scientifically useful information than most other alternatives available. In particular, the conduct of a purely marketing exercise under the guise of a postmarketing surveillance study, not designed to collect useful scientific information, is to be condemned [7]. It is misleading and could endanger the performance of future scientifically useful studies, by resulting in prescribers who are disillusioned and, thereby, reluctant to participate in future studies.

Pharmacoepidemiologic studies can also be useful to reposition a drug that is already on the market; that is, to develop new markets for the drug. One could explore different types of outcomes resulting from the use of the drug for the approved indication, for example the impact of the drug on the cost of medical care (see Chapter 34) and on patients' quality of life (see Chapter 42). One could also explore the use of the drug for the approved indication in types of patients other than those included in premarketing studies, for example in children, in the

elderly, or in patients with multiple comorbidities and/or taking many concomitant medications. By exploring unintended beneficial effects, or even drug efficacy (see Chapter 33), one could obtain clues to and supporting information for new indications for drug use. Finally, whether because of questions about efficacy or questions about toxicity, drugs are sometimes approved for initial marketing with restrictive labeling. For example, bretylium was initially approved for marketing in the US only for the treatment of life-threatening arrhythmias. Approval for more widespread use requires additional data. These data can often be obtained from pharmacoepidemiologic studies.

Finally, and perhaps most importantly, pharmacoepidemiologic studies can be useful to protect the major investment made in developing and testing a new drug. When a question arises about a drug's toxicity, it often needs an immediate answer, or else the drug may lose market share or even be removed from the market. Immediate answers are often unavailable, unless the manufacturer had the foresight to perform pharmacoepidemiologic studies in anticipation of this problem. Sometimes these problems can be specifically foreseen and addressed. More commonly, they are not. However, the availability of an existing cohort of exposed patients and a control group will often allow a much more rapid answer than would have been possible if the study had to be conducted *de novo*. One example of this is provided by the experience of Pfizer Pharmaceuticals, when the question arose about whether piroxicam (Feldene®) was more likely to cause deaths in the elderly from gastrointestinal bleeding than the other nonsteroidal anti-inflammatory drugs. Although Pfizer did not fund studies in anticipation of such a question, it was fortunate that several pharmacoepidemiologic research groups had data available on this question because of other studies that they had performed [8]. McNeil was not as fortunate when questions were raised about anaphylactic reactions caused by zomepirac. If the data it eventually was able to have [9] had been available at the time of the crisis, they might not have removed the drug from the market. Later, Syntex recognized the potential benefit, and the risk, associated with the marketing of parenteral ketorolac, and chose to initiate a postmarketing surveillance cohort study at the time of the drug's launch [10–12]. Indeed, the drug was accused of multiple different adverse outcomes, and it was only the existence of this study, and its subsequently published results, that saved the drug in its major markets.

Legal

Postmarketing surveillance studies can theoretically be useful as legal prophylaxis, in anticipation of eventually having to defend against product liability suits (see Chapter 9). One often hears the phrase "What you don't know, won't hurt you." However, in pharmacoepidemiology this view is shortsighted and, in fact, very wrong. All drugs cause adverse effects; the regulatory decision to approve a drug and the clinical decision to prescribe a drug both depend on a judgment about the relative balance between the benefits of a drug and its risks. From a legal perspective, to win a product liability suit using a legal theory of negligence, a plaintiff must prove causation, damages, and negligence. A pharmaceutical manufacturer that is a defendant in such a suit cannot change whether its drug causes an adverse effect. If the drug does, this will presumably be detected at some point. The manufacturer also cannot change whether the plaintiff suffered legal damages from the adverse effect; that is, whether the plaintiff suffered a disability or incurred expenses resulting from a need for medical attention. However, even if the drug did cause the adverse outcome in question, a manufacturer certainly could document that it was performing state-of-the-art studies to attempt to detect whatever toxic effects the drug had. In addition, such studies could make easier the

defense of totally groundless suits, in which a drug is blamed for producing adverse reactions it does not cause.

