

Chapter 12

Research Methods for Pharmacoepidemiology Studies

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Abstract Pharmacoepidemiology (PE) is the discipline that studies the frequency and distribution of health and disease in human populations, as a result of the use and effects (beneficial and adverse) of drugs. PE uses methods similar to traditional epidemiologic investigation, but applies them to the area of clinical pharmacology. This chapter will review the factors involved in the selection of the type of pharmacoepidemiologic study design, and advantages and disadvantages of these designs. Since other chapters describe randomized clinical trials in detail, we will focus on observational studies.

Keywords Pharmacoepidemiology • Effectiveness trials • Pragmatic trials • Case-time control study

Pharmacoepidemiology (PE) is the discipline that studies the frequency and distribution of health and disease in human populations, as a result of the use and effects (beneficial and adverse) of drugs. PE uses methods similar to traditional epidemiologic investigation, but applies them to the area of clinical pharmacology [1]. Many of the same precepts hold for PE studies as has been discussed in previous chapters, however, this chapter can serve as a review of many of the same principles; but, then as they specifically apply to PE research.

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In the last few years, PE has acquired relevance because of various drug withdrawals from the market; and, as a result of public scandals related to drug safety and regulatory issues. Some of these withdrawn and controversial drugs include troglitazone, [2–4] cisapride, [5, 6] cerivastatin, [7–10] rofecoxib, [11–13] and valdecoxib [13–15]. One of the major allegations cited with each of these drug withdrawals were flaws in the study designs that were used to demonstrate drug efficacy or safety. Furthermore, the study designs involved with these withdrawn drugs were variable and reported conflicting results [16]. An example of the controversies surrounding drug withdrawals is the association of nonsteroidal antiinflammatory drugs (NSAID) with chronic renal disease [17–21]. The observation that one study may produce different results from another, presumably similar study (and certainly from studies of differing designs) is, of course, not unique to PE, as has been discussed in prior chapters.

Pharmacoepidemiologic studies have been used with many purposes, for example to: examine the natural history of a disease, determine the incidence rates of events in the general population, characterize safety signals associated with medications, describe drug utilization patterns, determine risk factors for specific events, assessing the benefits and risks of products or evaluating strategies to enhance the benefit/risk balance [22].

In addition, pharmacoepidemiology is growing around the world because of availability of electronic databases (e.g. claims, medical records), advances in computers with more powerful software and hardware, and improvements in methodological approaches to deal with various types of confounding particularly confounding by indication [23].

This chapter will review the factors involved in the selection of the type of pharmacoepidemiologic study design, and advantages and disadvantages of these designs. Since other chapters describe randomized clinical trials in detail, we will focus on observational studies.

Selection of Study Design

Many of the considerations necessary to determine the optimal study in PE are similar to those discussed in prior chapters; however, a brief review here will serve as a necessary reminder. Thus, before one can select the appropriate study design, one needs an appropriate research question that includes the objective and the purpose of the study (as is true for traditional epidemiologic studies). There is a consensus that an appropriate research question includes information about the exposure, outcome, and the population of interest, and they are included in the protocol. For example, an investigator might be interested in the question of whether there is an association of rosiglitazone with cardiac death in patients with type 2 diabetes mellitus. In this case, the exposure is the antidiabetic drug rosiglitazone, the outcome is cardiac death, and the population is a group of patients with type 2 diabetes. Although this may seem simplistic, it is surprising how many times it is unclear what the exact research question of a study is, and what the elements are which are under study.

The key elements for clearly stated objectives are keeping them SMART: Specific, Measurable, Appropriate, Realistic and Time-bound (SMART) [24]. An

| | | | |
|---------------|------------------------------------|--------------------------|--------------|
| | Prevalence or Incidence of Outcome | | |
| | | Not Rare | Rare |
| Drug Exposure | Not Rare | Cohort or clinical trial | Case-control |
| | Rare | Cohort | Case-Cohort |

Fig. 12.1 Designs by frequency of exposure and outcome

objective is specific if it indicates the target; in other words, who and what is the focus of the research, and what outcomes are expected. By measurable, it is meant that the objective includes a quantitative measure. Appropriate, refers to an objective that is sensitive to target needs and societal norms, and realistic refers to an objective that includes a measure which can be reasonably achieved under the given conditions of the study. Finally, time-bound refers to an objective that clearly states the study duration. For example, a clearly stated objective might be: ‘to estimate the risk of rosiglitazone used as monotherapy on cardiac death in patients with type 2 diabetes treated between the years 2000–2007.’

