Principles of Epidemiology for Clinical and Formulary Management Professionals

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Basic Principles of Epidemiology

Measures of Disease Frequency

To describe measures of disease frequency, it is important that we distinguish incidence from prevalence. Incidence refers to new cases of a disease or an event; prevalence refers to the total number of cases of a disease or event in a population at a given time. Incidence and prevalence are important measures in epidemiology as they provide insights into the distribution and frequency of diseases within populations.
cases that already exist in the population. Risk, as a concept, is intuitive and is commonly communicated between providers and patients in clinical practice. In epidemiology, risk refers to the proportion of individuals (those at risk) who develop the outcome of interest over a specific time period.\(^6\)

\[
\text{cumulative incidence proportion (risk) } = \frac{\text{no. of participants who develop disease during a given time period}}{\text{no. of participants at risk at beginning of the time period}}
\]

The cumulative incidence proportion is interpreted as the average risk among the population of interest for a given period of time, and certain assumptions are inherent in its calculation. We assume that no participants are entering or leaving the study during follow-up and that there are no competing risks. In epidemiology practice, these assumptions are often violated and other measures are needed. It is imperative that risk estimates be presented and interpreted in relation to the appropriate time frame, because the incidence proportion is practically meaningless unless it is accompanied by its reference period.

Another commonly used measure of disease frequency, which is not affected by some of the problems inherent with the incidence proportion, is the incidence rate. To fully understand and interpret incidence rates, we must consider the concept of person-time, the summation of the at-risk time each individual is observed. Study participants contribute “exposed” time, “unexposed” time, or both. Specifically, participants do not need to be classified as exposed or unexposed for the entire follow-up interval. If the time of the participant’s exposure varies, person-time can be allocated appropriately. After the person-time classification, we can calculate an incidence rate as follows:

\[
\text{incidence rate } = \frac{\text{no. of disease occurrences}}{\text{sum of at-risk person-time spent in exposure category}}
\]

It is worthwhile to note that events classified in the numerator must have come from the person-time experience of those participants counted in the denominator. The use of person-time allows for a more exact quantification of time at risk, allowing the researcher to circumvent the often problematic assumptions involved in calculating a cumulative incidence proportion.

Unlike the two previously described measures of disease frequency (i.e., cumulative incidence and incidence rate), prevalence refers to the current disease status in a population; it is the proportion of individuals in the population who have the disease of interest at a specific time point.\(^6\) Alternatively, this can be stated as follows:

\[
\text{prevalence } = \frac{\text{no. of people with disease}}{\text{no. of people in the population}}
\]

Unlike those in the incidence calculations, participants in the denominator of prevalence need not be at risk to be considered in the calculation. Using prevalence as a measure is useful when the time of onset of the outcome is difficult to ascertain.

The prevalence pool is defined as the subset of individuals in the population of interest who have the disease. This is a dynamic patient population; that is, individuals may enter or leave. New disease occurrences add to the prevalence pool, whereas individuals who are cured and those who die exit. This is important to note when we consider prevalence as a measure of success in public health.

For example, let us consider a population of patients who have just experienced a reduced prevalence of infection with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). When using prevalence to determine whether this is the result of a successful public health intervention, we must determine whether the incidence decreased, the death rate increased, or both. Because HIV/AIDS is not curable at this time, no cures exist that would cause individuals to exit the prevalence pool. Depending on which of these scenarios actually occurred, our conclusions would differ significantly. It is noteworthy that the use of prevalence measures in pharmacoepidemiology is rare in relation to the described incidence measures.

Table 1 displays a population of patients receiving antihypertensive pharmacotherapy. To quantify the relation between a selected antihypertensive agent and the occurrence of cardiovascular outcomes, the study authors observed 5,000 participants for more than two years. From the information in the table, we can calculate the prevalence of a previous myocardial infarction to be 600/5,000 = 0.12, or 12%. The incidence proportion of new-onset ischemic stroke, assuming no loss to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics and the Occurrence of Selected Outcomes for an Exposed Group of Participants in a Hypothetical Cohort Study</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td><strong>Occurred</strong></td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>600</td>
</tr>
<tr>
<td>New-onset ischemic stroke</td>
<td>22</td>
</tr>
<tr>
<td>Serious adverse drug reaction caused by an antihypertensive agent</td>
<td>145</td>
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follow-up and no competing risks, is calculated as 22/5,000 = 0.0044, or 0.44% over two years.