Clinical

Hypothesis Testing

The major reason for most pharmacoepidemiologic studies is hypothesis testing. The hypotheses to be tested can be based on the structure or the chemical class of a drug. For example, the cimetidine study mentioned earlier [2] was conducted because cimetidine was chemically related to metiamide, which had been removed from the market in Europe because it caused agranulocytosis. Alternatively, hypotheses can also be based on premarketing or postmarketing animal or clinical findings. For example, the hypotheses can come from spontaneous reports of adverse events experienced by patients taking the drug in question. The tolmetin [5], piroxicam [8], zomepirac [9], and ketorolac [10–12] questions mentioned are all examples of this. Finally, an adverse effect may clearly be due to a drug, but a study may be needed to quantitate its frequency. An example would be the postmarketing surveillance study of prazosin, performed to quantitate the frequency of first-dose syncope [3]. Of course, the hypotheses to be tested can involve beneficial drug effects as well as harmful drug effects, subject to some important methodologic limitations (see Chapter 33).

Hypothesis Generating

Hypothesis-generating studies are intended to screen for previously unknown and unsuspected drug effects. In principle, all drugs could, and perhaps should, be subjected to such studies. However, some drugs may require these studies more than others. This has been the focus of a formal study, which surveyed experts in pharmacoepidemiology [13].

For example, it is generally agreed that new chemical entities are more in need of study than what are called "me too" drugs. This is because the lack of experience with related drugs makes it more likely that the new drug has possibly important, unsuspected effects.

The safety profile of the class of drugs should also be important to the decision about whether to conduct a formal screening postmarketing surveillance study for a new drug. Previous experience with other drugs in the same class can be a useful predictor of what the experience with the new drug in question is likely to be. For example, with the finding that troglitazone had an increased risk of liver disease [14], that became a concern as well with the later thiazolidinediones, pioglitazone and rosiglitazone [15]. Similarly, with the finding that rofecoxib was associated with myocardial infarction, that became a concern as well with celecoxib [16].

The relative safety of the drug within its class can also be helpful. A drug that has been studied in large numbers of patients before marketing and appears safe relative to other drugs within its class is less likely to need supplementary postmarketing surveillance studies. An extension of this approach, of course, is comparative effectiveness research (see Chapter 26).

The formulation of the drug can be considered a determinant of the need for formal screening pharmacoepidemiologic studies. A drug that will, because of its formulation, be used mainly in institutions, where there is close supervision, may be less likely to need such a study. When a drug is used under these conditions, any serious adverse effect is likely to be detected, even without any formal study.

The disease to be treated is an important determinant of whether a drug needs additional postmarketing surveillance studies. Drugs used to treat chronic illnesses are likely to be used for a long period of time. As such, it is important to know their long-term effects. This cannot be addressed adequately in the relatively brief time available for each premarketing study. Also, drugs used to treat common diseases are important to study, as many patients are likely to be exposed to them. Drugs used to treat mild or

self-limited diseases need careful study too, because serious toxicity is less acceptable. This is especially true for drugs used by healthy individuals, such as contraceptives. On the other hand, when one is using a drug to treat individuals who are very ill, one is more tolerant of toxicity, assuming the drug is efficacious.

Finally, it is important to know whether alternative therapies are available. If a new drug is not a major therapeutic advance, since it will be used to treat patients who would have been treated with the old drug, one needs to be more certain of its relative advantages and disadvantages. The presence of significant adverse effects, or the absence of beneficial effects, is less likely to be tolerated for a drug that does not represent a major therapeutic advance.

Safety versus Risk

Clinical pharmacologists are used to thinking about drug "safety": the statutory standard that must be met before a drug is approved for marketing in the US is that it needs to be proven to be "safe and effective under conditions of intended use." It is important, however, to differentiate safety from risk. Virtually nothing is without some risks. Even staying in bed is associated with a risk of acquiring bed sores! Certainly no drug is completely safe. Yet, the unfortunate misperception by the public persists that drugs mostly are and should be without any risk at all. Use of a "safe" drug, however, still carries some risk. It would be better to think in terms of *degrees of safety*. Specifically, a drug "is safe if its risks are judged to be acceptable" [17]. Measuring risk is an objective but probabilistic pursuit. A judgment about safety is a personal and/or social value judgment about the acceptability of that risk. Thus, assessing safety requires two extremely different kinds of activities: measuring risk and judging the acceptability of those risks [17]. The former is the focus of much of pharmacoepidemiology and most of this book. The latter is the focus of the following discussion. More detail is presented in Chapter 39.

Risk Tolerance

Whether or not to conduct a postmarketing surveillance pharmacoepidemiologic study also depends on one's willingness to tolerate risk. From a manufacturer's perspective, one can consider this risk in terms of the risk of a potential regulatory or legal problem that may arise. Whether one's perspective is that of a manufacturer, regulator, academician, or clinician, one needs to consider the risk of adverse reactions that one is willing to accept as tolerable. There are several factors that can affect one's willingness to tolerate the risk of adverse effects from drugs (see Table 5.2). Some of these factors are related to the adverse outcome being studied. Others are related to the exposure and the setting in which the adverse outcome occurs.