In summary, in PE as in other areas of clinical research, clearly stated objectives are important in order to decide on the study design and analytic approach. That is, when a researcher has a clear idea about the research question and objective, it leads naturally to the optimal study design. Additionally, the investigator then takes into account the nature of the disease, the type of exposure, and available resources in order to complete the thought process involved in determining the optimal design and analysis approach. By the ‘nature of the disease’ it is meant that one is cognizant of the natural history of the disease from its inception to death. For example, a disease might be acute or chronic, and last from hours to years, and these considerations will determine whether the study needs to follow a cohort for weeks or for years in order to observe the outcome of interest. In PE research, the exposure usually refers to a drug or medication, and this could result in a study that could vary in duration (hours to years), frequency (constant or temporal) and strength (low vs. high dose). All of these aforementioned factors will have an impact on the selection of the design and the conduct of the study. In addition, a researcher might be interested in the effect of an exposure at one point in time (e.g. cross-sectional) vs. an exposure over long periods of time (e.g. cohort, case-control).

Since almost every research question can be approached using various designs, the investigator needs to consider both the strengths and weaknesses of each design in order to come to a final decision. For example, if an exposure is rare, the most efficient design is a cohort study (provided the outcome is common) but if the outcome is rare, the most efficient design is a case-control study (provided the exposure is common). If both the outcome and exposure are rare, a case-cohort design might be appropriate where odds ratio might be calculated with exposure data from a large reference cohort (Fig. 12.1).

Study Designs Common in PE

Table 12.1 demonstrates the study designs frequently used in PE research. Observational designs are particularly useful to study unintended drug effects in the postmarketing phase of the drug cycle. It is also important to consider the comparative effectiveness trial that is used in postmarketing research (see Chap. 5).

Effectiveness trials can be randomized or not randomized, and they are characterized by the head-to-head comparison of alternative treatments in large heterogeneous populations, imitating clinical practice [25–27]. As it is mentioned in Chap. 3, randomized clinical trials provide the most robust evidence, but they have often limited utility in daily practice because of selective population (e.g. specific disease severity, number of comorbidities and concomitant medications), small sample size, low drug doses, short follow-up period, and highly controlled environment [28].

Descriptive Observational Studies

Recall that these are predominantly hypothesis generating studies where investigators try to recognize or to characterize a problem in a population. In PE research, for example, investigators might be interested in recognizing unknown adverse effects, in knowing how a drug is used by specific populations, or how many people might be at risk of an adverse drug event. As a consequence, these studies do not generally

Table 12.1 Classification of postmarketing studies

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|--|
| I. Descriptive observational studies |
| A. Case report |
| B. Case series |
| C. Ecologic studies |
| D. Cross-sectional studies |
| II. Analytical studies |
| <u>Observational studies</u> |
| A. Case-control studies |
| B. Cross-sectional studies |
| C. Cohort studies |
| D. Hybrid studies |
| 1. Nested case-control studies |
| 2. Case-cohort studies |
| 3. Case-crossover studies |
| 4. Case-time studies |
| <u>Interventional studies</u> |
| A. Controlled clinical trials |
| B. Randomized, control clinical trials |
| C. N of trials |
| D. Simplified clinical trials |
| E. Community trial |

measure associations; rather, they use measures of frequency such as proportions, rate, risk and prevalence.

