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Summary

Pharmacoepidemiology is the study of interactions between drugs and human populations, investigating, in real conditions of life, benefits, risks and use of drugs. Pharmacoepidemiology applies to drugs and their pharmacological evaluations, the different methods also used in epidemiology to assess in real conditions of life, benefits, risks and use of drugs. Pharmacoepidemiologic studies are ad-hoc studies or studies on databases. Specific methods exist to measure drug exposure, as well as indicators of compliance and misuse of drugs. Various designs for descriptive and explanatory studies exist, in a context in which a growing proportion of studies are carried out using medico-administrative data. The limits traditionally affecting the study designs are modified in this context, almost any design selected for the conduct of a study from these databases then deriving from a cohort in whom the information has been recorded prospectively and exhaustively.

KEYWORDS

Methods; Pharmacoepidemiology; Phase IV; Databases; Drug exposure; Study designs

Abbreviations

ADRs : adverse drug reactions
CPRD : clinical practice research datalink
DDD : defined daily dose
DSI : doctor shopping indicator
DSQ : doctor shopping quantity
EDSSM : enquête décennale sur la santé et les soins médicaux
EGB : *échantillon généraliste de bénéficaires*
IQUARE study : *Impact d'une démarche QUAlité sur l'évolution des pratiques et le déclin fonctionnel des résidents en Etablissement d'Hébergement pour Personnes Agées Dépendantes*
KML method : K-averages for longitudinal data method
MPR : medication possession ratio
NH : nursing home
NotS : spontaneous reports

OPPIDUM: *observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*

SCCS : self-controlled case series

SNIIRAM : *système national d'information inter-régimes de l'Assurance maladie*

WHO : World health organization

Introduction

Pharmacoepidemiology is a discipline of pharmacology that uses principles of epidemiology to study the use and effects of drugs (beneficial and adverse effects) in a large population setting and in real conditions. Thus, pharmacoepidemiology concerns the drug prescription in phase IV, i.e. after drug approval, far from the experimental limitations of clinical trials. Unlike clinical trials, pharmacoepidemiology starts from the reality of clinical practice to describe and explain the use of drugs [1].

Pharmacoepidemiology has come a long way since the mid-1960s when first drug utilization studies provided descriptive information on how drugs where used [2–5]. In the 1970s, pharmacoepidemiology was mainly developed to study and quantify risk of adverse drug reactions (ADRs) because of the identification of various major ADRs like clear cell adenocarcinoma of the cervix and genital malformations due to in utero exposure to diethylstilboestrol [6]. In the past 20 years, advances in both epidemiology and biostatistics have allowed for novel pharmacoepidemiological methods to control potential biases. For example, optimal methods of control selection have allowed for conducting more valid case-control studies [7]. Statistical methods have been developed in order to control the time-dependent nature of exposure to drugs that may have otherwise biased the results of cohort studies [8,9]. Use of propensity score defined by the conditional probability of being treated given different covariates, can be used to balance the covariates in two groups not randomized in historical cohort studies [10]. Finally, the case-crossover design helps to explore the association between transient drug exposures and acute events, like for ADRs related to vaccines [11].

Objectives and context for conducting pharmacoepidemiology studies

Descriptive studies vs. etiologic studies

Pharmacoepidemiology applies to drugs and their pharmacological evaluations, the different methods also used in epidemiology. Its methodology is therefore observational and, thus, is usually opposed to the experimental method (as defined by Claude Bernard) used in clinical trials [12]. Pharmacoepidemiology thus develops two complementary approaches.

The *descriptive (non-comparative) approach* observes phenomena retrospectively, prospectively or transversally. Descriptive studies are performed to study the modalities of the

exposure and the characteristics of the exposed and unexposed subjects. It allows quantifying the use of drugs, as for example the use of antibiotics at a national level [13]. Descriptive studies are also useful to explore wether the use of drugs is consistent with the conditions under which their benefits-harms balance was found to be favourable. Under this approach, we described the consumption of antibiotics with a high risk of antibioresistance defined as amoxicillin + clavulanic acid, third-generation cephalosporins and fluoroquinolones [14]. It is also possible to determine in what extent the treated population is within or away from the population evaluated in clinical trials [15].

