THERAPIES

HEADING: Pharmacovigilance

Pharmacovigilance - The next chapter

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Summary

The discovery and quantification of adverse drug reactions has long relied on the careful analysis of spontaneously reported cases. Causality assessment (imputation) was a fundamental feature of individual case report analysis. This was complemented by analysis of aggregated cases, and of disproportionality analyses in spontaneous reports databases. In the absence of more specific information sources, these have resulted in the discovery of many new adverse reactions, altering drug information. It has led to the withdrawal from the market of many drugs, but its use for risk quantification remains fraught with uncertainty. The recent access to population-wide claims or electronic health records databases have confirmed for spontaneous reporting a predominant role in hypothesis generation for serious adverse drug reactions, notably those that result in hospital admission or death. In these cases, the events are identifiable at the population level, and can be quantified precisely using the tools of modern pharmacoepidemiology, to generate specific benefit-risk analyses. Spontaneous reporting remains irreplaceable in signal and alert generation in drug safety, despite its inherent limitations. For signal strengthening and assessment, more systematic and quantitative methods should be sought, such as claims databases for reactions resulting in hospital admissions

KEYWORDS

Drug safety; Pharmacovigilance; Pharmacoepidemiology; Population databases

Abbreviations

ADRs: adverse drug reactions

BMI: body mass index

CPRD: clinical practice research datalink

DNA: deoxyribonucleic acid

E2B: clinical safety data management: data elements for transmission of individual case safety reports

EMA: European Medicines Agency

EnCEPP: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

FDA: Food and Drug Administration

GP: general practitioner

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceutical Use

ICSR: individual case safety reports

ITT: intent to treat

MedDra: medical dictionary for Drug regulatory activities

NSAIDs: non-steroidal anti-inflammatory drugs

ROR: reporting odds ratio

RUCAM: Roussel Uclaf causality assessment method

PRRR: proportional reporting rate ratio

SNDS: *système national des données de santé* (French national health data system)

WHO: World Health Organisation

Introduction

All drugs are dangerous, some may also be useful [1] All is poison, nothing is poison, the dose is what separates the drug from the poison [2].

In an earlier paper, we retraced the history of pharmacovigilance, with some views to its future [3]. Five years later, the world has changed a little. In addition to traditional spontaneous reporting by healthcare professionals, patient reporting has become mainstream. The use of social media has exploded, and is being mined in the hope of possibly identifying new safety issues [4]. Data resources such as countrywide healthcare systems databases have become readily available, and hospital based data repositories or electronic health records are opened new possibilities.

The objective of the present paper is to review these advances and try again to predict the future, the next chapter in pharmacovigilance. After previous chapters of spontaneous reporting, analysis of individual case reports, reporting patterns and report databases, will the next chapter be that of big data and pharmacoepidemiology in pharmacovigilance?

To set the frame of the reflection, the management of drug safety, or pharmacovigilance, follows a series of steps: identification of a signal, ascertainment of the signal, which then becomes an alert; quantification of the alert, which can become an alarm, and management of the alarm, which more or less follow the usual clinical management of disease: suspicion (symptoms), diagnosis (confirmation), evaluation (extent and severity), and treatment (followed by measure of the treatment's success). Each of these steps require different methods and proficiencies, just as there is no single exam or test that will do all in clinical medicine (Fig. 1).

These different steps can be put in relation with the methods cited:

- a) spontaneous reporting and evaluation of individual case reports;
- b) analysis of reporting patterns and of spontaneous reporting databases;
- c) use of population-based resources.