The incidence of a serious adverse drug event (ADE) is more difficult to calculate, because the patient population, to be considered at risk, must be exposed to the study drug. Poor adherence to the prescribed regimen may lead to an overestimate of the exposure time. Allocation of person-time exposure allows us to avoid this error. We assume that a sub-study was conducted to quantify adherence to the study drug regimen and has been found to be 60%.

To allocate person-time of drug exposure, we may multiply the total follow-up time for the population (5,000 participants over two years, or 10,000 person-years) by 60% to obtain a more accurate estimate of time at risk. Therefore, our denominator is 6,000 person-years, and the estimated incidence rate of serious ADEs is 145/6,000 person-years. The latter example is an oversimplification of the evaluation of ADEs, but it nicely illustrates the concept of incidence rates.

Measures of Association

The usual objective of pharmacoepidemiology is to quantify the effect of a drug exposure on an outcome, compared with no exposure or exposure to another medicinal agent. The outcome may be beneficial, such as the reduction of ischemic stroke in patients with atrial fibrillation who are using warfarin, or it may be harmful, such as serious ADEs caused by a newly marketed drug. Generally, we can quantify the effect by comparing the association between the exposure and the outcome in the drug-exposed group with another group, which is often unexposed. Regardless of which type of effect we aim to measure, we generally use one of the following measures of association.

Broadly, we may classify measures of association as absolute or relative. Common absolute measures include the risk difference, the incidence rate difference, and the prevalence difference. Their relative counterparts are the relative risk (cumulative incidence ratio), the incidence rate ratio (relative rate), and the prevalence ratio. Formulas for commonly used measures of association are shown in Table 2.

<table>
<thead>
<tr>
<th>Absolute Measure</th>
<th>Relative Measure</th>
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<tbody>
<tr>
<td>Risk difference = Risk(_A) - Risk(_B)</td>
<td>Relative risk = \frac{Risk(_A)}{Risk(_B)}</td>
</tr>
<tr>
<td>Incidence rate difference = IR(_A) - IR(_B)</td>
<td>Incidence rate ratio = \frac{IR(_A)}{IR(_B)}</td>
</tr>
<tr>
<td>Prevalence difference = P(_A) - P(_B)</td>
<td>Prevalence ratio = \frac{P(_A)}{P(_B)}</td>
</tr>
</tbody>
</table>

risk = cumulative incidence proportion; IR = incidence rate; P = prevalence.

Table 2  Calculation of Commonly Used Measures of Association

Researchers often use odds ratios as an alternative measure of association. Reporting of odds ratios is common in case-control designs and in the use of logistic regression for the control of confounding. In many cases, odds ratios can be used to estimate the relative risk directly, or they can be corrected to do so.6,8

A researcher’s choice of measure of association is often guided by his or her question of interest. For example, if an investigator were interested in the excess risk of an adverse outcome attributable to the exposure to a new medication, compared with the standard of care, he or she would probably choose to calculate an absolute measure. By contrast, if the investigator were interested in how much more likely a patient were to develop an outcome of interest, compared with another agent, he or she might choose a relative measure.6 However, because the magnitude of a relative measure is conditional on the extent of the occurrence in the comparison group, two groups with the same relative effect can have appreciably different absolute measures.6,9 Accordingly, two groups with the same absolute measure of association may have different relative effects. A full evaluation of the advantages and disadvantages of measures of association is outside the scope of this article.

A useful measure in clinical decision-making is the number needed to treat (NNT).10,11 In the context of a beneficial drug effect, the NNT is defined as the inverse of the risk reduction. For example, consider exposure “y,” which has shown a risk reduction (risk difference) of “x” compared with the standard
of care. The NNT, to prevent one adverse outcome, is $1/x$. An analogous measure is the number needed to harm (NNH). The NNH is calculated in the same manner as the NNT—but in the context of the study of harmful drug effects. Although these measures are not generally considered as core tools in epidemiology, they often allow for intuitive interpretations of medication effects and are useful for provider–patient interactions.

**Bias in Epidemiologic Studies**

Before we can make clinical and formulary decisions using information gained from medication research, we must understand the types of bias that afflict epidemiologic studies. Broadly, there are two types of error in epidemiologic research: random and systematic. A random error is a lack of statistical precision; systematic error refers to bias, which often takes the form of selection bias, information bias, or confounding. Each type of bias is discussed next.

