Chapter 11

Pharmacoepidemiological Approaches for Population-Based Hypothesis Testing

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Abstract

Pharmacoepidemiology aims to study the use and both the adverse and beneficial effects of drugs and vaccines in the population after market authorization. The efficacy of drugs is assessed in experimental studies before a drug is allowed on the market in a limited and usually selected group of patients. Therefore, after market authorization the focus is on serious and adverse effects in large groups of patients in daily clinical practice. Observational drug research is needed to establish and measure these effects. Observational research faces several challenges to minimize the chance of bias, including confounding by indication, which is caused by selective prescribing of drugs to certain patient groups. A comparison between treated and untreated subjects or between different drug regimens may be biased due to uneven distribution of risk factors for the outcome of interest. Important progress has been made during the past decade in controlling confounding by design and analysis in observational studies. The increasing accessibility of large electronic health record databases has fuelled various international initiatives to analyze multiple databases across countries using common protocols and common data models. Extensive sensitivity analysis across multiple designs, databases, and analytical techniques has provided more insight into causes of variation in results across studies and increases the confidence in findings of observational studies. Transparency of observational drug research through public registration of protocols and detailed reporting of methods should improve reproducibility and thereby reliability of pharmacoepidemiological studies.

Key words Confounding by indication, Immortal time bias, Study design, Type A adverse events, Type B adverse events, Channeling, Multi-database common protocol studies, ENCePP

1 Introduction

The discipline of Pharmacoepidemiology focusses on the study of the use and effects of drugs and vaccines in the population after they have been allowed on the market [1]. Before a drug is allowed on the market efficacy has to be demonstrated in experimental research. Once the drug is allowed on the market and the drug may be prescribed in daily practice studies will often be observational. This type of study is necessary because when drugs are allowed on the market efficacy is established by, at most, a few

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thousand patients. This is usually a selected group of patients avoiding high risk patient groups for example followed for a usually limited duration of treatment, often shorter than the time that patients use drugs in daily clinical practice—also in a controlled environment not necessarily mimicking real world use (e.g., drug utilization and adherence practices). At the time of launch of a drug it is known that the drug does what it is intended for, for example, lowering blood pressure, lowering of serum cholesterol, or reduction of symptoms in asthma. Furthermore, a number of side effects that occur fairly often and can be explained on the basis of the pharmacological effects of the drug, known as Type A side effects, will also have been established [2]. Examples of type A side effects are gastrointestinal bleeding due to aspirin use, or a dry mouth by antidepressant use. However, other effects, particularly rare unpredictable and potentially severe so-called type B side effects that occur in only 1 in 1000 or even 10,000 patients act, will not be known at that time. Examples of type-B side effects are allergic reactions, liver damage, and bone marrow suppression. Type-B side effects are reactions of the patient to the drug and can be detected, for instance, by means of spontaneous reporting systems such as those present in many countries and collected worldwide by the WHO Monitoring center in Uppsala. Spontaneous reporting of adverse drug reactions by patients and healthcare providers is important for generating a safety signal and hypotheses about a potential association between a drug and an adverse event (for more details see chapter on signal detection). Subsequently, pharmacoepidemiological studies are utilized for testing these hypotheses and this introduces a first important goal of a pharmacoepidemiological study, e.g., the quantification of the risk of type-B side effects in large numbers of patients. Study of drug effects in patients who have not been studied in pre-approval studies is an important second goal of pharmacoepidemiological studies. Patients in daily practice often differ from patients in the pre-registration studies. Women, elderly, children, patients with concomitant diseases, and/or medication use are often excluded from this type of research in order to obtain a valid estimate of the potential effect of the drug. However, the translation of the results of these studies to patients in everyday practice is getting more difficult. Consideration and development of a strategy for ongoing surveillance and study of a medicinal product after marketing approval is called Risk Management and this is discussed in detail in Chap. 12.