The *etiologic (comparative or analytic) approach* investigates putative associations between exposure to one (or more) drug(s) and occurrence of effects, adverse or beneficial. Numbers of studies quantified risk of various adverse drug reactions (ADRs). We can cite birth defects related to isotretinoin [16], or risk of pulmonary arterial hypertension with amphetamine appetite-suppressant drugs [17]. This approach investigates also associations between exposure to a drug and a beneficial effect. Studies of effectiveness of beta-blockers in preventing mortality in patients with acute myocardial infarction and incident coronary events were performed [18,19]. Etiologic studies can also be used to identify the determinants of treatment response, occurrence of ADRs or their seriousness, or of the development of good or bad use behaviours, including misuse and diversion. The major difficulty of this approach involves several confounding factors that can influence the measurement and comparison [20].

Ad-hoc studies vs. studies on databases

Pharmacoepidemiology studies can be performed by collecting specific information. They are called *ad-hoc studies*, since no ongoing system of information is available to perform such studies. They are descriptive or etiologic studies. For example, an *ad-hoc* study can be performed by a systematically approach of physicians who are likely to prescribe a specific drug. To evaluate a new drug indicated in multiple sclerosis, one could solicit via mail the cooperation of all neurologists of a geographic area. Ad-hoc studies can also be used to perform etiologic study. For example, we previously evaluated mortality related to antipsychotic drug use in elderly patients with Parkinson disease in nursing home (NH) [21]. Data were provided by the IQUARE study (*Impact d'une démarche QUAlité sur l'évolution des pratiques et le déclin fonctionnel des résidents en Etablissement d'Hébergement pour Personnes Agées Dépendantes*), a non-randomized controlled multicentric study. Data were collected at baseline and after an 18-month interval. Information

about residents' characteristics and prescriptions was recorded by the coordinating physician or the coordinating nurse of each NH through direct completion of questionnaires on-line on a website developed specifically for the study. In addition, the coordinating physician sent to the research team all drug prescriptions for each resident participating in the study.

As in North American and other European countries, French medico-administrative databases are increasingly used for pharmacoepidemiology studies [22]. For this purpose, their accessibility to researchers is regularly improved. These databases offer preregistered data and can be used for dedicated studies or combined with other data sources. French health insurance databases are organized since 2003 into a huge digital data warehouse, the "*système national d'information inter-régimes de l'Assurance maladie*" (SNIIR-AM). It covers the entire French population (65 million inhabitants). In order to facilitate studies on more frequent conditions, a random sample of 1/97th of national health system beneficiaries has been built since 2005, called the "*échantillon généraliste de bénéficiaires*" (EGB). French health insurance databases include demographic, out-hospital reimbursement (including drug dispensing), medical (costly long- term diseases, occupational diseases, sick-leaves…), and in-hospital data. All these data are prospectively recorded, individualized, made anonymous and linkable. Consequently, the SNIIR-AM is a very useful data source for pharmacoepidemiological studies, particularly for rare events. Unlike SNIIRAM data, EGB data is available on a long-term basis. It is also appropriate for long-term research on more frequent diseases. Indications of drugs prescribed are not recorded within the SNIIRAM databases. Treatment durations are also not recorded and have to be derived from quantity dispensed using pharmacoepidemiological methods for building treatment episodes [23]. Moreover, it should be remembered that claims data refer only to quantity dispensed and reimbursed and that real patient intake always remains unknown (which is also the case with all other data-bases, based on prescription or reimbursement data).

Methods for drug exposure measurement in Pharmacoepidemiology

Principles of drug exposure measurement

Quantitative data on drug use can be used to measure drug exposure. The usefulness of each type of measure depends on the purpose of the study.

For descriptive studies, we can use the number of patients in a population who ingested a specific drug during a defined time frame. Data available are approximations of this, issued from ad-hoc studies (surveys), drugs sales or medico-administrative databases. They are usually expressed in terms of cost (total cost or unit cost) or volume (global or by unit volume sold). Number of tablets, capsules or doses is closer to the number of patients exposed than cost data, which can be influenced by price fluctuations. Number of prescriptions is a measure frequently used. To obtain the number of patients exposed from the number of prescriptions, we must divide it by the average number of prescriptions per patient. Another volume unit is the number of defined daily doses (DDD). The DDD system has been developed by an independent scientific committee assisting the World health organisation (WHO) collaborating centre for drugs statistics methodology in order to measure and compare drug use at an international level [24]. This unit is worldwide used and very useful for comparisons accross countries. Nevertheless, since DDD is based on a theoretical daily dosage, it does not necessarily reflect the recommended or prescribed daily dose.