**Selection Bias**

Selection bias, which results from the manner in which study subjects are chosen to participate, can lead to distorted measures of effect. If selection forces guiding participation are related to the outcome of interest, the estimate of effect can be biased. Because the relationship between participation and the outcome is not usually known, the presence of selection bias is often not observed but inferred.

For example, a group of public health researchers are investigating a new procedure for detecting atherosclerosis. We can assume that there are two study groups, so that the investigators are comparing the new procedure with coronary angiography. They hypothesize that both approaches have nearly the same capability (i.e., sensitivity and specificity) of detecting atherosclerosis. The angiography group is selected among those patients who have recently presented for an emergent coronary intervention; the "new procedure" group is sampled from the general population.

Suppose that if the measured prevalence in each group of patients is comparable, the investigators will conclude that the detection procedures are equivalent. Because the angiography group is much more likely to have prevalent atherosclerosis, this would be an erroneous conclusion, attributable to selection bias. Many forces guide participation in studies, and readers are urged to consider them when interpreting the medical literature. It is often possible to predict the direction of the bias introduced, thereby making selection bias useful and worthy of consideration.

**Information Bias**

Error can occur in the process of obtaining information necessary to make the comparisons of interest between the two or more study groups. We discuss two types of information bias: measurement error (or "misclassification") and recall bias. Measurement error occurs in all types of study designs; recall bias is generally restricted to case-control designs.

The terms measurement error and misclassification describe the same concept with regard to different variable types. Measurement error is used in the context of continuous variables, whereas misclassification refers to discrete variables. In this article, misclassification refers to both types. As with selection bias, it is often possible to predict the direction of bias introduced.

Broadly, misclassification may be considered to be differential or nondifferential. When we measure exposure, misclassification is differential when it is related to the outcome and it is nondifferential when it is not related to the outcome; thus, it is differential when it occurs to a greater extent in one of the comparison groups; it is nondifferential when it occurs at a comparable rate in each group.

Identifying which type of misclassification is present in a particular study is important for estimating the direction of the introduced bias. Nondifferential misclassification of the exposure or the outcome generally leads to an estimate of effect that is biased toward showing no association between the exposure and outcome. Differential misclassification of the exposure or outcome can lead to an estimate of effect that is spuriously inflated or diluted, depending on the direction of misclassification.

Figure 1 depicts a theoretical example of nondifferential misclassification of the outcome in a cohort study using 2×2 tables. Although we can sometimes correct for misclassification in the analysis, it is best avoided during data collection. At a minimum, clinicians and policymakers should be aware of the types and direction of misclassification biases to better shape their decisions.

Recall bias occurs in case-control studies (and in some retro-

<table>
<thead>
<tr>
<th>Perfect Classification</th>
<th>Nondifferential Misclassification</th>
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<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td><strong>No Exposure</strong></td>
</tr>
<tr>
<td>Outcome</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>30</td>
</tr>
<tr>
<td>No outcome</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>200</td>
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<tr>
<td></td>
<td>200</td>
</tr>
<tr>
<td>Estimated relative risk = ( \frac{150}{30} ) = 6.0</td>
<td>Estimated relative risk = ( \frac{135}{27} ) = 5.0</td>
</tr>
</tbody>
</table>

Figure 1  Dilution of the estimate of effect caused by nondifferential misclassification of the outcome by 10% (cohort study).
spective cohort studies) as a result of differential recall of pertinent exposures during the interview process. Generally, patients who have experienced adverse health outcomes (cases) are considered to be better at recalling relevant exposures from their past than participants who are not sick. This type of bias is most salient in case-control studies because the participants are sampled on the outcome of interest rather than on exposure status. The outcome has occurred for patients and is considered to be a catalyst for recall of their related history.

Controls have not usually experienced the outcome at the time of their interview. As a result, they do not often experience the same catalyst for recalling relevant exposures. This differential recall can lead to bias in a study result, and it is often possible to predict the direction of the bias.

One common way to combat the problem of differential recall in case-control studies is to sample the controls from a population of patients who have experienced a health outcome that is similar to, but unrelated to, the disease of interest. For instance, in a hospital-based case-control study of dietary exposures relevant to the occurrence of myocardial infarction, one may choose controls from the same hospital who have been admitted for urgent orthopedic care. We could argue that these two groups of patients are likely to have comparable recall of dietary exposure, thereby attenuating recall bias.

