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Pharmacovigilance: The Subsequent Section

Pathan Musab Haji Farukh[1], Mirza Sharjil Beg Raees Beg[2], Shaikh Zeeshan Shaikh Sajid[3]
Dr. Taarique Deshmukh[4], Dr. Rashid Akhtar Nehal Ahmad[5]
Students, Royal College of Pharmaceutical Education and Research, Malegaon, Maharashtra, India[1,2,3]
Teacher, Royal College of Pharmaceutical Education and Research, Malegaon, Maharashtra, India[4]
Principal, Royal College of Pharmaceutical Education and Research, Malegaon, Maharashtra, India[5]

Abstract: *Analyzing spontaneously reported cases with great care has long been the foundation for the identification and measurement of adverse drug reactions. An essential component of the analysis of individual case reports was the assessment of causality (imputation). Analysis of aggregated cases and disproportionality analyses in databases of spontaneous reports were added to this. These have changed drug information by leading to the discovery of numerous new adverse reactions in the lack of more focused information sources. Many drugs have been pulled off the market as a result of it, but its application to risk quantification is still unclear. The generation of hypotheses for serious adverse drug reactions, particularly those that lead to hospital admission or death, is largely dependent on spontaneous reporting, as evidenced by the accessibility of databases holding electronic health records or claims data for the entire population. In these situations, the events can be precisely quantified using the instruments of contemporary pharmacoepidemiology to produce benefit-risk analyses that are specific to the population. Despite its inherent limitations, spontaneous reporting is still essential for generating signals and alerts related to drug safety. Further systematic and quantitative methods, like claims databases for reactions resulting in hospital admissions, should be pursued for signal strengthening and assessment*

Keywords: Drug safety, population databases, pharmacovigilance, and pharmacoepidemiology

I. INTRODUCTION

While all drugs have risks, some may also have benefits [1]. The dose is what distinguishes the drug from the poison; everything is poison and nothing is poison [2].

We reviewed the development of pharmacovigilance and offered some predictions for the future in a previous paper [3]. After five years, not much has changed in the world. Patient reporting has become commonplace in addition to the custom of healthcare professionals reporting on their own initiative. Social media usage has skyrocketed, and its usage is being studied in an attempt to find potential new safety concerns [4].

Hospital-based data repositories and electronic health records have created new opportunities, and data resources like databases for the nation's healthcare systems are now easily accessible.

Reviewing these developments and attempting to forecast the future—the next phase of pharmacovigilance—are the goals of this paper. Will the upcoming chapter on big data and pharmacoepidemiology in pharmacovigilance follow the ones that dealt with spontaneous reporting, individual case report analysis, reporting patterns, and report databases in previous chapters?

The framework for this reflection is that drug safety management, also known as pharmacovigilance, is comprised of the following steps: identifying a signal, determining the signal, which subsequently becomes an alert; quantifying the alert, which may become an alarm; and managing the alarm. These steps essentially mirror the standard clinical management of disease, which includes suspicion (symptoms), diagnosis (confirmation), evaluation (scope and severity), and treatment (followed by a measure of the treatment's effectiveness). Just as no one exam or test can do all the work in clinical medicine, each of these steps requires a different set of skills and methods (Fig. 1).

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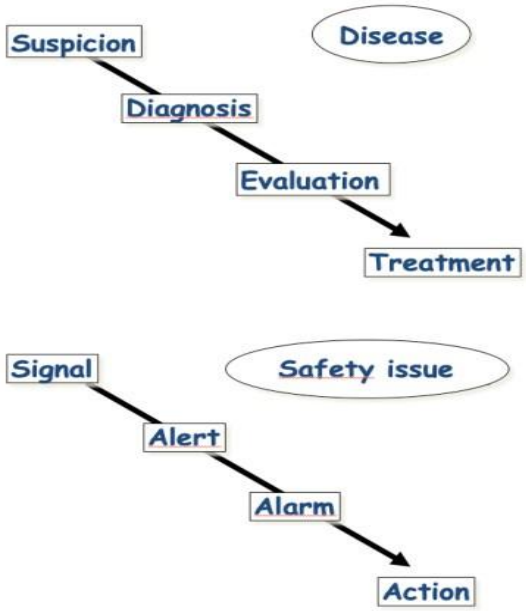

Fig. 1. Management of disease and of safety issues.