2 Observational Drug Research

Typical for observational drug research is that the choice of treatment is made by the physician and the patient in daily practice, and not by a researcher assigning patients (at random) to one or the

other drug or no drug (the term "drug" is being used throughout this chapter in the widest sense to represent any medicinal product). The investigator is in the first case, as it were, on the sidelines and observes the use of drugs in relation to their effects. In the latter case, in which the choice for pharmacotherapeutic intervention is determined by the investigator, one speaks of experimental drug research. The strength of the experimental drug trials in which patients on the basis of chance alone, are assigned to a treatment group, is that the treatment groups are similar with respect to reasons for the outcome of treatment to be studied. This leads to an overall equal distribution of risk factors, both observed and non-observed factors, and thus more or less equal prognosis of treatment groups that are compared, allows a reliable estimation of treatment effects—as the impact of these risk factors can be excluded and focus is solely on the differential impact of treatments to one another. Observational studies, where no randomization has been conducted, need to consider not only the impact of chance (as for any study) but also bias. The impact of chance can be addressed by quantifying the variability in effect estimates (e.g., confidence intervals). The purpose of sample size calculation in observational studies with large healthcare databases is somewhat different than for experimental studies and observational studies that involve direct data collection from subjects. When utilizing existing data sample size is already known and the purpose is to assess whether the study has sufficient power to detect an association of a certain size, whereas for studies that involve primary data collection the purpose is to calculate the number of subjects on which data has to be collected to assure sufficient power to detect the association of interest.

3 Confounding by Indication

Sometimes unintended and intended effects of a drug counteract against each other and the observational study of such effects is complex. This can be illustrated by a study by Bruce Psaty on the effect of antihypertensive drugs on the risk of myocardial infarction [3]. At the time of publication, only a few classes of blood pressure lowering drugs were known to lower the risk of cardiovascular disease. Calcium antagonists were known to lower blood pressure, however, while the lowering of blood pressure was expected to reduce the risk of cardiovascular treatment, the direct effect on the risk of cardiovascular disease, the ultimate goal of the treatment, had not been established. The calcium channel blockers primarily used in this study were short-acting. Previous research had shown that short-acting calcium channel blockers due to a rapid fall in blood pressure increased heart rate, and this could cause what is an

unintended effect that may increase the risk of myocardial infarction [4].

Psaty in his study among people with high blood pressure compared the use of different classes of blood pressure lowering drugs among people who had suffered a myocardial infarction and those who had not experienced a myocardial infarcion—a so-called case-control study. This study revealed that calcium channel blockers were used more often by patients who had experienced a myocardial infarction than patients who had experienced no myocardial infarction. A major criticism of this study was the examination of an outcome that was related to the reason for prescribing these drugs. An antihypertensive drug is indeed prescribed to reduce the risk of a myocardial infarction. Calcium antagonists are not only prescribed to lower blood pressure but also to treat the heart condition angina (caused by coronary disease and characterized by attacks of chest pain on exertion). Patients taking calcium antagonists are therefore more likely to have heart disease than those patients who receive, for example, a thiazide diuretic which are used mainly to reduce blood pressure. An increased risk of myocardial infarction among users of calcium channel blockers compared with users of thiazide diuretics is therefore to be expected due to its increased presence of angina among users of calcium channel blockers. This does not necessarily have to be caused by the drug, but may also be due to the type of patient the drug is prescribed. As stated by John Urquhart: "Did the product bring the problem to the patient, or the patient's did bring the problem to the product" [5]. This phenomenon of selective prescribing is a classic problem in pharmacoepidemiology and is also referred to as "channeling," and can be the cause of a major source of bias in observational drug, also known as confounding by indication [6–8]. Confounding or distortion of results of pharmacoepidemiological study occurs when a factor is present (e.g., the indication angina) which is both a determinant of drug use (calcium antagonists) as a risk factor for the outcome (myocardial infarction) (Fig. 1).

In order to avoid and correct confounding a variety of methods were used. The main method was as simple as it is effective, i.e., all patients who had a cardiac and/or vascular disease (including patients with angina) were excluded from this study. Subsequently

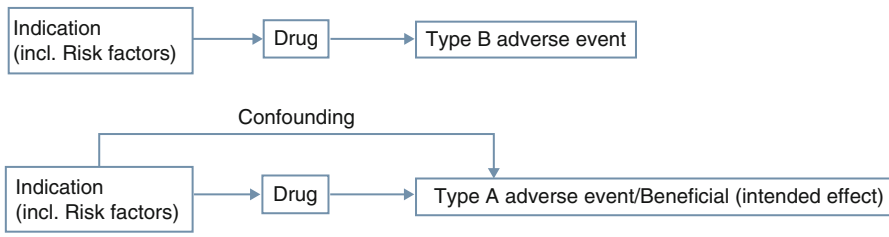

Fig. 1 Relation between indication, confounding, and type of event in pharmacoepidemiological studies

users of calcium channel blockers were compared with users of beta-blockers which are also indicated for the treatment of angina pectoris and thus comprise a comparable group of patients. The increased risk of a myocardial infarction remained present even after multiple methods to control for confounding such as restriction, matching, and multivariable regression were applied. An important strength of this study was the quality of data collection which involved secondary use of routine healthcare data (claims) and primary data collection (chart review and telephone interview of patients) allowing to control for many important risk factors (including lifestyle factors) of myocardial infarction. There are several published observational studies, some confirming, some contradicting this finding, but none with the same methodological quality as the original study [9]. Experimental studies have subsequently shown that certain types of long-acting calcium channel blockers reduce the risk of cardiovascular disease [10].