Confounding

Confounding is one of the major hurdles in the study of intended and unintended effects of drugs, especially in observational studies. When we compare a measure of association between two groups of individuals, it is not certain that the drug exposure is wholly responsible for the observed difference. Instead, the estimated effect could be partially or completely explained by other factors that differ between the comparison groups.

Ideally, when examining the effect of a drug exposure, we would like to compare the effect in the same people at the same time. That is, we would like participants to be in both the exposed and unexposed groups concurrently so that there are no differences between them except for the drug exposure. Because this situation is impossible, such a scenario is often referred to as the “counterfactual ideal.”6,7 Certain study designs allow us to approach this ideal, but we are never able to fully realize this concept.

Rothman defines confounding as “a distortion in the estimated exposure effect that results from differences in risk between the exposed and unexposed that are not attributable to exposure.”6,7 The effect of the exposure (variable 1) on the outcome (variable 2) under study is mixed with the effect of a third variable, called a confounder. For a variable to be a confounder, it must meet the criteria listed in Figure 2.

Each of these criteria is necessary but not sufficient. Therefore, if any one of the criteria does not hold, or if they are broken as a function of the study design, the variable cannot confound. Many of the design and analysis techniques used by epidemiologists are aimed at eliminating confounding.

For example, a group of investigators wish to determine whether working in a bar might be associated with the incidence of lung cancer. Their exposed group is a set of employees from the pubs near their office, and their unexposed group has been sampled from a nearby supermarket. Because it is known that smoking is a strong predictor of lung cancer, the researchers control for this potential confounder by excluding all smokers. Upon completing their analysis, the investigators conclude that there is an association between working in pubs and the occurrence of lung cancer.

One non-causal explanation for this finding is that people who work in the pubs are much more likely to be exposed to second-hand smoke than employees who work in the supermarket. Therefore, because second-hand smoke is an independent risk factor for lung cancer, the relation is confounded.

The control of confounding can be executed at the study’s design phase or analysis phase. In the design phase, three methods are commonly implemented:

- randomization
- restriction (exclusion)
- matching

Randomization and restriction are described in this article, but a full explanation of matching is beyond the scope of this discussion. In the analysis phase, epidemiologists use stratification (subclassifcation), often followed by pooling or standardization, or regression modeling (e.g., logistic regression).

| 1. The variable must be associated with the outcome as a cause or a proxy for a cause, and |
| 2. The variable must be associated with the exposure (differentially distributed), and |
| 3. The variable must not be in the causal path between the exposure and the outcome. |

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Figure 2  Criteria for and a visual depiction of confounding in pharmacoepidemiology. (Data from Rothman KJ, Greenland S. Modern Epidemiology, 2nd ed.6; and Rothman KJ. Epidemiology: An Introduction.)

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The hallmark of experimental studies is the investigator’s assignment of the exposure to the study participants. Randomization of participants to two or more study groups generally creates comparability with respect to potential confounders between the comparison groups. Randomization is the only technique in drug research that creates comparability between groups with respect to known and unknown confounders. Therefore, when randomization is successful, the association between all measured and unmeasured potential confounders and the exposure is broken and the variables cannot confound. Randomization does not always prevent confounding; however, as the study sample size increases, the probability of a differential distribution of potential confounders decreases.7

Restriction (exclusion) is used in both experimental and in observational studies to control for confounding by eliminating the potential confounder. Unlike randomization, restriction cannot control for confounding by variables that are unknown or unmeasured. However, because restriction completely removes the presence of the potential confounder from the study, we can be certain that it will not confound.7 The primary disadvantages of restriction, however, are the loss of external validity and the potential shrinking of sample size.6

Study Designs in Medication Research

Epidemiologists use a variety of study designs, including (1) experiments, (2) cohort studies, and (3) case-control studies. Each design has specific advantages and disadvantages.

Deciding which design to use depends on the characteristics of the relationship under study and the available data. This decision is a function of many determinants, including the availability of the data, the cost, the induction and latency periods, the prevalence of exposure, the incidence of the outcome, and ethical considerations. Before we present the relative benefits of each study design, we must understand the concept of validity.