This paper is based on the science of pharmacovigilance, the identification and prevention of adverse drug reactions, as a medical expertise, that of drug-induced diseases. Pharmacovigilance has become very much a regulatory issue, but this paper will not discuss the relevance of regulations or definitions, of International Council for Harmonisation of Technical Requirements for Pharmaceutical Use (ICH) section clinical safety data management: data elements for transmission of individual case reports (E2B), individual case safety reports (ICSR) or medical

dictionary for drug regulatory activities (MedDRA), Food and Drug Administration (FDA) or European Medicines Agency (EMA). There are websites full of very good information and recommendations such as the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [<http://www.encepp.eu>] and good pharmacovigilance practices (<https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices#final-gvp-modules-section>), which are a mandatory read for anyone working in the field, at least if they do not want to have serious legal problems. However, pharmacovigilance is not limited to these legal aspects, and there is place to think and progress beyond counting bodies and making sure that reports are sent on time. Though they are a mandatory prerequisite, we will not elaborate on regulations.

Spontaneous reporting

The history of drug safety was changed when in 1961 McBride published in the Lancet a short letter stating *"in recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide during pregnancy as an antiemetic of a sedative, to be about 20%.../. Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?"* [5] This led to the understanding of the usefulness of the reporting of adverse reactions by observant professionals, the creation of national and international adverse drug reaction (ADR) reporting systems [6], and the concept of pharmacovigilance [7] At the time there were no population databases, and very little computing power. Most of what was known of drug safety came from clinical trials (of limited size, and often with small and poorly-representative populations). This has not really changed much [8]. The main resource to identify the existence of new adverse drug reactions not predicted by pharmacology became spontaneous reporting, and this has not really changed since. The real utility of spontaneous reporting has however been better circumscribed and hopefully understood.

Individual case reports

Individual case reports describe what happened to a patient in relation to a drug. The standard report is based on an identified reporter, an identified patient, a drug and an event [9-11] That is the regulatory basic dataset, which is unfortunately essentially useless for assessment purposes, when limited to this minimal information set. For an event to be really evaluable for an association with a given drug in a given patient, what Jeff Aronson calls "anecdotes as evidence" [12] one needs to know patient characteristics (age, sex, concomitant disorders, concomitant medication, genetic susceptibilities), drug characteristics (dose, duration of treatment, indication for use, dechallenge and rechallenge [if any]), and for the event, the start date (including of first symptoms, not just of diagnosis), the diagnostic certainty (including relevant lab tests) and the exclusion of other potential causes for the event, with dates in relation to possible dechallenge and rechallenge [12-14]. All this information is indispensable for an analysis of potential causality and needs to be gathered as early as possible, ideally as the reaction is ongoing, to get the information (other medication, lab tests for instance) while the case is still warm, and possibly even generate information if it is missing (e.g., lab tests, other causes)

Causality

Once these elements are gathered, any number of causality assessment methods, also called imputation or imputability can be applied. Over the years, several dozen methods to assess causality in individual case reports have been developed, and more continue to be invented regularly [15-37] Different causality methods may give different results, probably because of different objectives [21, 24, 25, 30]. The classic definition of an adverse drug reaction is an unwanted and deleterious effect occurring during normal drug use, though more recent regulations have added other dimensions such as overdose, medication errors, drug abuse or dependence which may change the causality methods [27].

A difference between methods is the inclusion of previous knowledge of a possible association between the drug and the event, the difference between intrinsic imputability (relating to the case itself) and extrinsic imputability (relating to previous knowledge of similar cases). The objective of causality may be, for a prescriber, to identify in a given patient what drug would be the most likely culprit in the adverse reaction, and should be stopped first. For a pharmaceutical company, it might be to identify any mitigating factor, and whether any other drug or disease might be involved. For regulator, the important point is the discovery of new signals, i.e., whether any of the drugs taken by the patient might be involved, especially newer drugs for which there is little information.

Obviously with very different objectives the way the same data are processed will be different. The use of pre-existing information could explain discrepancies in results provided by different methods [21, 25, 30, 38].

Another, very useful objective is to eliminate drugs for which causality is excluded or very unlikely, restricting the field of investigation to a limited number of possible suspects. Exclusion will be mainly limited to chronological impossibility, when the drug is given after the start of the reaction, since no clinical event can be formally excluded as not being potentially associated with a drug, if the chronological sequence is compatible.

a) The major criterion in causality is the timeline: the drug must have been used before the onset of the event. This implies that the start of the event must be identified accurately, to avoid protopathic bias (or reverse causality), the drug being given for early symptoms of the event. A parallel to protopathic bias is indication bias: the drug is given for an indication that is associated with the event, such as pain, fever or infection and myocardial infarction [39].