Case Report

Case reports are descriptions of the history of a single patient who has been exposed to a medication and experiences a particular and unexpected effect, whether that effect is beneficial or harmful. In contrast to traditional research, in pharmacoepidemiologic research, case reports have a privileged place, because they can be the first signal of an adverse drug event, or the first indication for the use of a drug for conditions not previously approved (off-label indications by the regulatory agency e.g. Food and Drug Administration). As an example, case reports were used to communicate unintended adverse events such as phocomelia associated with the use of thalidomide [29]. Case reports also make up the key element for spontaneous reporting systems such as MedWatch, The FDA Safety Information and Adverse Event Reporting Program. The MedWatch program allows providers, consumers and manufacturers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use. By law, manufacturers, when they become aware of any adverse effect, must submit a case report form of serious unintended adverse events that have not been listed in the drug labeling within 15 calendar days [30].

Case Series

Case series is essentially a collection of ‘case reports’ that share some common characteristics such as being exposed to the same drug; and, in which same outcome is observed. Frequently, case series are part of phase IV postmarketing surveillance studies, and pharmaceutical companies may use them to obtain more information about the effect, beneficial or harmful, of a drug. For example, Humphries, et al. reported a case series of cimetidine carried out in its postmarketing phase, in order to determine if cimetidine was associated with agranulocytosis [31]. The authors followed new cimetidine users, and ultimately found no association with agranulocytosis. Often, case series characterize a certain drug-disease association in order to obtain more insight into the clinicopathological pattern of an adverse effect; such as, hepatitis occurring as a result of exposure to nitrofurantoin [32]. The main limitation of case series is that they do not include a comparison group(s). The lack of a comparison group is critical, and the result is that is difficult to determine if the drug effect is greater, the same or less than the expected effect in a specific population (a situation that obviously complicates the determination of causality).

Ecologic Studies

Ecologic studies evaluate secular trends and are studies where trends of drug-related outcomes are examined over time or across countries. In these studies, data from a single region can be analyzed to determine changes over time; or, data from a single time period can be analyzed to compare one region vs. another. Since ecologic studies do not provide data on individuals (rather they analyze data based on study groups), it is not only impossible to adjust for confounding variables; but, it does not reveal whether an individual with the disease of interest actually used the drug (this is termed the ecologic fallacy). In ecologic studies, sales, marketing, and claims data-bases are commonly used. For example, one study compared urban vs. the rural areas in Italy using drug sales data to assess for regional differences in the sales of tranquilizers [33, 34]. For the reasons given above, ecologic studies are limited in their ability to associate a specific drug with an outcome; and, invariably there are usually other factors that could also explain the outcome.

Cross-Sectional Studies

Cross-sectional studies are particularly useful in drug utilization studies and in prescribing studies, because they can present a picture of how a drug is actually used in a population or how providers are actually prescribing medications. Cross-sectional studies can be descriptive or analytical. Cross-sectional studies are considered descriptive in nature when they describe the ‘big’ picture about the use of a drug in a population, and the information about the exposure and the outcome are obtained at the same point in time. Cross sectional designs are used in drug utilization studies because these studies are focused on prescription, dispensing, administration of medication, marketing, and distribution; and, also address the use of drugs at a societal level, with special emphasis on the drugs resultant effect on medical, social, and economic consequences. Cross-sectional studies in PE are particularly important to determine how specific groups of patients, e.g. elderly, children, minorities, pregnant, etc. are using medications. As an example, Paulose-Ram et al. analyzed the U.S. National Health and Nutrition Examination Survey (NHANES) from 1988 to 1994 in order to estimate the frequency of analgesic use in a nationally representative sample from the U.S. From this study it was estimated that 147 million adults used analgesics monthly, women and Caucasians used more analgesics than men and other races, and more than 75 % of the use was over the counter [35].

Analytical Studies

Analytic studies, by definition, have a comparison group and as such are more able to assess an association or a relationship between an exposure and an outcome. If the investigator is able to allocate the exposure, the analytical study is considered to be an interventional study; while if the investigator does not allocate the exposure; the study

is considered observational or non-experimental (or non-interventional). Analytical observational pharmacoepidemiologic studies quantify beneficial or adverse drug effects using measures of association such as rate, risk, odds ratios, rate ratios, or risk difference. Analytic pharmacoepidemiologic studies are particularly important when there are uncommon or delayed adverse events because clinical trials would be impractical and/or unfeasible especially if event rates are lower than 1:2,000 or 1:3000 [36].