Features of the Adverse Outcome

The severity and reversibility of the adverse reaction in question are of paramount importance to its tolerability. An adverse reaction that is severe is much less tolerable than one that is mild, even at the same incidence. This is especially true for adverse reactions that result in permanent harm, for example birth defects or death.

Another critical factor that affects the tolerability of an adverse outcome is the frequency of the adverse outcome in those who are exposed. Notably, this is *not* a question of the relative risk of the disease due to the exposure, but a question of the excess risk attributed to the drug of interest (see Chapter 3). Use of tampons is extraordinarily strongly linked to toxic shock: prior studies have shown relative risks of between 10 and 20. However, toxic shock is sufficiently uncommon that even a 10- to 20-fold increase in the risk of the disease still contributes an

Table 5.2 Factors affecting the acceptability of risks.

A) Features of the adverse outcome
1) Severity
2) Reversibility
3) Frequency
4) "Dread disease"
5) Immediate versus delayed
6) Occurs in all people vs. just in sensitive people
7) Known with certainty or not
B) Characteristics of the exposure
1) Essential versus optional
2) Present vs. absent
3) Alternatives available
4) Risk assumed voluntarily
5) Drug use will be as intended vs. misuse is likely
C) Perceptions of the evaluator

extraordinarily small excess risk of toxic shock syndrome in those who use tampons [18].

In addition, the particular disease caused by the drug is important to one's tolerance of its risks. Certain diseases are considered by the public to be "dread diseases," those that generate more fear and emotion than others. Examples are AIDS and cancer. It is less likely that the risk of a drug will be considered acceptable if it causes one of these diseases.

Another relevant factor is whether the adverse outcome is immediate or delayed. Most individuals are less concerned about delayed risks than immediate risks. This is one of the factors that have probably slowed the success of antismoking efforts. In part this is a function of denial; delayed risks seem as if they may never occur. In addition, the economic concept of "discounting" plays a role here. An adverse event in the future is less bad than the same event today, and a beneficial effect today is better than the same beneficial effect in the future. Something else may occur between now and then that could make that delayed effect irrelevant or, at least, mitigate its impact. Thus, a delayed adverse event may be worth incurring if it can bring about beneficial effects today.

It is also important whether the adverse outcome is a type A reaction or a type B reaction. As described in Chapter 1, type A reactions are the result of an exaggerated but otherwise usual pharmacologic effect of a drug. Type A reactions tend to be common, but they are dose related, predictable, and less serious. In contrast, type B reactions are aberrant effects of a drug. Type B reactions tend to be uncommon, are not related to dose, and are potentially more serious. They may be due to hypersensitivity reactions, immunologic reactions, or some other idiosyncratic reaction to the drug. Regardless, type B reactions are the more difficult to predict or even detect. If one can predict an adverse effect, then one can attempt to prevent it. For example, in order to prevent aminophylline-induced arrhythmias and seizures, one can begin therapy at lower doses and follow serum levels carefully. For this reason, all other things being equal, type B reactions are usually considered less tolerable.

Finally, the acceptability of a risk also varies according to how well established it is. The same adverse effect is obviously less tolerable if one knows with certainty that it is caused by a drug than if it is only a remote possibility.

Characteristics of the Exposure

The acceptability of a risk is very different depending upon whether an exposure is essential or optional. Major adverse effects are much more acceptable when one is using a therapy that can save or prolong life, such as chemotherapy for malignancies. On the other hand, therapy for self-limited illnesses must have a low risk to be acceptable. Pharmaceutical products intended for use in healthy individuals, such as vaccines and contraceptives, must be exceedingly low in risk to be considered acceptable.

The acceptability of a risk is also dependent on whether the risk is from the presence of a treatment or its absence. One could conceptualize deaths from a disease that can be treated by

a drug that is not yet on the market as an adverse effect from the absence of treatment. For example, the six-year delay in introducing beta-blockers into the US market has been blamed for resulting in more deaths than all recent adverse drug reactions combined [19]. As a society, we are much more willing to accept risks of this type than risks from the use of a drug that has been marketed prematurely. Physicians are taught *primum non nocere* – first do no harm. This is somewhat analogous to our willingness to allow patients with terminal illnesses to die from these illnesses without intervention, while it would be considered unethical and probably illegal to perform euthanasia. In general, we are much more tolerant of sins of omission than sins of commission.