Secondary timeline criteria are dechallenge: event abates when the drug is stopped or the dose reduced (within the usual pharmacokinetics of the drug, and the natural evolution of the event). Here again the reason for stopping the drug should be documented: was the drug stopped because of the event was thought to be drug-related, and then the patient got better, or was the drug stopped because the patient was already getting better? (Another form of protopathic bias). Or did the reaction abate because of specific treatment, whether the drug was stopped or not. Rechallenge is usually described as the linchpin that confirms the strength of the association between the drug and the event in a given patient, if the event recurs when the drug is given again, for whatever reason. Rechallenge may also be related to protopathic or indication bias, if the drug is given again for a recurrence of the event. Rechallenge would usually be accidental, especially for allergic reactions,

which may be more severe the second time. Reintroduction could be considered at a lower dose for pharmacological reactions.

b) A weaker set of criteria are related to event description: signs and symptoms may confirm the pharmacological nature of the reaction, related to the drug's properties (e.g., hypokalaemia with diuretics, or neutropenia with cytotoxic cancer chemotherapies). Of course, this is context-dependent, in that recent drugs may have direct pharmacological effects that are not yet described, as may be the case for targeted therapies whose targets' distribution may be ill defined. So the fact that a reaction has not been deduced from a drug's known effects does not necessarily exclude a direct causality.

c) Absence of alternate cause is another common criterion for causality: these are more subjective and depend on the intensity of the search for these other causes, which may be related to the conviction of drugs involvement. In addition, new causes may appear over time, so that a report with no other identifiable cause than the drug of interest might well result from another cause that will appear in due time.

The data items needed to assess individual case reports have been collated in recommendations for datasets in published reports [13].

These different data items can be combined and used in many different ways, feeding algorithms, A classic one is the French Imputability model, where data is fed into a 3-way table (Table 1) to result in partial and global imputability scores [6, 15, 40].

Bayesian approaches or scores, or computer assisted probabilities [17-19, 29, 36, 41]. There are also event specific causality approaches such as Roussel Uclaf causality assessment method (RUCAM) for drug-induced liver injury [33, 42-44], or similar applications for skin reactions [45], haemolytic anaemia [46]. The major issue in causality assessment is lack of information, resulting generally in a causality that is not excluded (not impossible, but not enough information to conclude formally). That can be summarized in the European ABO classification where A is the association seems reasonable (plausible), B the association is possible, and O there is not enough information [34].

Causality has also been used to classify reports for analysis, which again is mostly related to information content.

Biases in spontaneous reporting

There are many biases in spontaneous reporting, such as notoriety bias, also known as the Casablanca syndrome (“round up the usual suspects”) [47]. Where a reaction is attributed to a drug known to be a common cause, when in fact another drug is more probably involved; protopathic bias, where the drug is given for early signs or symptoms of the event (e.g., antibiotics for fever before agranulocytosis) [48, 49]; or indication bias, where the drug is given for a disease that can cause the effects (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] for acute pain, which can by itself cause myocardial ischemia) [50]. Many other biases can affect spontaneous reporting or causality [39].

Objectives of causality assessment:

If the objective of the causality assessment is to select the drug most likely to be involved in a given patient, then certainly previous description of the association may point to the drug to stop first among a patient’s many drugs. If the objective is to identify previously unknown reactions, then the fact that the reaction has not been previously reported is irrelevant: new drugs or new associations by definition will not be identified if only known reactions are sought. On the opposite, previously unreported reactions with high apparent causality may be of special interest, as was the case with thalidomide and phocomelia.

Different methods with different objectives will give different results.

For individual patient management by prescribers, methods that consider or give weight to previous description of similar events (including labelling of the reaction in the summary of product characteristics) would be the most useful, by pinpointing the drugs with the highest probability of being actually involved. If you’re a prescriber in front of a patient, and you hear hoofbeats, think horse.