For etiologic studies, exposure data have to be related to the reasons for the drug use and to health events. Data on morbidity and mortality may be obtained from medico-administrative databases, from registries, from hospital or physician records, and from patient or household surveys. The "*enquête décennale sur la santé et les soins médicaux*" (EDSSM) is a good example of such a survey. This survey is a source of information on health and ambulatory consumption care that has been conducted every 10 years since 1960 [25]. It uses a one-stage probability sampling procedure based on the last population census. The sampling unit is the household (all persons living in each house sampled are included), and the survey covers a 3-month period. All household members are asked to note every medical event, physician consultation, diagnosis as stated by the practitioner, and drug purchase that occurred during the 3-month period. Investigators visit households five times during this period, checking the accuracy of each individual's information. Results of this survey, based on broad representative samples of the French population (> 20,000 inhabitants) with a response rate over 90%, are representative for one year whole, except summer months.

Other methods can be helpful to quantify more precisely drug exposure: for example, time-dependent drug exposures for drugs prescribed for varying time periods [26,27], and drug exposures considered as exposure trajectories according to the KML method (K-averages for longitudinal data) corresponding to a classification of longitudinal data [28].

Rational use of drug must be assessed by taking into account indication of drug, patient

characteristics, drug dosage, concomitant diseases, and concomitant drugs. All this information is generally not available in a single data source.

Specific measures for drug exposure: indicators of compliance and misuse

Specific indicators have been developed to measure compliance and misuse of specific drugs.

Indicators of compliance (adherence and persistence)

Observance concerns mainly chronic treatments. Adherence refers to whether a patient takes a prescribed drug. Persistence indicates if a patient stays on therapy (or time between initiation and discontinuation of the treatment). Increasing use of medico-administrative databases helps to approximate these two indicators. Different types of measures of adherence and persistence are commonly used: the medication possession ratio (MPR), the discontinuation or continuation of the drug (persistence), switching, and medication gaps [29,30]. The most frequently used indicator, the MPR, is defined as the proportion of days' supply obtained during a specific time period or over a period a refill interval. The refill interval is the interval between the first and the last delivery of a drug plus number of days considered as duration of the last box delivered [31]. Discontinuation is defined by gaps between one dispensing drug and a subsequent dispensing, depending on the days' supply of drug and quantity of tablets delivered. Switching refers to a specific time period after dispensing, and is defined as a delivery of a different drug within this period. Medication gaps correspond to the proportion of days without a drug during a specified time interval. It is determined for each refill interval using days' supply information and the duration between refills.

The terminology, definition, and methods to determine adherence and persistence differ greatly in the published literature. The appropriateness and choice of the specific measure employed should be determined by the objective of the study, as well as the relative advantages and limitations of the measures.

Use of the databases has a number of limitations, including the inability to determine if the patient actually consumed the dispensed drug. However, use of medico-administrative databases for studies of adherence and persistence in large populations in a real-life setting is highly advantageous.

Indicators of misuse

Indicators of misuse or drug abuse have been developed in medico-administrative databases in order to identify the relative abuse liability of several psychoactive drugs in real-life setting. One of them is the doctor shopping quantity (DSQ), defined by the quantity obtained by overlapping prescriptions from several prescribers. The doctor shopping indicator (DSI) is calculated by the DSQ divided by the total dispensed quantity and measures the proportion of the drug obtained by doctor shopping among the overall quantity of the drug reimbursed [32]. A signal of abuse by doctor-shopping is considered meaningful when the DSI is superior to 1%. Below this value, one considers that there is no clear signal of abuse. This threshold of 1% is empirical: it is derived from different published studies [32–34], from other national surveys among patients from drug dependence centres [35], and from surveys related to falsified prescriptions by pharmacies [36]. These indicators have been used to describe potential abuse of buprenorphine and other opioids [33,37], but also benzodiazepines [38], tianeptine [34], methylphenidate [39] and narcotic drugs [40]. Doctor shopping behaviour is thought to be one of the principal means of diversion for prescriptions medications and has also been linked to death related to substance disorders in different studies [41,42].

Other approaches can be used to characterize drug misuse in France, as spontaneous reports (NotS) of drug misuse or dependence, and specific surveys like the annual cross-sectional "*observation des produits psychotropes illicites ou détournés de leur utilisation médicamenteuse*" (OPPIDUM) study conducted in specialized care centres dedicated to drug dependence [43].

Main study designs and methods for controlling biases

Throughout this section, the study designs and methods used in pharmacoepidemiology will be presented in the current context of drug evaluation in the population, a context in which a growing proportion of studies are carried out using medico-administrative data. In these databases, information on drug exposure and health events is present for large populations, with a follow-up now reaching up to 10-15 years in France, and sometimes several decades in other countries [44]. The limits traditionally affecting the study designs are modified in this context, almost any design selected for the conduct of a study from these databases then deriving from a cohort in whom the information has been recorded prospectively and exhaustively.

