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## Pharmacoepidemiology

# What is pharmacoepidemiology? Definition, methods, interest and clinical applications

Short title: What is pharmacoepidemiology?

**Jean-Louis Montastruc\*, Justine Benevent, François Montastruc, Haleh Bagheri, Fabien Despas, Maryse Lapeyre-Mestre, Agnès Sommet**

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*Service de pharmacologie médicale et clinique, centre de pharmacovigilance, de pharmacoépidémiologie et d'informations sur le médicament, UMR INSERM 1027, CIC INSERM 1436, faculté de médecine - centre hospitalier universitaire, 31000 Toulouse, France*

\*Corresponding author. Service de pharmacologie médicale et clinique, pharmacopôle Midi-Pyrénées, centre Midi-Pyrénées de pharmacovigilance, de pharmacoépidémiologie et d'informations sur le médicament (CRPV), équipe de pharmacoépidémiologie INSERM U 1027, CHU de Toulouse, faculté de médecine, 37 allées Jules-Guesde, 31000 Toulouse, France.

*E-mail adress:* jean-louis.montastruc@univ-tlse3.fr (J.-L. Montastruc)

## **Summary**

Clinical evaluation of drugs before approval is based on the experimental design of clinical trial with randomization of drug exposure. Unfortunately, conclusions of clinical trials are necessarily limited to patients included into the trials. It is thus necessary to compare these experimental data coming from clinical trials with the real use of drugs in clinical practice. 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 the methods and/or reasoning of both pharmacology and epidemiology. The development of pharmacoepidemiology should improve the “rational drug use”.

## **KEYWORDS**

Drugs; Pharmacoepidemiology; Efficacy; Effectiveness; Drug risk; clinical evaluation; adverse drug reactions

## **Abbreviations**

ADRs: adverse drug reactions

Anti-TNF: anti-tumor necrosis factor

HERG: human ether a go-go related gene

PD-PE: pharmacodynamics – pharmacoepidemiology

WHO: World health organization

*“ A desire to take medicine  
is, perhaps, the great feature  
which distinguishes  
man from other animals “*

Sir William OSLER, 1891

Clinical evaluation of drugs before their approval is based on a specific methodology: experimental design of the comparative clinical trial with randomization of exposure [1-3]. Thus, clinical trials with their three phases (phase I: healthy volunteers, phase II: first trials in patients, phase III: large multicenter trials) are performed, like any experimental study, according to a very strict methodology, following previously defined inclusion and exclusion criteria. Comparative clinical trials, which are the basis of clinical pharmacology, remain the only one allowing the formal attribution of the factor of interest to the studied drug.

### **The mandatory insufficiencies of clinical trials**

Unfortunately, conclusions of clinical trials are necessarily partial and limited. They are only true for the patients included in the trials. Clinical trials do not take into account heterogeneity of the patients in the conditions of real life, as well as the different clinical forms of the disease, drug interactions and differences between physicians, countries or treated populations... Thus, discrepancies ranging from 30 to more than 60% between the characteristics of populations receiving drugs in clinical trials and those treated in real life have been shown [4].

These data are often summarized as “*the five too*” of clinical trials [5]:

1. Clinical trials include too few patients, no more than 1500 before drug approval;
2. Clinical trials are too simple, not including usually poly pathological or polymedicated patients, i.e. the main populations later exposed to drugs;

3. Clinical trials are too often concerned with median ages, excluding very young or old subjects. However, subjects over 65-70 years old and beyond are those primarily receiving both old and new medications;

4. The clinical trials are too “narrow”, respecting very restrictive and well-defined indications, not followed in daily clinical practice;

5. Clinical trials are finally too brief, including for example patients treated for only a few months for a chronic disease!

The comparative design of clinical trials leads, from a statistical point of view, to quantitatively compare an “average” patient to another “average” patient. In fact, daily prescriptions, subject to the hazards described above, are never confronted with this “average” patient (who is in fact only statistical and theoretical and thus does not exist in clinical practice). Thus, it is absolutely necessary to study drugs in real conditions of use from medical as well as economic and populational points of view: this is the goal of pharmacoepidemiology.