On the other hand, for a pharma company the main objective of causality assessment may be to exonerate their drug, by identifying other possible reasons for a reaction in a patient.

For a regulatory agency, the main objective would be to identify new signals, i.e., cases in which there is good chronological causality, no other cause found, and the event has not been

previously associated with the drug concerned (initial index cases). If you're a regulator, hear hoofbeats and are wary of new associations, think zebra, perhaps, and conclude to horse only after having made certain there is no zebra.

New regulatory definitions of adverse reactions that include medication errors, misuse, abuse or dependence create new issues that are not covered by the traditional imputability methods and might require new and different methods should one desire to study their causality [27].

Individual drug assessment is however limited: it can demonstrate that in certain circumstances a drug can probably cause a certain reaction (index cases, high imputability cases, "smoking gun case") [14], but a single case or anecdote cannot provide enough information to make regulatory decisions. It could however generate a clear signal that will justify further exploration.

Case groups and disproportionality analyses

In the absence of smoking gun cases other elements can convince of the reality of the association, and generate an alert, relying on the existence of multiple cases.

If the reported cases are similar, it can be a strong suggestion that there is something that is happening (or that all the cases share the same indication or protopathic biases).

Disproportionality analysis is a pseudo-epidemiological approach, in which the proportion of an event reported with a drug among all events reported for the drug is compared to the same proportion for a comparator population (Fig. 2).

This will provide reporting odds ratios (ROR) [51, 52] or proportional reporting rate ratios (PRRR) [53, 54] or any number of other measures of disproportionality, of varying complexity, but providing similar conclusions as long as there are at least 3 reports [55] This measure of disproportionality is just an indicator of a potential signal or alert, but it has the advantage of providing quantitative analysis with confidence intervals, which can be construed as probabilities, and maybe even generate P-values. One might forget that these are only disproportionalities in reporting of events, not their occurrence. There is a tendency to state that events are more common,

when it is only their relative reporting that is. Regulatory authorities of the FDA or EMA recommend disproportionality analysis by holder of marketing authorizations on a regular basis for regular safety signal detection (See GVP VIII, IX).

Disproportionality is based on the null hypothesis that reporting is random, and a given event may be attributed randomly to any of the drugs taken by the patient. If there is an association of the event with a drug, that drug will be found more often than expected from chance. Disproportionality must therefore be studied using all reports mentioning the drug, whether suspect or not, without making any use of individual causality, to avoid adding causality biases to the biases inherent to reporting and disproportionality [56].

Biases in disproportionality analyses

Because the data is declarative and not systematic, there are many potential biases, beyond those involved in the reporting of the individual cases that feed the analysis (protopathic, indication, notoriety) [56]. Many factors that may spuriously affect disproportionality analyses have been reported [57-65]

A reporting ratio can be increased by more reporting of the event of interest or less reporting of the other events. A drug that is very well tolerated with few other reports will generate a much stronger signal than another drug with exactly the same risk but more reporting of other reactions because of poor tolerability. These change over time in reporting (the Weber effect). A highly publicised adverse reaction that may lead to regulatory activity may also generate signals in other drugs of the same family, or in other drug families concerning the same event [63] Common drug associations may generate signals with both drugs concerned, when only one should be concerned [62]. Event masking by other drug-event associations has also been described, even in the absence of interactions [58].

The choice of the comparator can also be crucial. This can be the whole database, which is probably not appropriate if risk factors for the event are not equally distributed in the whole population, or the comparators may be drugs used in similar indications, or other drugs in the same family. If

possible, these should be drugs marketed at the same time, to avoid distortion by the Weber effect, and in the absence of any identified alert, concerning the drug of interest or the comparator [56].

These biases need careful consideration, and are open to manipulation: increasing the reporting of non-specific (even serious) or well-known reactions will increase “b”, thus masking the emergence of new signals. Increasing the reporting of trivial events is a sure way of masking new alerts.