Descriptive studies: cross-sectional and non-comparative cohort studies

Descriptive studies are extremely important in pharmacoepidemiology. In this field indeed, the study of the modalities of drug use (or drug exposure) and the characteristics of users and non-users is fundamental. They are of primary importance to help determining the extent to which drugs are used, the extent to which their use is consistent with the conditions under which their benefit-risk balance was considered favourable and to what extent the treated population or joint population is similar to or differing from the population assessed in the clinical trials or target population. The designs traditionally used for these studies are classic cross-sectional studies (otherwise known as prevalence studies), repeated cross-sectional studies, and cohort studies (comparative or not) since a longitudinal follow-up is necessary to study patterns of use such as adherence or persistence for instance.

The validity of these studies is conditioned by two types of elements:

- the quality of exposure measurement: in this area, the limitations of field studies in terms of comprehensiveness of the collection of drug exposure, and database studies in terms of the reality of drug consumption for drugs identified as prescribed (or reimbursed) are well known;

- the representativeness of the sample studied: the limit here is not specific to pharmacoepidemiology studies but to all observational studies. The objective is to describe a

behaviour or a population, it is necessary to make sure that the sample is well representative of the population and use one aims at studying.

For these studies, apart from the statistical methods traditionally used to carry out descriptions, it is worth mentioning the time series or time series analyses. By repeating over time the measurement of an indicator in a population, they make it possible to study the evolution of this in terms of trend. These designs are therefore particularly useful for estimating, for instance, how the use of the drug or the choice of treatment changes over time in a given therapeutic field (Fig. 1) [45,46]. They can also be useful in determining how the quality of drug intake changes in terms of the prevalence of appropriate use and, finally, to estimate if changes in drug use especially consecutive to interventions have resulted in changes in patients' health [47].

Explanatory studies

The most frequent objective of pharmacoepidemiological explanatory studies is to study the association between the use of a drug and the occurrence of a health event, whether this association reflects a benefit or a risk. They can also be used to identify the determinants of treatment response, the occurrence of adverse effects or their severity, or the development of appropriate or inappropriate use behaviours, including misuse and diversion.

Cohort studies and cohort-related designs

These studies, in which the follow-up of the subjects or patients starts with the exposure and advances forward in time towards the search for an event still constitutes the gold standard design

for observational studies. Their implementation, difficult when conducted on the field and sometimes requiring very long follow-up periods, has been greatly simplified by the use of medico-administrative databases. In the constraint context of regulatory needs in which time is always limited, these data sources make it possible to consider conducting cohort studies or analyses much more frequently for drug evaluation. While these databases also allow considering comprehensively a large number of concomitant drug exposures, they are often limited in terms of accuracy regarding the severity of co-morbidities presented by patients. Moreover, with regard to the French bases in particular, they lack almost completely of indicators concerning patients' lifestyle and health behaviours, with the limits that this implies in terms of confusion bias. To overcome this limitation, the use of techniques to minimize, as far as possible, the confusion related to unmeasured variables became widespread in the conduct of studies from medico-administrative databases. The use of propensity scores (that reflect the estimated probability of a patient being exposed to treatment) and disease risk score (that reflects the estimated probability of a patient developing the event of interest) has thus widely spread in these studies, the high-dimension versions of these scores constituting the most performing tools [48]. Several modalities exist for the use of these scores, from the simple adjustment to the individual matching. The latter, however, leads to a selection of subjects that some people prefer to avoid by using the techniques of population standardizations based on the inverse propensity score weighting methods. Altogether, by allowing the use of these techniques, the large amount of information contained in the medico-administrative databases reinforces the validity of the results of observational cohort studies by limiting the risk of unmeasured confounding. The results obtained can therefore be comparable to results obtained in the presence of information, as was observed for instance for the study conducted in France SNIIRAM database concerning the risk of bladder cancer associated with the use of pioglitazone [49]. Indeed, its results were fully consistent with those obtained from the clinical practice research datalink (CPRD) [50], despite the SNIIRAM lacked information on tobacco use, a major risk factor for bladder cancer (two hypotheses could actually be discussed here: either unmeasured confounding was very efficiently dealt in the SNIIRAM study, either tobacco use was not a confounder in these studies…).

Finally, the accuracy of the information contained in these databases also makes it possible to consider exposures and related risks in a time-dependent manner. In addition to the greater precision that this allows in the estimates, this approach is also essential to avoid obtaining results affected by immortal time bias, to which cohort studies are exposed when they study risks associated to cumulated exposures [8,9].