Cross-Sectional Studies

Cross-sectional studies can be analytical if they are attempting to demonstrate an association between an exposure and an outcome. For example, Paulose-Ram et al. used the NHANES III data to estimate the frequency of psychotropic medication used among Americans between 1988 and 1994; and, to estimate if there was an association of sociodemographic characteristics with psychotropic medication use. They found that psychotropic medications were associated with low socioeconomic status, lack of high school education, and whether subjects were insured [37]. The problem with analytical cross-sectional studies is that it is often unknown whether the exposure really precedes the outcome because both are measured at the same point in time. This is obviously important since if the exposure does not precede the outcome, it can not be the cause of that outcome. This is especially important in cases of chronic disease where it may be difficult to ascertain which drugs preceded the onset of that disease.

Case-Control Studies (or Case-Referent Studies)

Case control and cohort studies are designs where participants are selected based on the outcome (case-control) or on the exposure (cohort) Fig. 12.2. In PE case-control studies, the odds of drug use among cases (the ratio exposed cases/unexposed cases) are compared to the odds of drug use among non cases (the ratio exposed controls/unexposed controls). The case-control design is particularly desirable when one wants to study multiple determinants of a single outcome [38]. The case-control design is a particularly efficient study when the outcomes are rare, since the design guarantees a sufficient number of cases. For example, Ibanez et al. designed a case-control study to estimate the association of non-steroidal anti-inflammatory drugs (NSAID) (common exposure) with end-stage renal disease (a rare outcome). In this study, the cases were patients entering a local dialysis program from 1995 to 1997 as a result of end-stage renal disease; while controls, were selected from the hospital where the case was first diagnosed (in addition, the controls did not have conditions associated with NSAID use). Information on previous use of NSAID drugs (exposure) was then obtained in face-to-face interviews (which, by the way, might introduce bias – this type of bias may be prevented if prospectively gathered prescription data are available, although for NSAIDs the over-the-counter use is almost never registered on an individual basis).

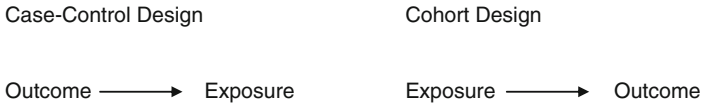


Fig. 12.2 Case-control and cohort designs

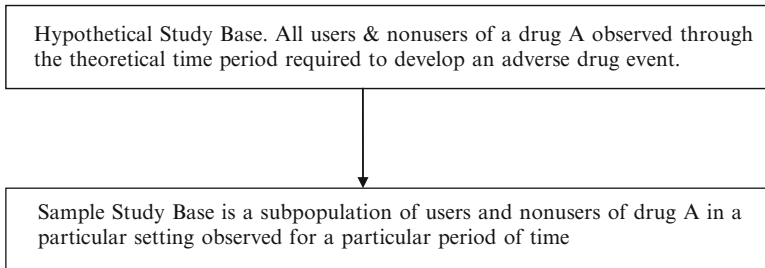


Fig. 12.3 Study base and sample study base

As implied above, case-control studies are vulnerable to selection, information and confounding bias. For example, selection bias can occur when the cases enrolled in the study have a drug use profile that is not representative of all cases. For instance, selection bias occurs if cases are identified from hospital data and if people with the medical condition of interest are more likely to be hospitalized if they used the drug (than if they did not). Selection bias may also occur by selective nonparticipation in the study, or when controls enrolled in a study have a drug use profile that differs from that of the 'sample study base' (Fig. 12.3). Selection bias can then be minimized if controls are selected from the same source population (study base) as the cases [39, 40].

Since the exposure information in case-control studies is frequently obtained retrospectively—through medical records, interviews, and self-administered questionnaires, case-control studies are often subject to information bias. Most information bias pertains to recall and measurement bias. Recall bias may occur, for example, when interviewed cases remember more details about drug use than non-cases. The use of electronic pharmacy databases, with complete information about drug exposure, could reduce this type of bias. Finally, an example of measurement or diagnostic bias occurs when researchers partly base the diagnosis or interpretation of the diagnosis on knowledge of the exposure status of the study subjects.