Disproportionality is very sensitive to reporting biases, and especially to notoriety biases, which may create false alerts, or on the other hand generate spurious alarms. Ideally one should look at disproportionality measures of events before any alert, or any case published. As soon as an alert is identified and made public, spontaneous reporting analysis becomes meaningless [60-64].

Individual case reports indicating strong causality and disproportionality analyses in the absence of apparent biases may indicate that there is indeed a signal, maybe even an alert that needs to be investigated. When spontaneous reporting was the only available source of information, many regulatory decisions were made on such cases. And it might still be the case when there is a flurry of rare serious events known to be drug-related, strongly associated with a single new drug entity.

In other cases, when the events are rare and may have several causes, and the drugs have been long on the market, no decision should be made without a careful analysis of population data and pharmacoepidemiology.

The management of identified problems falls under the chapter of risk management, which cannot and should not rely only on spontaneous reporting of individual reactions, but on systematic evaluation using the resources available for population analytics.

Pharmacoepidemiology

Spontaneous reporting of unexpected or serious reactions is probably the most efficient way of generating new drug safety signals. Safety signals may also come from the known effects of similar drugs, indication-specific issues, or from knowledge of drug pharmacology. They may also arise from pre-marketing clinical trials, especially when the representativeness of the clinical trials is uncertain. These could be known at the time of drug marketing and will generate regulatory requests for post-authorization safety studies. They may also appear from alerts related to other drugs with the same pharmacological, chemical or therapeutic characteristics [66].

Typically, these alerts would warrant systematic studies, which should be devised even before the drug is put on the market [66, 67].

Data sources in pharmacoepidemiology

Pharmacoepidemiological studies can involve secondary (claims databases, electronic health records) or primary collection of data (field studies) [68].

Primary data collection

In primary data collection, studies are devised ad hoc, much as in clinical trials, and specific information, such as quality of life or blood samples for drug concentrations, or deoxyribonucleic acid (DNA) samples can be acquired. Field studies may be obligatory when the data needed is not in the claims or EHR databases, such as the side of an ocular injection, or the presence of lifestyle characteristics, or again the reasons for which a drug may have been stopped. Because these studies involve contact with patients and the generation of primary data, they are subject to patient safety requirements and informed consent. The rules for reporting adverse events will also not be the same as for secondary data (EMA good pharmacovigilance practices chapter 6, www.encepp.eu).

Studies may also combine data from an ad-hoc field study and claims databases, either directly where patients are identified, characterized and recruited by prescribers, but then followed in claims databases [69-72], or indirectly, by verifying in the field study potential association of confounders with prescribing. In the absence of an association (e.g. a drug is not preferentially prescribed in smokers), then that potential confounder is just a risk modifier and can be neglected in database studies.

Secondary sources of data

In secondary data sources, all the data is already present at the time of the study, and it would generally not be possible to enrich the dataset, though new developments in clinical data repositories might change this in the near future. These data sources might be

- Claims databases (e.g. *système national des données de santé* (French national health data system – SNDS), Medicare,...) [73]

Claims databases contain a recording of all healthcare encounters that are covered by the healthcare system or insurance company. This may include outpatient medical consultations, drugs or devices dispensed, lab test or imaging, paramedical interventions, but also hospital admissions including diagnoses and procedures. In some countries there are outpatient diagnoses, or records of chronic conditions. The data in claims databases are collected prospectively and concern all the information for all the patients covered by the healthcare system. This might be lifelong for the whole population as in France or in Nordic Countries, or limited to specific areas (in Germany, Italy or Canada), or to specific ages, social status and resources (as in the US), which may limit the usefulness or representativeness of such claims databases [74, 75].

These data might be linked to specific registries such as cancer, diabetes or rare disease registries, or death registries including or not its cause.