Cohorts conducted from medico-administrative databases, however, cannot be compared to field cohorts on at least one very important aspect. In field cohorts, the protocoled and standardized procedure for the screening / diagnosis of the event of interest guarantees that its discovery is done under conditions that do not depend on exposure. This important force is not encountered in the studies carried out from medico-administrative databases.

Three major patterns are related to cohort studies:

- nested case-control studies and case-cohort studies;
- prior event rate ratio studies;
- self-controlled case series.

Only the last two are presented here; nested case-control studies and case-cohort studies are discussed with case-control studies.

Prior event rate ratio studies

Prior event rate ratio studies have been designed to specifically account for the baseline risk of presenting with a potentially recurrent event, when this baseline risk is difficult to compare between compared groups [51]. In a prior event rate ratio study, two cohorts of patients are constituted: a cohort of patients initiating a drug and a cohort of control patients, often constituted after matching on age and sex to the subjects of the exposed cohort. From these cohorts, two estimates are made to derive an assessment of the association between drug exposure and the risk of the event (Fig. 2). The first estimate is the evaluation of the risk difference of the event rate between cohorts for the period preceding the exposure, which allows approaching the difference in basic risk between these two groups. The second is the estimate of the risk difference in the post-exposure period, which is roughly equivalent to a classical relative risk. This estimated relative risk for the follow-up period starting with the exposure (or for the corresponding period in the non-exposed cohort) is then “ratio-ed” to the estimated relative risk for the period preceding the exposure, in order to correct the

assessment of the association for a potential difference of the baseline risk of the event between the compared cohorts.

Self-controlled case series

Self-controlled case series (SCCS) are designs in which the subject constitutes her/his own reference (hence the self-controlled qualifier). They were initially developed to study vaccine safety in the context of acute events, when the event is expected to be an early treatment effect [52]. Their originality ensues from the fact that the studied sample, which allows obtaining an estimation of association with good precision, consists only of exposed cases. For this design to be used under the best conditions, both the exposure and the event must be potentially recurrent (*i.e.* not chronic), and the occurrence of the event must not influence the likelihood of the subject being exposed again. As in a classical cohort, the onset of exposure, and therefore the start of a drug treatment episode in pharmacoepidemiology, usually marks the reference date. The entire follow-up of the patient is divided according to this date into the periods prior to exposure and into different periods following treatment initiation, during which the possibility of an occurring event being related to the use of the drug is considered more or less plausible according to the underlying suspected mechanism. Usually, time periods immediately following drug initiation are considered at higher risk of drug-induced events, and more distant ones are considered at lesser or null risk of such (Fig. 3). The association is then estimated by reporting, for each subject, the incidence of the event found in the risk windows (estimated in person-time) to the incidence found in the other time windows (periods prior to exposure and periods not at risk after the reference date). Since the subject thus constitutes her/his own control, the design is self-adjusted for all potential confounding factors that do not change over time. An additional adjustment may be introduced for any important variable that may vary over time; in particular, the estimates are systematically adjusted for age. Since the risk of presenting the event in each window is very small for each subject, the data analysis generally uses Poisson models. The interest of this design in terms of power and protection against the confusion induced by non-measurable variables (genetic factors, etc.) has been demonstrated by comparison with classical cohort or case-control schemes. In spite of their important solidity, self-controlled

case series are exposed, as all other observational designs, to two important biases: indication bias and protopathic bias.

The introduction of a drug implies that the subject has, at a moment in time, an indication that she/he did not present before and that constitutes a time-dependent variable which occurrence cannot be detached from that of the exposure. To eliminate the indication bias this potentially conveys, the simplest is to estimate the association with the event for a drug with comparable indication but which properties exclude, *a priori*, a potential causal relationship to the event of interest [53].

In the self-controlled case series design, the division of subject's follow-up into time periods considered differently with regards to the risk of drug-induced event they present, involves to have very accurate information for the dating of the drug exposure and the events. A key assumption is that the occurrence of the event should not to significantly affect the subsequent probability of drug exposure. This can occur when the occurrence of an event delays exposure, when the event is a contraindication to treatment, or when the event may result in (or is) death. This assumption also implies that the event should not determine the timing of the end of the observation period. Ignoring this hypothesis can potentially produce biased estimates; however, there are various extensions to the SCCS method that can help mitigating the potential biases. If the event temporarily delays exposure, this will result in a deficit of events in the period immediately preceding the exposure, decrease the overall incidence in the reference period, and result in estimates that will be biased upwards. One way to correct this bias is to individualize, within the period prior to exposure, a specific “pre-exposure period” that would allow censoring follow-up for the period where the prior event conditions the possibility of exposure. Such a period can also be applied if there is a short-term increase in the probability of exposure after an event, which would correspond to an indication bias, which could then potentially underestimate the associations.