### **Definition of pharmacoepidemiology**

Post-marketing surveillance of drugs goes beyond the sole purpose of pharmacovigilance (i.e. the study of adverse drug reactions [ADRs]) [6, 7]. It concerns conditions of their use (or misuse), analysis of medical, economic or rational factors of their use, large-scale verifications of their long-term effectiveness, quantification of their ADRs, quality of drug informations, monitoring of self-medication ...

All these questions define the field of pharmacoepidemiology or study in real conditions and in large populations of use, effectiveness and risks of drugs [2, 3, 8]. Pharmacoepidemiology therefore concerns the drug prescription in phase IV, i.e. after drug approval. This new branch of clinical pharmacology investigates the use of the drug in real conditions of life after marketing and thus, 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.

### **Methods in pharmacoepidemiology**

Pharmacoepidemiology applies to drugs and their pharmacological evaluations, the different methods of epidemiology. Its methodology is therefore observational and, thus, is usually opposed to the experimental method (as defined by Claude Bernard) used in phase I, II or III of clinical trials. Pharmacoepidemiology thus develops two complementary approaches.

*The descriptive (non-comparative) approach* observes phenomena retrospectively, prospectively or transversally. An example of these so-called cross-sectional studies is the demonstration of the (too) strong prescription of drugs during pregnancy (on average more than 13 drugs per woman, most of them not evaluated in their risk-benefit balance) [9-11].

*The analytic (comparative or etiologic) approach* investigates putative associations between occurrence of (favorable or not) effects and exposure to one (or more) drug (s). It allows identifying the different determinants and quantifying their role. The major difficulty involves several parasitic factors that can influence the measurement and comparison [12]. To avoid what is called confounding bias, clinical pharmacologists uses matching in clinical trials (in subjects' selection). In contrast, pharmacoepidemiologists perform adjustments (in the statistical analysis). In this analytical approach, one of the first methods commonly used, especially for the study of ADRs in a pharmacovigilance database, is the case / non-case method, which investigates disproportionality between the number of ADRs registered with the drug of interest and the average number of ADRs recorded with all other drugs [13, 14]. It is thus possible to validate a safety signal which will be later confirmed using a quantitative and confirmatory approach, like case-control or cohort studies. These methods of disproportionality (which are an example of "data mining") allowed in recent years to study the digestive ADRs of coxibs [15], to highlight a signal erectile dysfunction [16] or lupus [17] with statins or anti-tumor necrosis factor (TNF) alpha drugs [18]. More recently, this method allowed defining the risks of arrhythmias and QT prolongation with citalopram and escitalopram among antidepressant serotonin reuptake inhibitors [19] or cardiac failure with dopamine ergot derivatives [20]. Moreover, this disproportionality method allows comparing ADRs within a same therapeutic class of drugs with, for example, a signal of ketoacidosis with SGLT2-inhibitors in comparison with other glucose-lowering drugs [21]. It also permits to detect within a same pharmacological class, the more at risk drugs: for example, among statins, the major signal of diabetes was found with atorvastatin [22] whereas none signal was detected with fibrates [23]. This method also allowed to strength the link between venous thromboembolism and exposure to fibrates [24].

Of course, pharmacoepidemiology also uses the conventional methods of analytical epidemiology, including retrospective (case-control) or prospective studies (such as cohort

surveillance). In pharmacoepidemiology, a case-control study allows to measure the association between a drug and a (desirable or not) event undetectable during clinical trials (for the reasons described above). Since case-control studies first include cases for the analysis, they especially allow detecting rare or delayed onset events. In contrast, cohorts are the method of choice for studying a high frequency drug event. Other methods [25-27] are also used: meta-analyses, database cross-referencing, case-population studies...