Cohort Studies

Recall, that in cohort studies, participants are recruited based on the exposure and they are followed up over time while studying differences in their outcome. In PE cohort studies, users of a drug are compared to nonusers or users of other drugs with

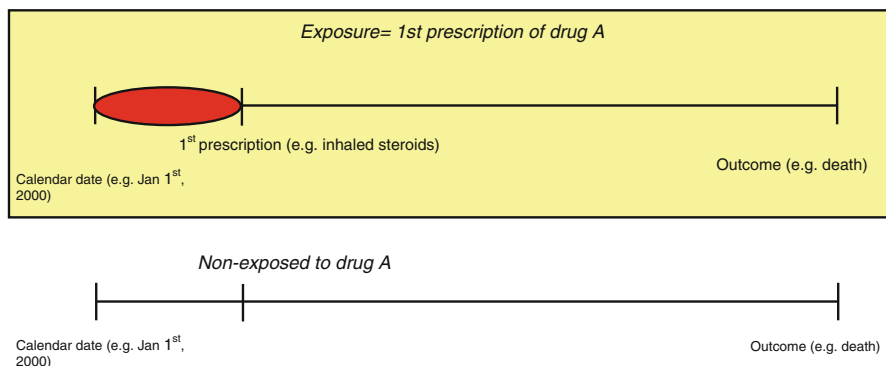


Fig. 12.4 Immortal time bias in exposed (Study) and non-exposed (Control) groups (Adapted from Refs. [44–49])

respect to rate or risk of an outcome. PE cohort studies are particularly efficient for rarely used drugs, or when there are multiple outcomes from a single exposure. The cohort study design then allows for establishing a temporal relationship between the exposure and the outcome because drug use precedes the onset of the outcome. In cohort studies, selection bias is generally less likely to occur than in case-control designs. Selection bias is less likely to occur, for example, when the drug use profile of the sample study base is similar to that of subjects enrolled in the study.

The disadvantages of cohort studies include the need for large number of subjects (unless the outcome is common, cohort studies are potentially uninformative for rare outcomes – especially those which require a long observation period); they are generally more expensive than other designs, particularly if active data collection is needed. In addition, they are vulnerable to bias if a high number of participants are lost during the follow-up (high drop-out rate). Finally, for some retrospective cohort studies, information about confounding factors might be limited or unavailable. With retrospective cohort studies, for example, the study population is frequently dynamic because the amount of time during which a subject is observed varies from subject to subject. PE retrospective cohort studies are frequently performed with information from automated databases with reimbursement or health care information (e.g. Veterans Administration database, Saskatchewan database, PHARMO database).

A special bias exists with cohort studies, the immortal time bias, which can occur when, as a result of the exposure definition, a subject, cannot incur the outcome event of interest during the follow up. For example, if an exposure is defined as the first prescription of drug ‘A’, and the outcome is death, the period of time from the calendar date to the first prescription where the outcome does not occur is the immortal time bias (red oval in Fig. 12.4). If during that period, the outcome occurs (e.g. death), then the subject won’t be classified as part of the study group, rather,

that subject will be part of the control group. This type of bias was described in the seventies when investigators compared the survival time of individuals receiving a heart transplant (study group) vs. those who were candidates but did not receive the transplant (control group). They found longer survival in the study group [41, 42]. A reanalysis of data demonstrated that there was a waiting time from diagnosis of cardiac disease to the heart transplant, where patients were ‘immortal’ because if they died before the heart transplant, they were part of the control group [43]. This concept was adopted in pharmacoepidemiology research and since then, many published studies have been described with this type of bias [44–49]. (Fig. 12.4).

As prior mentioned, the consequence of this immortal time bias is the spurious appearance of a better outcome in the study group such as lower death rates. In other words, there is an underestimation of person-time without a drug treatment leading to an overestimation of a treatment effect [50]. One of the techniques to avoid immortal time bias is time-dependent drug exposure analysis [51].