Rothman distinguishes between internal validity (the validity of the inferences with respect to the source population) and external validity (the validity of the study inferences with respect to people outside the study population).6 Internal validity may be thought of as a lack of systematic error. External validity refers to the ability to generalize the study results to patient populations with characteristics that differ from those of the study population. Although a full discussion of this distinction is outside the scope of this article, it is very important to ensure internal validity.6

Two other key concepts in study design are efficiency and precision. Precision is defined as a lack of random error.6 In epidemiologic studies, it is usually measured by the use of confidence intervals (CIs) and hypothesis testing. Precision is a function of sample size, apportionment of the exposure groups, and the magnitude of the effect; consequently, measures of precision can be misleading.

We strongly suggest that readers not rely solely on the statistical significance of P values and on the positioning of confidence intervals in the decision-making process. Statistical significance is an arbitrary dichotomy that is not grounded in the clinical relationship under study. Furthermore, it is possible (and perhaps common) for a valid study to inform us of a clinically meaningful result even though it might not be statistically significant. Conversely, a study may be internally invalid, thereby being uninformative even though it reaches statistical significance.

It is a common mistake to confuse “statistical precision” with “internal validity.” Readers are encouraged to consider the role of precision with caution and only after evaluating a study’s internal validity. Clinical experts can gain more information by first evaluating the internal validity of the study and then using their prior knowledge to put the information obtained into context.

A study is considered more efficient than another if it achieves greater statistical precision with the same sample size.6 Efficiency is important as a rationale for choosing a particular study design or analytical technique. In this article, efficiency is discussed in the context of case-control studies.

Cohort Studies

A cohort generally refers to “a group or band of people.”13 In epidemiology, it can mean a group of individuals who are exposed or unexposed to a medication.6 A dynamic cohort is one in which members may enter and leave (e.g., a group of people living in a particular neighborhood). Members of a closed cohort are generally defined in relation to a specific event in time, and they do not leave the cohort until death (or in practice, are lost to follow-up).6 An example would be the group of individuals in attendance when the Boston Red Sox won the World Series in 2004.

Cohort studies involve samples of non-diseased individuals according to their exposure status who are observed over time for the occurrence of the outcome of interest. Generally, the goal of the study is to compare the disease rates or proportions between two or more cohorts, although odds ratios may be calculated if desired.7

Cohort studies may be executed prospectively or retrospectively. With a prospective cohort study, participants are actively recruited, often according to their exposure classification, and the participants are followed over time while pertinent information about them is collected. Retrospective cohort studies use existing data sources to sample individuals according to their exposure, and participants are followed retrospectively over time for disease occurrence. Although the general structure of a cohort study is straightforward, we must consider the issues of validity discussed earlier.

Cohort studies are advantageous because they allow for the assessment of multiple outcomes and for the direct calculation of risk and rates.8 They often enable the researchers to classify person-time to allow rates to be calculated. Cohort studies are not subject to recall bias, because the exposure is ascertained prior to the outcome. The advantages and disadvantages of each study design are presented in Table 3.6,7,14

A major disadvantage of a cohort design is the potential for
the loss of participants to follow-up. When groups of people are followed up over time, it is inevitable that some participants will leave the study or die as a result of competing risks. This is more likely when the follow-up time is long, but evaluation of this phenomenon is important to all cohort studies. When loss to follow-up is related to the exposure and the outcome, the resulting estimate of effect may be biased.6 The extent of the potential difficulty introduced by loss of subjects to follow-up is proportional to the length of the induction and latency periods of the disease under study. The longer the participants must be followed, the higher the probability of any one subject being lost.

When interpreting cohort studies (including clinical trials), we should consider the implicit assumptions made about the induction and latency periods and about the timing of exposure. The timing of exposure is important when we estimate the effect of that exposure on an outcome. Specifically, if the exposure occurs outside of the relevant etiological time frame, it is analogous to being unexposed, and the measure of association underestimates the true effect.

Similarly, all exposure–disease relations can be considered to have both an induction period and a latency period. If the measurement of the outcome occurs before the induction and latency periods have elapsed, the estimate of effect will be diluted. Rothman provides a full discussion of these issues.15,16

Prospective cohort studies are generally time-consuming and expensive to execute because of the huge amount of work involved with data collection and follow-up. In contrast, retrospective cohort studies are faster and relatively inexpensive, but they rely on pre-existing data that were probably collected for a different purpose. This can open the door to information bias. The decision of which approach to take is often based on available funding.

Case-Control Studies

Case-control studies differ from cohort and experimental designs, in that the comparison groups are sampled on the outcome. The goal of a case-control study is the same as a cohort design, that is, to quantify the relation between some exposure and some outcome. However, a case-control design aims to achieve this goal more efficiently through the use of sampling.7 When case-control studies are correctly executed, they provide valid epidemiologic evidence.