4 Inconsistency in Observational Drug Effect Studies

It is not uncommon that observational drug studies contradict each other such as the link between bisphosphonates to treat osteoporosis and the risk of esophageal cancer [11–13], and the use of statins, a group of cholesterol-lowering drugs, and fracture risk [14–16].

What these examples have in common is that individual studies often were not only carried out in different databases (for a discussion on longitudinal observational databases suitable for pharmacoepidemiology studies, *see* Chap. 7), they also differed in the methodology applied. This makes comparison and interpretation of results from observational studies very difficult, especially since the reporting of methods sometimes lacks sufficient detail for a proper comparison of studies. Following the STROBE guidelines for reporting observational epidemiological studies and the specific extension of the RECORD statement for reporting studies with routinely collected health data need to make improvement in this respect [17, 18]. When the same dataset is analyzed by various researchers to answer the same question it becomes clear what the impact if methodological choices on the results is. Tjeerd van Staa, for example, studied the link between the use of statins and the risk of a fracture in a large database of prescribing data and diagnoses of British GPs [14]. No association was found while a researcher from Switzerland in the same database did find a link, specifically a protective effect [15]. de Vries, van Staa, and others subsequently demonstrated that different methodological choices such as selection of patient populations, the definitions of drug exposure, and way of age adjustment could explain the apparent discrepancy in study results and in the end concluded there was insufficient evidence for a protective effect of statins on the risk of a fracture

[16]. Another major difference was that the initial investigation that found a large protective effect of statins was distorted by what is termed "immortal time bias" [19]. This form of bias is a major threat to the validity of observational drug studies. In a review of 20 observational studies that reported unlikely large beneficial effects of drugs, Samy Suissa showed that all these studies were to a greater or lesser extent distorted by immortal time bias [19]. This type of distortion is easily prevented by proper classification of exposure and selection of patients, although the complexity of databases and their data inclusion criteria, and drug-specific exposure variation make such classification challenging and careful study design an essential element of a pharmacoepidemiological study.

5 Observational Versus Experimental Studies

In addition to examples of conflicting results between observational drug studies, there are also differences in results between observational and experimental studies. For example, there are several observational studies on the effects of drug treatment of hypertension in daily practice and the risk of cardiovascular disease. Many of these studies have shown an increased risk which is curious because the effectiveness of this treatment in reducing the risk of cardiovascular diseases such as myocardial infarction and stroke is clearly demonstrated in randomized clinical trials [20]. Confounding by indication in observational studies is an important explanation for this discrepancy [21]. Persons who are being treated with blood pressure lowering drugs get these agents because they have an indication for the treatment, namely, an increased blood pressure, while individuals who do not get blood pressure-lowering drugs are also very likely not to have elevated blood pressure. Because high blood pressure is a risk factor for the development of cardiovascular disease, people who use an antihypertensive drug at this stage have a higher risk of cardiovascular disease compared to people who do not use antihypertensive drugs. Such a comparison is therefore not valid and has resulted in a number of observational studies with the misleading conclusion that drug treatment of hypertension in daily practice is not beneficial, or even harmful.

By selecting a similar group of individuals who have elevated blood pressure and also had additional cardiovascular risk factors, known as candidates for treatment, we were able to show that treatment with antihypertensive drugs in Dutch daily practice reduced the relative risk of stroke to the same extent as in the randomized trials [22].

Another example of a conflicting result from experimental and observational studies is that of the effect of oestrogen therapy in postmenopausal women at risk of coronary heart disease. In observational studies postmenopausal women who used estrogen

therapy compared with women who did not do so had a 35–50% lower risk of coronary heart disease was observed [23].

However, a few years later, the results from randomized trials on the effect of estrogen therapy on the risk of coronary heart disease revealed an increased risk during the first years of use compared to the women who had received a placebo [24]. An important difference between the observational studies and the trials was that in the trials, the women were followed from the time they started the estrogen therapy, while in the observational studies, the women were often tracked from a moment when they had already used estrogen therapy for a long time. These women were already beyond the time of an increased risk of coronary heart diseases such as was observed in the trials and were within a period of treatment in which the risk was lower. From a reanalysis of the observational studies in which the users of estrogen therapy were followed from the start of their therapy, the results proved to be similar to as seen in the trials, an increased risk of coronary heart disease during the first years of use and therefore consistent with the experimental studies [25].