If the use of several of these methods to answer a question generally helps to strengthen the association studied, it may happen that discordant results are observed between different studies using different methods. This is the case, for example, for pancreatitis with incretinomimetic hypoglycemic drugs: the association, highly significant during the non-case case approach [28], was not found in a cohort study [29]. This allow to stress the absolute need to use multiple (and therefore complementary) data sources and approaches in pharmacoepidemiology.

The difficulties of pharmacoepidemiological studies in France are often stressed because of the presumed absence of drug databases. In fact, despite that, in contrast to northern European countries, the freely available French bases are essentially medico-administrative and therefore do not generally contain medical diagnoses, several pharmacoepidemiological studies of great scientific and medical interest are possible and were performed in France [30-32].

### **Application fields of pharmacoepidemiology**

Pharmacoepidemiology, by supplementing and expanding data from clinical trials, develops three main areas of interest.

#### **Prescription and drug consumption studies**

World health organization (WHO) defines the use of drugs as “marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” [33]. These studies define the conditions of the real use of drugs after their marketing. They investigate the quantitative and qualitative characteristics of treated patients, prescribers or prescribed quantities. They also consider national or regional differences in drug use, determinants of prescription and differences from validated indications. These studies show that prescription and consumption depend on multiple factors, some rational (ensuing from conclusions

of clinical trials) and other irrational (linked to symbolic images of drugs or social, economic and educational factors ...). The importance of these last factors in every day practice is steadily increasing. These studies underline several inconsistencies between the basic pharmacological data, the conclusions of clinical trials and the prescription and use in real life of drugs [2, 34]. For example, in the current field of prescription in older patients or in those suffering from dementia, it is possible to show the high prescription level of atropinics (anti-muscarinic) or benzodiazepines (two pharmacological classes with well-established and theoretically well-known deleterious effects on memory) [35-38], but also the too low prescription of analgesics [39, 40].

### **Study of drug effectiveness**

In pharmacoepidemiology, efficacy of a drug is studied by focusing on two essential aspects (not taken into account in clinical trials): first, its long-term action, over several months or better several years, in order to bring closer to the daily clinical practice and the prescriber's goal. Then, the drug effects are investigated on the so-called “hard” criteria, i.e. clinical criteria translating a quantitative improvement of the patient's health. These are only three clinical criteria for such an evaluation: 1) decrease in morbidity, 2) decrease in mortality (total mortality and not specific mortality like cardiovascular one) and 3) improvement of quality of life (analyzed using appropriate and valid scales). The clinical criteria therefore differ from the intermediate criteria (i.e. biological, electrocardiographic, radiographic, ultrasonic... criteria) often used in clinical trials which, obviously, are not a relevant final objective for the medical prescription.

These notions of intermediate criteria and clinical criteria allow discussing the notion of drug efficacy. Two words can summarize and differentiate this notion. First, the word “efficacy” describes the effect of drugs on intermediate criteria (i.e. biological, electrocardiographic, radiographic, ultrasonic ... criteria) and, second, the word “effectiveness” describes the effects of drugs on the three clinical criteria relevant to patient’s health, as defined above (table 1) [41, 42].

Thus, some drugs can be effective (“efficacy”) without “effectiveness” in the pharmacoepidemiological sense as defined above: for example, fibrates, although decreasing decrease triglyceride and cholesterol levels, have no effect on total mortality or cardiovascular deaths [43].

It is now important to understand that the use of non-experimental plans (i.e. use of pharmacoepidemiology methods) also makes it possible to study the benefit of drugs. These studies

are important since they evaluate the drug in real life, i.e. in patients coming from all over, taking many drugs, often discontinuously and suffering from diseases at different stages... For example, it is not necessary to perform a comparative clinical trial to demonstrate the interest of an antagonist in agonist intoxication (such as naloxone in methadone overdoses). Cohort studies have demonstrated the effectiveness of anticoagulants in the prevention of venous thromboembolism. The use of the case-control method has proved the place of lidocaine, beta-blockers or anticoagulants in the prevention of death after myocardial infarction, or the interest of antibiotics in the prophylaxis of endocarditis after infection. In these examples, the comparative clinical trials came only several years later to confirm these results from these non-experimental studies [42]. The example of vaccines is even clearer since they are marketed only after studies using intermediate (virological) criteria [42]. These studies also reveal new long-term favorable effects but also allow to compare the effects of drug versus other therapeutic choices (drug or not), not evaluated before marketing. They also investigate the consequences of variations in dosage, repartition of doses during the day as well as the characteristics of the disease (seriousness, clinical subtype, etc.) or the patient (age, sex ethnicity, socio-economic factors, geographic location, nutritional status ...) in the effects of the drug.