Consider that, conceptually, all case-control studies arise from a source population, which is the population of participants who would have been studied in a cohort design.7 Instead of sampling participants according to their exposure and following them over time, the case-control design identifies cases and samples controls from the person-time experience from which the cases came. The prevalence of the exposure for each group is then determined, and the appropriate measure of association is calculated. In practice, odds ratios are usually calculated because of a lack of information about the study base.

The goal of the control group is to estimate the prevalence of exposure in the source population (i.e., ensuring that they are a sample of the source population that gave rise to the cases), making it imperative that controls are sampled independent of their exposure status.6,7 Case-control studies are particularly useful for identifying risk factors for a condition or when little is known about a disease, because we can easily study multiple exposures. As discussed elsewhere,6 it is sometimes possible to estimate risk and rates from case-control studies despite the widespread use of odds ratios.

Experimental Studies and Clinical Trials

Experiments are the cornerstone of scientific research, and they focus on the study of an intervention under well-controlled conditions. In medication research, they are generally referred to as clinical trials.6 The hallmark of a clinical trial and other experimental designs is the investigator’s assignment of the exposure to the participants. Assignment of the study exposure is usually (and should be) done in accordance with a study protocol that is intended to increase internal validity.5
The clinical trial is the workhorse for evaluating the efficacy of medications and is familiar to most clinicians and policymakers. Clinical trials have not come to the forefront of evidence-based medicine by accident; rather, it is this key characteristic of investigator-assigned exposure that has made this design so useful.

Randomization has become routine in clinical trials. This is the process of assigning participants to categories of exposure by chance. The result is two or more exposure categories that are, on average, comparable with respect to known and unknown, as well as measured and unmeasured, confounders. Randomization is the only epidemiologic tool that reliably prevents confounding caused by unknown confounders, and it has thus become a prominent tool in medication research. Because of the significant attenuation of potential confounding biases by randomization, clinical trials are considered the gold standard in the study of beneficial drug effects.

Because of the significant attenuation of potential confounding, randomized clinical trials are considered the gold standard in the study of beneficial drug effects. Randomization is the only epidemiologic tool that reliably prevents confounding caused by unknown confounders, and it has thus become a prominent tool in medication research. Because of the significant attenuation of potential confounding, randomized clinical trials are considered the gold standard in the study of beneficial drug effects.

Clinical trials generally integrate the use of placebos and the process of blinding (masking) into their design by keeping involved individuals unaware of the assignment of treatment. Blinding is intended to prevent information bias associated with the knowledge of which participants have been assigned which treatment. It is essential that the assessor be blinded, but it is advantageous for the patient to be blinded as well.

Placebos are inert treatments that are similar to the active drug in all respects except for the active moiety. The purpose of a placebo is to ensure comparability between the exposure groups with respect to the psychological effects of treatment, which are considered powerful. Placebos also facilitate blinding in such a way that the perceived treatment experience is identical for both exposure categories.

Clinical trials are not always feasible. For instance, because of their ability to achieve high internal validity, clinical trials are the gold standard for determining the efficacy of medications. Clinical trials also validly quantify ADEs related to the exposure, provided that these events occur at a sufficiently high incidence to be detected and that the induction and latency periods are short enough to be covered by the study time frame. Because of the high expense associated with conducting clinical trials, they are often limited to short periods and small sample sizes. Therefore, ADEs not meeting these criteria may not be detected in the course of a clinical trial. This is especially interesting when one considers that clinical trials are often sufficient for a new drug to gain approval by the Food and Drug Administration (FDA).

The FDA has recently taken steps to ensure the safety of approved and unapproved products and has recommended the use of observational study designs. This approach allows for earlier detection of potentially serious ADEs. Early detection facilitates the application of risk-management strategies that may restrict a medication’s use, yet it would allow useful drugs to remain on the market for those in need.

Efficacy and Effectiveness

When we consider the beneficial effects of a medication, we should distinguish between the agent’s efficacy and effectiveness. Conceptually, and in terms of study design, efficacy is often evaluated in randomized, controlled clinical trials that commonly use restriction (exclusion). The resulting populations are homogeneous within the study, but the results are not necessarily generalizable to the population most likely to use the drug in clinical practice. Furthermore, clinical trial investigators often choose populations in which it is easier to show an effect in order to combat their limited sample sizes.