Hybrid Studies

In PE research, hybrid designs are commonly used to study drug effects and drug safety. These designs combine several standard epidemiologic designs with resulting increased efficiency. In these studies, cases are selected on the basis of the outcome; and, drug use is compared with the drug use of several different types of comparison groups (see Table 12.2). These designs include: nested-case control studies, case-cohort design, case-crossover design, case-time-control design, and self-controlled case series [52].

Nested Case-Control Studies

Recall that a nested case-control study refers to a case-control study which is nested in a cohort study or RCT. In PE, nested case-control studies, a defined population is followed for a period of time until a number of incident cases of a

Table 12.2 A description of some hybrid postmarketing study designs

| Design | Control group |
|-----------------------------|--|
| Nested case-control | Subjects in the same cohort, without the case condition |
| Case-cohort | A sample of the cohort at baseline (may include later cases) |
| Case-crossover | Cases, at an earlier time period |
| Case-time-control | Cases, at an earlier time period but time effect is considered |
| Self-controlled case series | Cases are their own controls |

disease or an adverse drug reaction is identified. If the case-control study is nested in a cohort with prospectively gathered data on drug use, recall bias is no longer a problem. In PE as in other clinical research, nested case-control studies are used when the outcome is rare or the outcome has long induction time and latency. Frequently, this type of design is used when there is the need to use stored biological samples and additional information on drug use and confounders are needed. When it is inefficient to collect the aforementioned data for the complete cohort, (a common occurrence) a nested case-control study is desirable.

Case-Cohort Studies

Recall that this type of study is similar to a nested case-control design, except the exposure and covariate information is collected from all cases, whereas controls are a random representative sample selected from the original cohort [53, 54]. Case-cohort studies are recommended in the presence of rare outcomes or when the outcome has a long induction time and latency, but especially when the exposure is rare (if the exposure in controls is common, a case-control study is preferable). In PE case-cohort studies, the proportion of drug use in cases is compared to the proportion of drug use in the reference cohort (which may include cases). An example of the use of this design was to evaluate the association between immunosuppressive therapy (cyclophosphamide, azathioprine and methotrexate) and haematological changes in lung cancer, in patients with systemic lupus erythematosus (this was based on a lupus erythematosus cohort from centers in North America, Europe and Asia, where exposure and covariate information for all cases was collected). Cases were defined as SLE, with invasive cancers discovered at each center after entry into the lupus cohort; and, the index time for each risk set was the date of the case's cancer occurrence. Controls were obtained from a random sample of the cohort (10 % of the full cohort) and they represented cancer free patients up to the index time. Authors found that immunosuppressive therapy may contribute to an increased risk of hematological malignancies [55].

Case-Crossover Studies

Recall that the case-crossover design was proposed by Maclure, and in this design only cases that have experienced an outcome are considered. In that way, each case contributes one case window and one or more control windows at various time periods, and for the same patient. In other words, control subjects are the same as cases, just at an earlier time, so cases serve as own controls (see Chap. 4) [56, 57]. This type of

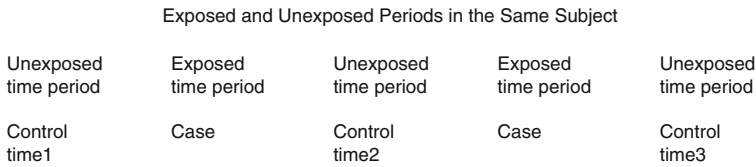


Fig. 12.5 Case-crossover design

design is particularly useful when a disease does not vary over time and when exposures are transient, brief and acute [56, 58]. The case-crossover design contributes to the elimination of control selection bias and avoids difficulties in selecting and enrolling controls. However, case crossover designs are not suitable for studying chronic conditions [59]. In PE, case-crossover studies might compare the odds of drug use at a time close to onset of a medical condition compared with odds at an earlier time (Fig. 12.5).

Case-crossover designs have been used to assess the acute risks of vehicular accidents associated with the use of benzodiazepines [60] and also to study changes in medication use associated with epilepsy-related hospitalization. In this latter study, Handoko et al. used the PHARMO database from 1998 to 2002. For each patient, changes in medication in a 28-day window before hospitalization, were compared with changes in four earlier 28-day windows; and, pattern of drug use, dosages, and interaction with medications were analyzed. Investigators found that patients starting with three or more new non antiepileptic drugs had a five times higher risk of epilepsy-related hospitalization [61]. In case-crossover designs, conditional logistic regression analysis is classically used to assess the association between event and exposure [62, 63].