### **Risks associated to drugs**

These studies complement the role of alert and identification of adverse drug reaction profile played by spontaneous reporting and pharmacovigilance *stricto sensu*. Pharmacoepidemiology quantifies risk at the population level [2, 44]. Following the pioneer pharmacoepidemiological work measuring the risk of pulmonary arterial hypertension with amphetamine appetite-suppressant drugs [45], several studies were performed and pharmacoepidemiological studies are now part of any pharmacovigilance survey [44, 46]. The analysis of the methods used to withdraw drugs in France over 10 years clearly shows the increasing importance of pharmacoepidemiology methods in these decision-making [47-49].

More recently, the importance of coupling signal detection methods in large databases, such as pharmacovigilance ones, with some pharmacological (pharmacodynamic or pharmacokinetic) characteristics of drugs (receptor affinity, for example) allowed to investigate in humans, the mechanism of adverse drug reactions. Thus, data on the mechanism of these adverse drug reactions do not only derive now from experimental data, but also from clinical evidence. This method, called

PD-PE (pharmacodynamics - pharmacoepidemiology) have been able to show that the risk of prolongation of QT interval (and thus that of torsades de pointes) can be explained in humans by blockade of HERG potassium (human ether a go-go related gene) cardiac channels [50]. Using this method, it was possible to demonstrate that the onset of diabetes in neuroleptics in general and second generation in particular is correlated to serotonin 5HT<sub>2C</sub> receptor antagonism [51] or to investigate the mechanism of antipsychotic-induced movement disorders in humans [52].

## Conclusion

Pharmacoepidemiology, investigating the real use of the drug, is now the mandatory complement of clinical trials. Pharmacoepidemiology asks the following questions about drugs and their use:

- What is the practical scope of the sophisticated informations surrounding drugs at the time of marketing?
- To what extent and on what criteria do drug users differ from patients included in clinical trials?
- Do the notions of market, motivations and informations of physicians, pharmacists and patients interfere as confusion or coherence factors for drug prescription?
- Does adequate scientific information really and timely influence doctor's prescription?
- Is the criterion of innovation valid for all products, or is it enough to update by labels or advertising obsolete products without clinical utility?

The knowledge of pharmacoepidemiology is now essential, in the era of big data [53], for practitioners concerned with the proper use of drugs. This is in accordance with the WHO definition of pharmacoepidemiology: “the study of the use and effects/side-effects of drugs in large number of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes” [33]. Promoting pharmacoepidemiological studies allows to avoid therapeutic escalation and prevent the appearance or even the accumulation of adverse drug reactions ... Following this strategy allows to ensure a better prescription of drugs by taking care to, not only biological, paraclinical or physiopathological data, too often anecdotal (and even not decisive for the patient), but to clinically validated effects on complications of the disease, mortality and quantified risks of adverse drug reactions.

Pharmacoepidemiology, a modern branch of clinical pharmacology, works for the patient and the prescriber to evaluate the clinically relevant effects of drugs.

### **Disclosure of interest**

Authors have no competing interest to declare.

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**Table 1.** Efficacy and effectiveness of drugs: two words, two worlds

<b>EFFICACY</b>	<b>EFFECTIVENESS</b>
Intermediate endpoints (biomarkers)	Clinical endpoints
Clinical trials (phases I, II, III)	Real life (phase IV)
Theoretical world	Real world
Universitary word	Clinical practice
Industrial world	Patients' requirement
Clinical pharmacology	Pharmacoepidemiology
Needed for drug approval	Mandatory for a right prescription