Whether any alternative treatments are available is another determinant of the acceptability of risks. If a drug is the only available treatment for a disease, particularly a serious disease, then greater risks will be considered acceptable. This was the reason zidovudine was allowed to be marketed for the treatment of AIDS, despite its toxicity and the limited testing that had been performed [4]. Analogously, studies of toxic shock syndrome associated with the use of tampons were of public health importance, despite the infrequency of the disease, because consumers could choose among other available tampons that were shown to carry different risks [18].

Whether a risk is assumed voluntarily is also important to its acceptability. We are willing to accept the risk of death in automobile accidents more than the much smaller risk of death in airline accidents, because we control and understand the former and accept the attendant risk voluntarily. Some people even accept the enormous risks of death from tobacco-related disease, but would object strongly to being given a drug that was a small fraction as toxic. In general, it is agreed that patients should be made aware of possibly toxic effects of drugs they are prescribed. When a risk is higher than it is with the usual therapeutic use of a drug, as with an invasive procedure or an investigational drug, one usually asks the patient for formal informed consent. The fact that fetuses cannot make voluntary choices about whether or not to take a drug contributes to the unacceptability of drug-induced birth defects.

Finally, from a societal perspective, one needs to be concerned about whether a drug will be and is used as intended or whether misuse is likely. Misuse, in and of itself, can represent a risk of the drug. For example, a drug is considered less acceptable if it is addicting and, so, is likely to be abused. In addition, the potential for overprescribing by physicians can decrease the acceptability of the drug. For example, in the controversy about birth defects from isotretinoin, there was no question that the drug was a powerful teratogen, and that it was a very effective therapy for serious cystic acne refractory to other treatments. There was no question either about its effectiveness for less severe acne. However, that effectiveness led to its widespread use, including in individuals who could have been treated with less toxic therapies, and a larger number of pregnancy exposures, abortions, and birth defects than otherwise would have occurred [20].

Perceptions of the Evaluator

Finally, much depends ultimately upon the perceptions of the individuals who are making the decision about whether a risk is acceptable. In the US, there have been more than a million deaths from traffic accidents over the past 30 years; tobacco-related diseases kill the equivalent of three jumbo jet loads every day; and 3000 children are born each year with embryopathy from their mothers' use of alcohol in pregnancy [21]. Yet, these deaths are accepted with little concern, while the uncommon risk of an airplane crash or being struck by lightning generates fear. The decision about whether to allow isotretinoin to remain on the market hinged on whether the efficacy of the drug for a small number of people

who had a disease which was disfiguring but not life threatening was worth the birth defects that would result in some other individuals. There is no way to remove this subjective component from the decision about the acceptability of risks. Indeed, much more research is needed to elucidate patients' preferences in these matters. However, this subjective component is part of what makes informed consent so important. Most people feel that the final subjective judgment about whether an individual should assume the risk of ingesting a drug should be made by that individual, after education by their physician. However, as an attempt to assist that judgment, it is useful to have some quantitative information about the risks inherent in some other activities. Some such information is presented in Table 5.3.

Table 5.3 Annual risks of death from some selected hazards.

Hazard	Annual death rate (per 100 000 exposed individuals)
Heart disease (US, 1985)	261.4
Sport parachuting	190
Cancer (US, 1985)	170.5
Cigarette smoking (age 35)	167
Hang gliding (UK)	150
Motorcycling (US)	100
Power boat racing (US)	80
Cerebrovascular disease (US, 1985)	51
Scuba diving (US)	42
Scuba diving (UK)	22
Influenza (UK)	20
Passenger in motor vehicle (US)	16.7
Suicide (US, 1985)	11.2
Homicide (US, 1985)	7.5
Cave exploration (US)	4.5
Oral contraceptive user (age 25–34)	4.3
Pedestrian (US)	3.8
Bicycling (US)	1.1
Tornados (US)	0.2
Lightning (US)	0.05

Source: Data derived from [21–23].

Conclusion

This chapter reviewed when pharmacoepidemiologic studies should be performed. After beginning with a discussion of the various reasons why one might perform pharmacoepidemiologic studies, it reviewed the difference between safety and risk. It concluded with a discussion of the determinants of one's tolerance of risk. Now that it is hopefully clear when one might want to perform a pharmacoepidemiologic study, the next part of the book will provide perspectives on pharmacoepidemiology from some of the different fields that use it.

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