Case-Time-Control Studies

The case-time control design was proposed by Suissa [64] to control for confounding by indication. In this design subjects from a conventional case-control design are used as their own controls. This design is an extension of the case-crossover design but it takes into account the time effect, particularly the variation in the drug use over time. This type of design is recommended when an exposure varies over time and when there are two or more points measured at different times, and it is expected to be able to separate the drug effect from the disease severity. Something to consider is that the same precautions used in case-crossover designs should also be taken into account in case-time-control designs, and the exposures of control subjects must be measured at the same points in calendar time as their cases.

Self-Controlled Case Series

In this design, case series are used to study the temporal association between a time-varying exposure and an adverse event (acute event) using data on cases only [52]. In this case, the effect of exposure is transitory and limited to a certain risk period, and then it returns to baseline. For example, if there is interest in studying thrombocytopenia associated with a vaccine administered at specific age, the risk period is limited to that age period. The assumptions of self-controlled case series include: the occurrence of an event must not alter the probability of subsequent exposure, the occurrence of the event must not affect the observation period and recurrent events should be independent or if they are not but the event is rare, only the first event can be used. The advantage of this design is that cases are their own controls which imply an adjustment of confounders (e.g. socioeconomic factors). In addition, it reduces the effort and cost of data collection [52].

Biases in PE

In PE, a special type of bias (confounding by indication) occurs when those subjects who receive the drug have an inherently different prognosis from those who do not receive the drug. If the indication for treatment is an independent risk factor for the study outcome, the association of this indication with the prescribed drug may cause confounding by indication. A variant of confounding by indication (confounding by severity) may occur if a drug is prescribed selectively to patients with specific disease severity profiles [65]. Some hybrid designs and statistical techniques have been proposed to control for confounding by indication. In terms of statistical techniques, it has been proposed that one use multivariable model risk adjustment, propensity score risk adjustment, propensity-based matching and instrumental variable analysis to control for confounding by indication. Multivariable model risk adjustment is a conventional modeling approach that incorporates all known confounders into the model. Controlling for those covariates produces a risk-adjusted treatment effect and removes overt bias due to those factors [66].

Propensity score risk adjustment is a technique used to adjust for nonrandom treatment assignment. It is a conditional probability of assignment to a particular treatment given a set of observed patient-level characteristics [67, 68]. In this technique, a score is developed for each subject based on a prediction equation and the subject's value of each variable is included in the prediction equation [69], and it is a scalar summary of all observed confounders. Within propensity score strata, covariates in treated and non-treated groups are similarly distributed, so the stratification using propensity score strata is claimed to remove more than 90 % of the overt bias due to the covariates used to estimate the score [70, 71]. Unknown biases can be partially removed only if they are correlated with covariates already measured and included in the model to compute the score [72–74].

Instrumental variable analysis is an econometric method used to remove the effects of hidden bias in observational studies [75, 76]. Instrumental variables are highly correlated with treatment and they do not independently affect the outcome. Therefore, they are not associated with patient health status. Instrumental variable analysis compared groups of patients that differ in likelihood of receiving a drug [77].

Summary

In pharmacoepidemiology research as is true for traditional research, the selection of an appropriate study design requires the consideration of various factors such as the frequency of the exposure and outcome, and the population under study. Investigators frequently need to weigh the choice of a study design with the quality of information collected along with its associated costs. In fact, new pharmacoepidemiologic designs are being developed to improve study efficiency.

Pharmacoepidemiology is not a new discipline, but it is currently recognized as one of the most challenging and growing areas in research, and many techniques and methods are being tested to confront those challenges. Pharmacovigilance (See Chap. 5) as a part of pharmacoepidemiology is of great interest for decision makers, researchers, providers, manufacturers and the public, because of concerns about drug safety. Therefore, we should expect in the future, the development of new methods to assess the risk/benefit ratios of medications.

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