For instance, it takes fewer participants and resources to demonstrate the beneficial effect of using a statin on the risk of heart attack in people who are at a high baseline risk for myocardial infarction. As a result, clinical trials of preventive interventions often evaluate secondary prevention, leading to a relative paucity of information about primary prevents. Clinical trial efficacy data are ubiquitous in comparison with effectiveness data, perhaps because of the FDA’s mandate of efficacy information for drug approval.

Studies of effectiveness often use observational methods to capture drug use in common clinical practice and to estimate the beneficial effects while controlling for myriad confounding factors. Compared with efficacy information, effectiveness data are generated inexpensively and quickly. Many pharmacoepidemiologists spend their careers analyzing secondary data and therefore have the knowledge and skills to efficiently evaluate beneficial drug effects that are relevant to everyday clinical and formulary decision-making.

The use of cohort designs that mimic clinical trials, except for randomization and restriction of study populations, is quite informative, and observational studies are likely to be underfunded because of money that has been earmarked for clinical trials. Information derived from effectiveness studies is helpful for identifying populations of patients who are most likely to benefit from a pharmaceutical and those individuals at highest risk of experiencing an ADE. Information gained from observational studies of beneficial drug effects is useful and relevant to clinical and policy decision-making, but practitioners need a knowledge of epidemiology to apply the principles.

Pharmacovigilance and Harmful Drug Effects

As discussed, clinical trials are not always best suited to evaluating harmful drug effects, either for ethical reasons or because of a lack of statistical power. In fact, ADEs that occur
less frequently than 1 in 2,000 to 3,000 participants are unlikely to be caught by most premarketing clinical trials. Furthermore, some ADEs exhibit long induction or latency periods; consequently, their incidence is often underestimated or completely missed in clinical trials.

The example of Merck’s rofecoxib (Vioxx) illustrates the problematic nature of long induction and latency periods for prospectively evaluating ADEs. Despite earlier safety signals, the increased risk of cardiovascular events after exposure to rofecoxib was not clear until 18 months into a study that was published in 2005. The use of an appropriately executed observational design, applied to retrospective data, might have helped to identify this risk earlier. For this and other reasons, the use of observational designs, especially case-control studies, has become widespread in the drug safety arena and will continue to influence clinicians and policymakers.

The World Health Organization defines pharmacovigilance as “the pharmacological science relating to the detection, assessment, understanding, and prevention of adverse effects, particularly long-term and short-term side effects, of medicines.” Recent advances in pharmacovigilance are a result of heightened awareness of potential ADEs, especially those that are avoidable through implementing risk-management strategies.

The role of observational study designs in pharmacovigilance is increasing, especially when the ADE is rare or when there is a need for an expedited answer. The work involved with pharmacovigilance shapes risk-management strategy, which is primarily concerned with preventing unnecessary ADEs and identifying populations at high risk. Increasingly, practitioners will be faced with the prospect of digesting evidence from observational studies of harmful drug effects; these studies will inspire their interactions with patients.

Conclusion

Evidence-based medicine (EBM) has the continuing opportunity to facilitate improved quality of care and to guide economically sensible health policy. The science of EBM has necessitated that clinicians also gain a working knowledge of epidemiology to improve their decision-making ability and their interactions with patients. It is through learning about epidemiology that practitioners will be able to efficiently and responsibly improve patient outcomes and make good use of scarce resources.

Clinical trials remain the standard for evaluating the efficacy of pharmaceutical products, but observational methods have had an increasingly important and expanding role in evaluating an agent’s relative effectiveness or harm and in better influencing health care professionals in risk management, economics, and clinical policy. Clinicians and policymakers today must have an appreciation of the underlying principles of epidemiology for application to real-world clinical cases and formulary management.

References


Conflict-of-Interest (COI) Statement

The content of this article has been reviewed under Jefferson’s Continuing Medical Education COI policy.

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Continuing Education Questions for Physicians and Pharmacists

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Expiration Date: April 30, 2007

TOPIC: Principles of Epidemiology for Clinical and Formulary Management Professionals

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Jefferson Medical College designates this continuing medical education activity for a maximum of one Category 1 credit toward the Physician’s Recognition Award (PRA) of the American Medical Association. Each physician should claim only those credits that he/she actually spent in the educational activity.