Experimental and observational research are complementary with experimental research needed for the evaluation of the intended effects of interventions, while observational research is needed for detecting and explaining side effects that are unexplainable and cannot be predicted [26]. Unexplainable and unpredictable are important additional considerations because if a side effect cannot be predicted, a physician will not be able to consider patient characteristics when prescribing a drug. The indication for treatment is therefore not related to the study outcome, and therefore confounding by indication can be excluded. This dichotomy is an important basis for the added value of both types of research and a warning for the interpretation of observational research on Type A side effects and intended effects of drugs. Nonetheless, there are also exceptions where observational studies may lead to a valid estimate of these latter drug effects. Examples are for instance when multiple drugs are used for the same indication and the relative effectiveness can be estimated, or when the indication population that is untreated can be identified ("candidates for treatment") and accurate and complete information on potential confounding factors is available to assess and control for confounding.

6 Improving Consistency in Observational Drug Effect Studies

Results from observational drug studies are only useful for weighing benefits and risks of medicines if the results from these studies are valid. How can the reliability and consistency of observational drug studies be improved?

This question was one of the main drivers of the European PROTECT project coordinated by the EMA, the European drug registration authority. The project was funded by the European Innovative Medicines Initiative (IMI), bringing together public and private partners. Within the PROTECT project the impact of methodological choices on results of observational drug research was studied [24]. Based on a common study protocol, data from general practitioners, pharmacists, hospitals, and more than 20 million patients from the Netherlands, the United Kingdom, Spain, and Denmark were analyzed. All protocols were recorded in the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) register of studies before the analysis of the data. The results from the individual databases were unblinded only after all the centers had completed the analyses according to the protocol. In this manner, the risk of centers analysts being biased by knowledge of each other's results is minimized. Any changes to the protocol for reasons of clarification were also documented and recorded in the ENCePP register. An important aspect of the approach was that the impact of different methodological choices on the results of the study was studied within one study protocol. One protocol thus comprised several studies involving variations in the design, definition of drug exposure, the definition of outcome, and methods to correct for confounding. Five adverse events were chosen and all were examined prior to study initiation and considered relevant with respect to impact for individual patients and public health, and also included as they had led to regulatory decisions such as withdrawal of a drug from the market, restriction of the indication, or the inclusion of warnings in the leaflet. Further criteria were that a series of methodological issues could be studied. For example, acute events were chosen that could be measured relatively easy in a health care database such as myocardial infarction and hip fracture, acute events that are difficult to measure, such as liver damage, and suicide, but also a long-term outcome cancer. These events were examined for association with up to six different drug groups. It is important that knowledge of the biological mechanisms that underlie the effects of drugs is taken into account in the design and conduct of epidemiological studies. For instance to study cancer in relation to the use of calcium channel blockers cumulative exposure was considered over a long term, whereas with benzodiazepines use at the time of hip fracture was a focus.

Different types of study designs have their strengths and weaknesses (*see* Table 1). An important advantage of the case cross-over and self-controlled case series with respect to the case-control and cohort approach is that in the first two designs individuals are compared with themselves at different times (with a focus on comparing risk within patients of an outcome when exposed to a drug to times when the same patients were unexposed). A big

Table 1
Main study designs in pharmacoepidemiology

	Cohort	Case-control	Case-cross-over	Self-controlled case-series
Strengths	– Estimation of absolute risk...	– Efficient when primary data collection involved...	– Control for unmeasured confounding...	– Control for unmeasured confounding – Efficient (more power with fewer subjects compared to cohort)...
Weaknesses	– Analysis of time-dependent exposure and control time-varying confounding complex – Inefficient when primary data collection involved	– Sometimes difficult to select appropriate controls	– Multiple assumptions needed for valid estimation (e.g., acute transient events and variation in exposure)	– Multiple assumptions needed for valid estimation (e.g., acute transient events and variation in exposure)