The advantage of the claims databases is that the data are collected systematically and prospectively, independently from any specific study, which avoids a number of potential biases. Depending on the data sources, they may contain very diverse information allowing for precise information on various potential confounders. For instance, if they do not contain such lifestyle information as smoking or body mass index (BMI), they do contain information on their medical consequences, such as chronic bronchitis, sinus infections, including use of antibiotics, peripheral arterial disease, tobacco cessation aids or devices, specialist consultations, etc. and BMI may be related to diabetes (identified directly or through its treatment), osteoarthritis and interventions such as knee or hip replacement, and the use of drugs in these indication, but also bariatric surgery and other interventions related to obesity. All these variables can be included in modern statistical analyses such as high-dimensional propensity scores and disease risk scores [76, 77].

- Electronic health records

Databases such as clinical practice research datalink (CPRD) are based on the voluntary recording by participating physicians of the clinical details of the patients they follow. This will

include outpatient diagnoses and prescriptions (not dispensing), results of lab tests and other exams (if entered) and results of specialist visits, or hospital discharge summaries, as well as lifestyle characteristics. The quality and completeness of the data depends on the health care professional's input. Ideally this will be done by a healthcare records management software, the data being transmitted to the database after anonymization. In this case the data will actually be used for patient management. Quality and completeness of the data needs to be regularly verified, and missing data may be an issue. The completeness of data may also be an issue and depend on the healthcare system. If the general practitioner (GP) is the overall curator of all the patient's healthcare, the data may be presumed complete, though hospital data may not always be fully transcribed, nor might some specialist visits [78].

- A third approach to secondary use of data is the concept of chart review, where patient files are examined for the presence of specific events such as indicators of cancer progression, which will usually not be found in the claims data [79-81]. Chart reviews may concern patients treated with specific drugs, or recorded drug exposure before events such as liver transplantation [82, 83].

Finally different data sources may be combined in datahubs, that would combine information for claims databases and from clinical records, in-hospital or outpatient, as well as data from registries, including results of lab tests or description of DNA sequencing or target information, as well as information from the emerging wearable devices [84].

Methods and designs for drug safety in pharmacoepidemiology

One may consider two main approaches to the evaluation of drug safety in pharmacoepidemiology: event-based or exposure-driven methods

Event-based methods

In this approach the event is the main driver, and case-based methods will be applied. The general approach is that cases of a given event of interest are identified, and exposures prior to that event are noted and compared to exposures in comparator patients without an event. The comparators might be the patients themselves in case-crossover methods or self-controlled case series; cases may be matched to selected controls in the classical case-control methods, with matching that may be more or less complex including (high-dimensional) disease risk scores, or at the simplest in case-population approaches, which considers the whole source population as the control population. This however require identification of all the cases in a given population. Such a method might be useful for repeated surveillance of all exposures associated with a given event, for instance hospital admissions for acute liver injury or liver transplantation. Using the national claims databases, or the national transplantation networks, these events are easy to identify. Because all events in a given territory are captured, one can compare drug exposure to the countrywide exposure to drugs identified before the event (sometimes limited to the age group that might be transplanted).

In most case-control methods, exposures in cases are compared to exposures in controls

	Cases	Controls
Exposed	a	c
Unexposed	b	d
	a+b	c+d

The usual measure of association here is the odds ratio (ad/bc)

Most commonly exposure in cases and controls are compared to non-exposure (i.e. users to non-users). However, this presupposes that exposure is random and has no link with the event, whereas exposure to drugs is not random, but determined by a disease that causes the prescription and might be associated with the event. For instance, one might expect that patients using NSAIDs have pain or inflammation, more than persons not using these drugs. Pain and inflammation may indicate an underlying disease. One would therefore expect patients using NSAIDS to be sicker and therefore die more than non-users, which indeed is the case. This bias will be common to all drugs that are thought to be curative and are given to treat diseases. When drugs are given to healthy patient for disease prevention, the comparison of users with non-user may be valid. In other cases certainly the use of active controls, drugs with the same indications would certainly be preferable.

Going from self-controlled case series to case-population is just changing the nature of the controls, from full matching in self-controlled methods to more or less tight matching in the case-control methods, to little or no matching in case-population approaches.