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Continuing Education Questions for Physicians and Pharmacists

**TOPIC:** Principles of Epidemiology for Clinical and Formulary Management Professionals

**APCE Program #079-999-06-016-H04**

**CE Evaluation:** Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

### Multiple Choice

**Select the one correct answer.**

1. **Which term defines new cases of a disease or an event?**
   a. prevalence
   b. incidence
   c. risk
   d. epidemiology

2. **Misclassification and recall bias are types of:**
   a. random error.
   b. selection bias.
   c. information bias.
   d. confounding.

3. **The proportion of the population having the disease of interest over a specific time period is known as:**
   a. the incidence rate.
   b. prevalence.
   c. the cumulative incidence.
   d. the relative risk.

4. **All of the following statements are true except:**
   a. Confounders are associated with the outcome.
   b. Confounders are associated with the exposure.
   c. Confounders are in the causal path between the exposure and the outcome.
   d. Confounders can usually be controlled for by using randomization, exclusion, and/or matching.

5. **Which one of the following is a significant disadvantage of a cohort study?**
   a. its inefficiency in studying multiple outcomes
   b. its inefficiency in studying rare outcomes
   c. the presence of selection bias
   d. a lack of clarity in temporal relation

6. **Which of the following is defined as a lack of random error?**
   a. efficiency
   b. precision
   c. efficacy
   d. effectiveness

7. **All of the following are statements that reflect advantages of case-control studies except:**
   a. They are efficient for studying disease with long latency periods.
   b. They are efficient for studying rare conditions.
   c. They are useful for studying multiple exposures.
   d. Temporal relations are easily evident.

8. **Studies in which the results are generalizable to populations with characteristics that differ from the source population are said to have:**
   a. high internal validity.
   b. high external validity.
   c. high efficacy.
   d. low systematic error.

9. **Which of the following statements is not true about clinical trials?**
   a. The investigator assigns exposure design.
   b. Randomization is commonly used in assigning exposure categories.
   c. Adverse drug effects with long latency periods are easily flagged.
   d. Clinical trials are very useful in assessing the efficacy of medications.

10. **The inverse of risk reduction in the context of a beneficial drug effect is defined as:**
    a. the number needed to treat.
    b. the number needed to harm.
    c. the relative risk.
    d. the odds ratio.
CE Registration and Evaluation Form

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Registration

Name: ____________________________________________________________ Degree: _______________________________________
Street address: ______________________________________________ City: ___________________________________ State: _________ Zip:__________ Telephone: _____________________________
E-mail Address: _______________________________________ Check one: □ Physician □ Pharmacist □ Other
Time needed to complete this CE activity in hours: □ 0.5 hr □ 1 hr □ 1.5 hr □ 2 hr □ Other _________________________
Certification: I attest to having completed this CE activity. ___________________________________________________________
                                      Signature (required) Date _______________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □ 6. a □ b □ c □ d □
2. a □ b □ c □ d □ 7. a □ b □ c □ d □
3. a □ b □ c □ d □ 8. a □ b □ c □ d □
4. a □ b □ c □ d □ 9. a □ b □ c □ d □
5. a □ b □ c □ d □ 10. a □ b □ c □ d □

Evaluation

Rate the extent to which:

<table>
<thead>
<tr>
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<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
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</table>
1. Objectives of this activity were met              | □         |      |          |     |          |
2. You were satisfied with the overall quality of this activity | □         |      |          |     |          |
3. Content was relevant to your practice needs      | □         |      |          |     |          |
4. Participation in this activity changed your      | □         |      |          |     |          |
    knowledge/attitudes                              |           |      |          |     |          |
5. You will make a change in your practice as a result of participation in this activity | □         |      |          |     |          |
6. This activity presented scientifically rigorous, unbiased, and balanced information | □         |      |          |     |          |
7. Individual presentations were free of commercial bias | □         |      |          |     |          |
8. Adequate time was available for Q&A              | □         |      |          |     |          |
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.               
   □ This activity will not change my behavior because I do not agree with the information presented.   
   □ I need more information before I can change my practice behavior. 
   □ I will immediately implement the information into my practice.  
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   □ Discuss new information with other professionals □ Consult the literature 
   □ Discuss with industry representative(s) □ Participate in another educational activity 
   □ Other ____________________________________ □ None

Send the completed form and $10 payment (make checks payable to P&T) to: Department of Health Policy, Thomas Jefferson University, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.