advantage of this approach is that risk factors that do not change over time, and factors that are not measured, cannot have any influence on the association between drug use and the adverse effect. Factors that do change over time can however distort the relationship between a drug and adverse event. These so-called case-only studies are therefore primarily only applicable to acute events that are of a transient nature. If a link between the use of a drug and a adverse effect is found consistently in different countries, with a range of different methods confidence in and usefulness of results of observational drug investigations increases. In the PROTECT project, the increased risk of hip fracture associated with antidepressants and benzodiazepines was consistently found in three different databases from the Netherlands, United Kingdom, and Spain with four different study designs and different ways of correction for confounding [24, 27–30] (Figs. 2 and 3). The association between antibiotics and increased risk of acute liver damage, the absence of an association between long-acting beta2-agonists in the treatment of respiratory disease, and the risk of myocardial infarction was found consistently in different databases with different study designs. The risk of antiepileptic drugs on suicide was despite following the same common study protocol inconsistent in the United Kingdom and Denmark. Suicidality is a challenging outcome to study in observational databases and discrepant findings are reason to further explore explanations for these

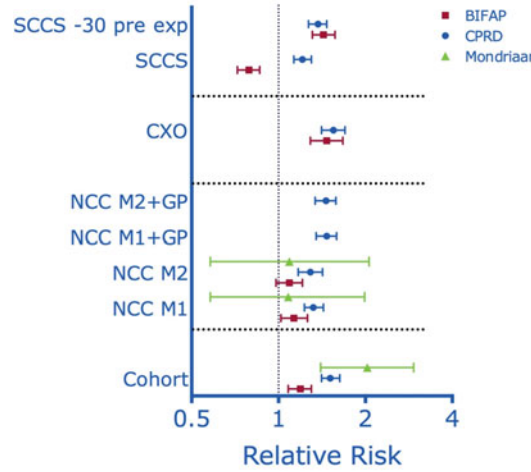

Fig. 2 Benzodiazepines and the risk of hip fracture. Impact of study design, database, and control for confounding (different matching strategies in case-control study). *SCCS* self-controlled case series, *CXO* case cross-over, *NCC* nested case-control, *M1* simple matching algorithm including sex, age (±2 years) and follow-up time, *M2* Euclidean distance matching algorithm including sex, age (±2 years) and follow-up time, *GP* general practice included as matching factor

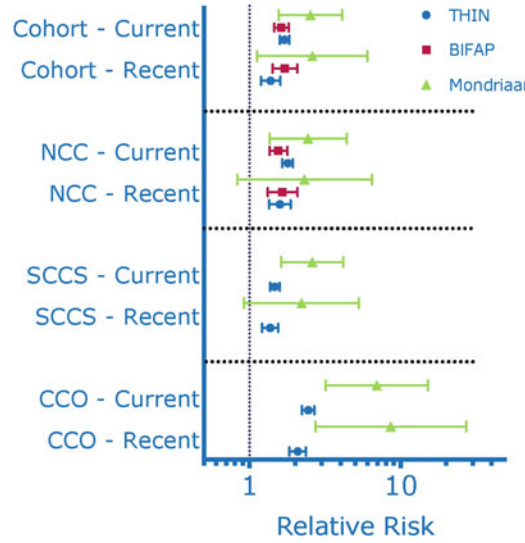

Fig. 3 Antidepressants and the risk of hip fracture. Impact of study design and database. *SCCS* self-controlled case series, *CXO* case cross-over, *NCC* nested case-control

differences. However, the results are currently not directly applicable to daily practice. Reuse of The PROTECT network of researchers and datasets can allow exploration of new safety signals in the future, and the capability to quantify associations [31]. The scope

and diversity of the populations across the PROTECT network also makes it possible to further examine specific products, rare disorders, and subgroups of patients.

7 Methods to Control for Confounding

As explained in the introduction of this chapter, confounding is a major threat to the validity of observational studies. During recent decades, the approaches to control for confounding have evolved greatly. A distinction can be made between methods that aim to correct for observed confounders, i.e., those that we have measurement of in a database, and methods that aim to correct for unobserved confounders, those that we do not have measurement of. Within the first category of methods, propensity scores are increasingly being applied [32]. The propensity score can be defined as the probability of getting a certain drug treatment which may be different for each patient and depends on the characteristics of the patient such as age, sex, additional diseases, and co-medication. In fact, all features which are considered risk factor for the outcome that is being investigated should be included in the propensity score calculation. The great advantage of this method is that all risk factors are reduced to a single variable, and thus the only confounder to be taken into account. Especially when the outcome is rare this has great advantages because the number of confounding factors which can be corrected for, depends on the number of outcomes/adverse events observed.