Case-based approaches would be useful in a pharmacovigilance setting when there is a suspicion or signal of the association of a drug with an event, where the first step would be to verify how the association compares to similar drugs with similar indications. They may also be used for systematic surveillance of known indicators of drug-related risks, such as the World Health Organisation (WHO) critical terms lists or the more common reason for removing drugs from the market. As a first approximation, these might be liver injury, renal failure, myocardial infarction, sudden death, cytopenia, gastro-intestinal bleeding. Such systematic surveillance might be automated.

Exposure-based methods

In this approach, new users of a drug will be included in a cohort, and followed for ulterior events. This would traditionally be done in field studies, using so-called registries (which are not), or phase-IV studies. In such studies with primary data collections, new users of a new drug are identified and described for factors associated with the prescription, including lifestyle factors, and followed for common events, such as drug cessation and the reasons thereof, or common adverse reactions. Except in very high-risk patients such as in cancerology, the event rates for serious events would be too low to allow quantification, in these studies of limited size. They may however provide invaluable information on less-serious common events that would not warrant hospitalization, and would not be captured in claims databases.

On the other hand, using the very large claims databases will provide for the detection and follow-up of the very first users of the drug, describe these, and how use might change over time. They will provide event rates for events resulting in hospital admissions (serious adverse reactions), or that may have therapeutic markers (such as the use of antidepressant drugs to identify depression) using prescription symmetry analysis [85-87].

These cohort studies can be very large, and will provide unbiased whole population event rates [88]. These event rates may be considered in the absolute, for instance in the absence of non-drug related occurrences of the event, or be compared to those observed with other drugs with the

same indication. In that case, the same methods used for comparative effectiveness studies can be applied. These will be conducted according to a "new user" cohort design, comparing two or more marketed drugs, reducing comparison biases with adapted methods. The inclusion only of new users in all comparison groups is necessary to avoid selection biases, or depletion of susceptibles, whereby patients who remain on a drug (prevalent users) are those who tolerate the drug or benefit from it [89]. It might also be that the use of a new drug might indicate failure of a previous drug, or poor tolerability of older drugs, or again that the new drug is indicated in a specific subset of the population with a different baseline risk. Only new users in the same indication and same patient groups are at equal risk of positive or negative events. It might be difficult to find new users in chronic diseases with a low incidence of new cases, where most patients have a long history of previous treatments.

The comparator

Comparing the use of a drug to non-use is irrelevant in real life: if a drug is used there is a reason, and that reason may be associated with adverse outcomes, that will be found only in treated (sick) persons not in untreated (healthy) persons. Most drugs when used in sick persons will be associated with a higher risk of disease. For instance users of low dose aspirin will have a much risk of cardiovascular events than non-users of low-dose aspirin [90]. Users of NSAIDs will have a higher death rate than non-users. This is a typical indication bias. Clinical trials will use for instance placebo to negate the indication bias, since all patients have the same initial disease state. In real life, to find patients with similar disease-related risk of events, one must choose drugs with if possible the same indications, i.e. active comparators. This is obviously true for cohort studies, but also in case-based analyses: a comparison with no treatment or untreated periods may simply measure the effect of the indication. It is therefore imperative to use active comparators in all pharmacoepidemiological studies. Ideally a comparator would be another new drug marketed within the same timeframe, and sharing pharmacological characteristics and indications.

Matching

The comparability of cohort groups may be enhanced by matching on variables known to be predictive of the outcome, and also associated with the use of the drugs of interest. These variables will be the most likely to be confounding variables, or to be associated with confounding variables. Presently the most extreme matching methods use high-dimensional propensity scores (hdPS), which are determined with several hundred variables among the thousands present in the datasets. They result in groups that are identical or very close on all measured variables, including those that are not part of the hdPS itself [76, 77, 91-93].

Among the benefits of these new users cohort studies are the possible comparisons with pivotal clinical trials for outcomes that were identified in these trials, including efficacy outcomes so that the applicability and representativeness of these trials can be appreciated [94]. Another benefit is that these studies will allow the evaluation of the risks associated with the drugs, and their possible benefits, with especially the final arbiter, all-cause death. This will inform the assessment of benefit-risk for drugs used in serious conditions, or to prevent serious outcomes.