Case-control studies and related designs

As explained in the preamble, the weaknesses usually attributed to case-control studies in comparison with cohort studies, which remain valid for field studies, are essentially corrected when carrying out studies from medico-administrative databases. The case-control studies performed within these are, in principle, studies to be considered as nested case-control studies, in which the recall bias is no longer a limit, and in which the detection bias is not different from that of the natural cohorts, *i.e.* cohorts without a standardized procedure for the screening or diagnosis of the event of interest. The principle here is inverted with respect to a cohort study: the reference point in time is the date of occurrence of the event (or the date of selection for the controls); the probability of exposure in one or several time period(s) preceding the reference date is then compared across the cases and controls groups in order to obtain the estimate of the association, namely the odds ratio in case-control studies. As in cohort studies, the propensity scores or disease risk scores are now most often used in case-control studies to lower the impact potential for confounding bias.

They most often constitute the tool retained to perform the matching that will allow selecting the controls who will best correspond to the cases. After such procedure has been performed, the comparability of the groups obtained is not ascertained using statistical tests that would make little sense but by estimating, for variables of interest, the standardized differences between groups [54]. In general, it is assumed that the groups have been rendered acceptably comparable when there is no difference in measurement between two groups exceeding 10% of the value of the variable observed in a group. In a simplified way, this means that if the prevalence of a characteristic is 20% in a group, it will not be considered that there is an imbalance that deserves consideration as long as the value in this prevalence in the comparison group is not less than 18% or greater than 22%. In the case where such difference remains after matching on a propensity score or a disease score, a further adjustment of the analyses on the variables that do not fulfil the conditions of comparability is carried out. By allowing the selection of more likely cases-specific controls and eliminating the possibility of recall bias, the use of medico-administrative databases helps raising the level of evidence of case-controls studies in a way that is not currently taken into account in the scales used for the categorization of evidence levels. Actually, these sales now appear largely outdated and too simplistic in view of the developments performed in observational study schemes, statistical tools for the mitigation of biases, and of the diversification of the data sources of information used in pharmacoepidemiology. Strictly speaking, it is wise to remembering that such scales, often put forward when evaluating the risks and benefits of marketed drugs, would only classify the studies that demonstrated the association between tobacco and the risk of lung cancer as providing with an evidence level 3 [55].

As for the cohort studies, designs adopting the logic of case-control studies were developed in which the case constitutes its own control. These are so-called case cross-over and case-time control studies. We will not detail the less generally accepted case-case-control scheme for which the number of pharmacoepidemiology studies is still low.

Case cross-over and case-time-control studies

These studies were initially used in accidentology to eliminate, as in the case of self-controlled serial case studies, non-quantifiable differences between individuals. The problem posed in accidentology was that of the individual risk of having an accident with regard to his behaviours, abilities, and habits, a very variable risk between individuals and very difficult to quantify. Faced with the difficulty of finding witnesses for a valid comparison with the cases in this situation, the solution was obvious: to use only cases.

As in self-controlled case series, in case cross-over studies, the quantification of an association is made possible here by the division of the subject's follow-up time into different time periods, at-risk period where event may be related to exposure in a potentially causal manner, and non-risky periods (control periods) where such a link cannot be expected (Fig. 4) [11]. Instead of comparing the exposure score between cases and controls, the exposure score between the case windows (window at risk) and the corresponding control windows in each case of the population is compared. Since the measurements performed in the same subject (*i.e.* in the same case subject) are not independent, the analyses use conditional logistic models as for a case-control study with matching between cases and controls.

As self-controlled case series designs, case cross-over studies allow self-adjustment for all potential confounding factors that do not change over time. And as for studies in self-controlled case series it is possible to make an additional adjustment on characteristics of interest that may vary in time. Finally, as previously stated for self-controlled case series studies, the indication bias is not eliminated by this design. It is therefore recommended to evaluate the association for a

comparable indication exposure but for which no mechanistic association to the event of interest is a priori possible.