In addition to the prevention of unobserved confounding by design (e.g., self-controlled case series and case-cross over designs) the method of instrumental variables has been explored as a way to control for unobserved confounding. An instrumental variable is defined as a variable that is associated with the exposure of interest, but not directly, nor indirectly (e.g., through association with confounders) with the outcome of interest. Randomization in a randomized controlled trial can be considered a perfect instrumental variable. However, in observational studies one has to identify such a variable from the dataset that is available, and usually the conditions for a valid IV are not met [33]. This method is therefore not commonly applied.

Other important initiatives in Europe are the EU ADR alliance and the CARING project on safety of diabetes medications [34, 35]. The Canadian CNODES initiative is similar to that of PROTECT [36]. A joint protocol is executed in parallel in several Canadian provinces with their own data sets, and if results are consistent summarized in one overall effect estimate through a meta-analysis. In the future, results from one network could be more readily and often replicated in other networks so that confidence in results of observational studies can be further increased.

An important US initiative is the FDA Sentinel project in which data from 190M persons is combined through a common data model for the purpose of analyzing drug safety signals [37]. Besides the size of the population and the automated approach of analyzing data, an additional important strength of the program is the validation of various important health outcomes of interest.

Harmonization of data at the level of the least detailed database does not use the value of individual databases with the highest level of detail, although it holds some benefits for rapid query analysis capability. Meta-analysis techniques in which account is taken of this diversity may be able to offer a possible solution. In addition to these aspects of dealing with data from various sources and countries remain important to take existing knowledge of biological mechanisms in the design of observational drug analysis. Modeling as realistic as possible of exposure based on a drug data and biological mechanisms is an important focus of future research.

After the introduction of a new drug, benefits and risks in daily practice should be weighed continually and significant changes detected as soon as possible. Methodologically, it is a big challenge because new drugs especially in the early stages when newly introduced on to the market frequently are prescribed to a limited and selective group of patients. For instance, patients who have not responded to conventional treatments, or have experienced side effects, would be prescribed new drugs with the expectation that they would be more effective or may have fewer side effects. A comparison of patients who are put on the new drug with patients who do well on the standard will often be problematic in observational studies. It is important, therefore, in order to properly map these new users, to determine whether or not a fair comparison is possible with regard to the intended effects, but also the unintended effects. Randomizing patients in the daily practice without too much change to routine health care and minimal exclusions and following these patients through routine data collected from the field may also provide a solution for the study of the effectiveness of drugs in the daily practice [38].

8 Transparency and Independence

The debate between researchers, industry, and medicine authorities around controversies in drug research can be heated, the stakes are often high for each of these different parties. That is precisely why it is important to understand conflicting results and look to explain them.

In addition to applying the best methodology, transparency and independence of scientific observational drug research, it is very important to increase confidence in the results of observational research. Clear separation of the role of the sponsor of a study and

the executive researcher with freedom to publish must be guaranteed regardless of the outcome of a study. The recording of the protocol before the study is carried out with the public having access to such protocols.

These measures are now a precondition for observational drug trials that the EMA may impose on drug manufacturers and is enshrined in the so-called Code of Conduct ENCePP [39]. There are now more than 150 centers that have joined this European network. It should be emphasized that the purpose of registering protocols of observational drug research is greater transparency and that the methodological quality and reliability of such studies are not guaranteed. To achieve this goal, it is especially important to promote and follow guidelines for the proper execution of pharmaco-epidemiological studies and to all parties concerned to improve education in pharmacoepidemiology. An important prerequisite for reliable pharmaco-epidemiological study in addition to the correct application of the optimal methodology, is a solid infrastructure in which access to valid data on drug use, risk factors, and outcomes such as side effects is well organized.

9 Conclusion

Different methods of approaching a problem can lead to new insights and these different methods of approaching different sources of data should already be considered and articulated (and appropriate registrations obtained if necessary) from the beginning, actually at the study design stage. In this way, the time-consuming process of years in which one study is followed serially by another should be avoided as far as possible, so situations where the field must explain why similar studies with years in between have contradictory results could be reduced significantly, perhaps to less than a year—supporting public health and also increasing credibility of the field by more capability of discovering and understanding across study discrepancy. A thorough knowledge of pharmacoepidemiological methods and understanding the context of the use of drugs ensures the value of observational drug research, and the added contribution that such work adds to that of experimental drug research. Transparency of observational drug research through public registration of protocols and detailed reporting of methods should improve reproducibility and thereby reliability of these Pharmacoepidemiological studies further reinforcing their contributory role in combination with experimental drug research in better understanding the risks of marketed medicinal products.

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