Analysis

Typical analysis of the cohort studies is the determination of the relative risk, comparing event rates in exposed and comparator groups:

	Events	No Event	All
Treated	a	b	a+b
Control	c	d	c+d

Relative risk is $a/(a+b)/c/(c+d)$

In these studies, any comparative analysis would be on treatment, as exposed. Intent to treat (ITT) analyses may be justified in clinical trials, where the majority of treatment will be continued until the end of the study, so that the off-treatment period will be but a very small part of the total study period. Using ITT is essentially meaningless when the initial treatment period is short compared to potentially unlimited observation time, or when stopping treatment materially alters outcomes, or again when diseases are spontaneously reversible, or the main objective is the timing of outcomes

(most patients will eventually die). ITT can however be used when the duration of follow-up is limited to the expected duration of treatment.

Analysis will commonly use time-dependent variables in survival analysis methods with Kaplan-Meier curves and Cox proportional hazards analyses. When death is a common occurrence that may act as a competing risk, specific analyses such as Fine and Gray competing risk model should be used for the other, non-fatal outcomes [95].

Cohort studies can provide absolute risks and added risks, which may be important to make regulatory decisions.

There are many other methodological approaches or considerations, that are amply discussed each year during the annual ICPE meeting (www.pharmacoepi.org), with the use of big data, or the enrichment of claims data with data from patient data warehouses or new data sources that include not only health expenditures, but also clinical, pathology, societal or genetic information.

In summary

Spontaneous reporting of medical drug-related anecdotes has been the mainstay of drug safety or Pharmacovigilance for years, with derived analyses such as causality (imputology) or disproportionality analyses. If the absence of other information possibilities, it has served for many regulatory decisions to restrict or remove drugs from the market.

The development of large population databases such as electronic health records or claims databases allows for the more precise evaluation of the association of exposure to drugs of interest with specific events of interest, using scientifically validated methods. These should become the main source of information for regulatory decision-making.

Spontaneous reporting would be used for that which it is best suited: an alert or hypothesis generating system. Once the alert has been sounded, then other methods can be used to measure the reality and strength of the alert, understand the mechanism and possible risk factors, using adapted methods: case-based for individual events of interest, exposure based to assess comparative real-life risk-effectiveness, that will inform on more data-driven decision making [96].

Disclosure of interest

Authors have no competing interest to declare.

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Fig. 1. Management of disease and of safety issues.

$$OR = ad/bc$$

$$RRR = a/a+b / c/c+d$$

	AE+	AE-
D+	a	b
D-	c	d

Fig. 2. Disproportionality analysis. a) are the reactions of interest (ROI) in which the drug of interest (DOI) is present; b) are other reports with the same DOI; c) are the ROI associated with other drugs, and d) are all the cases that have neither the ROI nor the DOI.

Table1. The French imputation method [6, 15, 40]

Chronological imputation							
Challenge	Very suggestive			Compatible			Impossible
Dechallenge	R+	R0	R-	R+	R0	R-	
Suggestive	C3	C3	C1	C3	C2	C1	C0
Inconclusive	C3	C2	C1	C3	C1	C1	C0
Unsuggestive	C3	C1	C1	C1	C1	C1	C0

R: rechallenge; R+: positive rechallenge; R-: negative rechallenge; R0: no rechallenge or uninterpretable rechallenge

Semiological imputation						
	Suggestive of drug involvement of favorizing factor			Other cases		
Alternate non-drug explanation	L+	L0	L-	L+	L0	L-
Absent	S3	S3	S1	S3	S2	S1
Present	S3	S2	S1	S3	S1	S1

L: lab test specific of the implication of the drug in the event; L+: present and positive; L-: present and negative; L0: non-existent or not done.

Global imputation			
	S1	S2	S3
C0	I0	I0	I0
C1	I1	I1	I2
C2	I1	I2	I3
C3	I3	I3	I4