In addition, cross-case studies expose an additional bias: if the general trend is to increase the use of a drug over time in the population, then it is possible to find frequencies of greater exposure in the period of risk close to the event than in periods more remote in time. This trend bias can lead to finding associations in crossover studies with no relation to a possible relationship between the use of a drug and the occurrence of an event. Case-time-control studies provide a solution to this problem, and were in this perspective used for instance to study the safety of drugs used during pregnancy [56]. The temporal association linked to the trend is studied by constituting, in addition to the group of cases needed to perform a case cross-over analysis, a reference group for this trend, comprising only subjects free from the event. In these subjects, selected at dates corresponding to the dates of occurrence of the events in the cases, a ratio of the odds of exposure will be estimated comparing the exposure assessed in the time period preceding the selection date (corresponding to the at-risk period of cases) and that assessed in control periods (corresponding to the control periods in cases). In order to eliminate the influence of a potential trend bias, the estimate obtained after performing the case-crossover analyses in the case group will then be "ratio-ed" to the estimate obtained in the reference group for the exposure trend (Fig. 4).

Detection studies: sequence symmetry studies

The symmetry sequence study initially compared the initiation sequence of two exposures to drug A and B in a given time window, with exposure to drug A being drug exposure and exposure to drug B serving as a marker of occurrence of a potential adverse effect. Among all new users of drug A, if the exposure to A induces the occurrence of an adverse effect leading to the prescription of B, then the number of patients with a temporal sequence where A precedes B will be greater than the number of patients presenting a temporal sequence where B precedes A. This design thus allowed the detection of potential adverse effects based solely on prescription or reimbursement data, thus offering an interesting tool in the case where diagnostic data would not be available [46]. Events, however, can obviously be identified more directly by data of this type, hospital or outpatient. As in

a case-crossover design, the raw sequence ratio obtained is not affected by non-time varying confounders, but is, conversely, sensitive to changes in prescribing patterns. An adjustment of the estimate using a reference group to quantify the trend has also been proposed [55].

Many other designs exist that we do not present here because they remain little used in pharmacoepidemiology. We also do not present the designs and methods considered for signal detection using supervised machine learning techniques. To date, their use has, so far, not been associated with satisfactory performances in terms of signal detection or drug post-marketing evaluation. Important research remains needed in that area before the place these methods will take can be defined.

Conclusion

The methods that can be used for the pharmacoepidemiological evaluation at the drug in real life are numerous. Access to information from medico-administrative databases, which has been available for about 10 years in France, and over 30 years in other countries, has considerably modified the context for conducting these studies. The limitations usually encountered in terms of study power and duration, comprehensiveness of recorded information, or ability to eliminate biases to which any observational research is exposed have been considerably reduced. However, other limits remain, which fully justify maintaining the use of field studies: the French medico-administrative bases are limited for clinical aspects and do not contain information on the habits of life of patients. The current limits of pharmacoepidemiology in France, compared to other countries, lie in this lack of information (diagnosis associated with a prescription and indicating the severity of the disease, intra-hospital prescription data, test results biological or radiological, etc.). This integration is in part a reflection on the current health data hub. After the opening of administrative health data to research, it is now the result of the health data hub reflection that will condition the future developments of pharmacoepidemiology and quality of drug evaluation in France.

Disclosure of interest

Authors have no competing interest to declare.

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Figure 1. Use of time-series to study the temporal trend in drug use : Evolution of the number of reimbursements for glinides in the French "*échantillon généraliste de bénéficiaires"*, with individualization of a level effect after pioglitazone withdrawal decision by French health authorities (adapted from Pariente et al. [46]

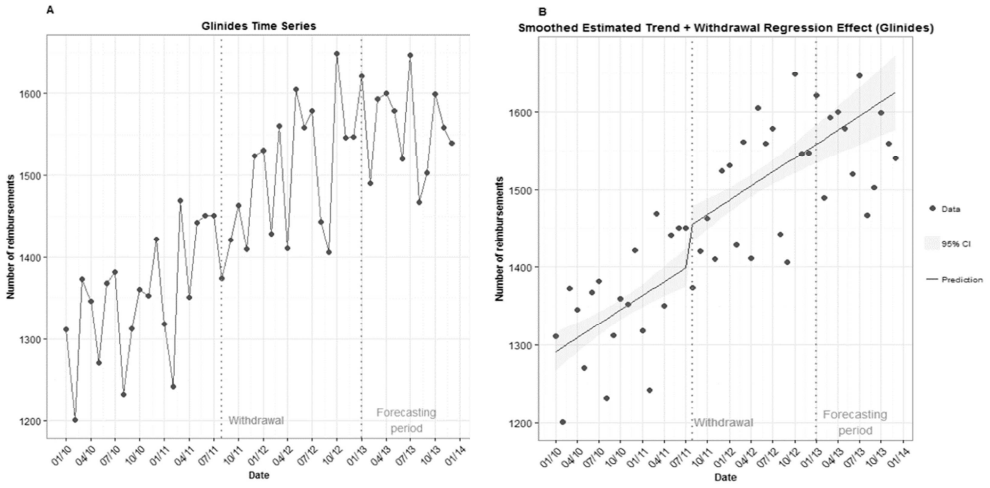

Figure 2. Representation of a *prior event rate ratio* design.

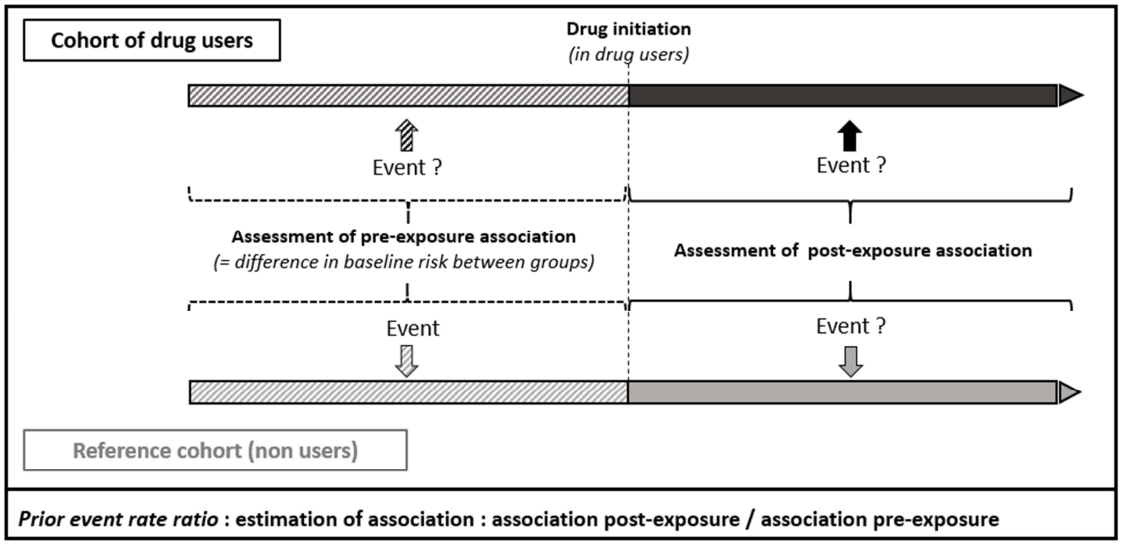

Figure 3. Representation of a *self-controlled case-serie* design.

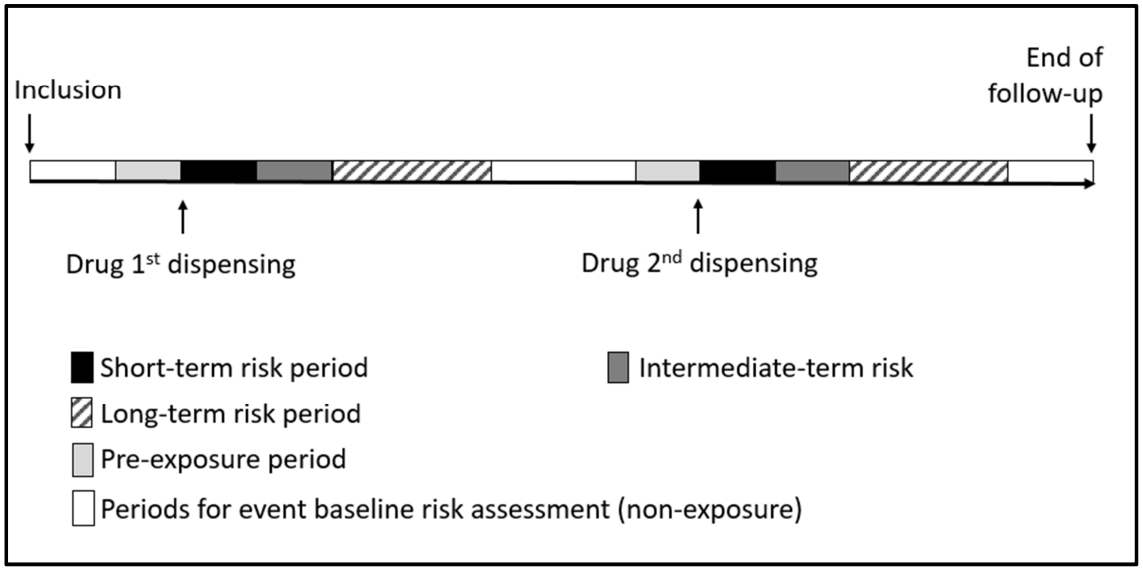

Figure 4. Representation of a *case cross-over* and a *case time-control* design.