The following steps can be related to the methods mentioned:

a) evaluation of individual case reports and spontaneous reporting;

b) analysis of reporting patterns and databases of spontaneous reporting; and

c) utilization of population-based resources.

This paper is based on medical knowledge about drug-induced diseases and the science of pharmacovigilance, which is the detection and prevention of adverse drug reactions. The relevance of definitions and regulations from the Food and Drug Administration (FDA), European Medicines Agency (EMA), Individual Case Safety Reports (ICSR), Individual Case Reports (E2B), International Council for Harmonization of Technical Requirements for Pharmaceutical Use (ICH), or the Medical Dictionary for Drug Regulatory Activities (MedDRA) will not be discussed in this paper. Pharmacovigilance has become a highly regulated issue. 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-authorization/pharmacovigilance/goodpharmacovigilance-practices#final-gvp-modules-section) are two websites that are a must-read for anyone employed in the field, at least if they want to avoid major legal issues. Pharmacovigilance, however, goes beyond simply keeping track of bodies and ensuring that reports are submitted on time. It is not just about these legal considerations. Regulations are a necessary prerequisite, but we won't go into detail about them here.

Spontaneous reporting

McBride's 1961 brief letter published in the Lancet, "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, changed the history of drug safety." of a sedative, to be roughly 20%... Have any of your readers observed comparable anomalies in infants born to mothers who took this medication while pregnant "[5] As a result, systems for reporting adverse drug reactions (ADRs) were created on a national and worldwide level [6-7], professionals who are vigilant realized the importance of ADR reporting, and the idea of pharmacovigilance. There were no population databases and very little processing power available at the time. The majority of information regarding drug safety was derived from small-scale, frequently poorly representative clinical trials. Not much has changed in this regard [8]. Spontaneous reporting emerged as the primary means of detecting the occurrence of novel adverse drug reactions not

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anticipated by pharmacology, and this has remained largely unchanged ever since. However, the true value of spontaneous reporting has been more clearly defined and, hopefully, comprehended.

Reports on specific cases

Individual case reports detail a patient's experience with a particular medication. An identified patient, an identified reporter, a medication, and an event serve as the foundation for a typical report [9–11]. That is the regulatory basic dataset, which, when restricted to this minimal information set, is regrettably essentially meaningless for assessment purposes. What Jeff Aronson refers to as "anecdotes as evidence" is necessary for an event to be truly evaluable for a correlation with a particular drug in a particular patient [12]. Drug characteristics (dosage, length of treatment, indication for use, dechallenge and rechallenge [if any]), patient characteristics (age, sex, concomitant disorders, concomitant medication, genetic susceptibilities), and event details (start date, including first symptoms, not just diagnosis), diagnostic certainty (including pertinent lab tests), exclusion of other potential causes, and dates regarding potential dechallenge and rechallenge) are all important to know [12–14]. For an analysis of potential causality, all of this information is essential and should be obtained as soon as possible, ideally while the reaction is still occurring. This will allow for the collection of information (such as additional medication or lab tests) while the case is still fresh and may even allow for the generation of missing information (lab tests, other causes, etc.).

Causality

After gathering these components, a variety of techniques for determining causality—also known as imputation or imputability—can be used. Numerous techniques for determining causality in individual case reports have been developed over the years, and new ones are constantly being developed [15–37]. Because they may have different goals, different causality approaches may produce different results [21, 24, 25, 30]. An undesirable and harmful effect that arises during regular drug use is the traditional definition of an adverse drug reaction; however, more recent regulations have added additional dimensions, such as overdose, medication errors, drug abuse, or dependence, which may alter the causality methods [27].

The inclusion of prior knowledge of a potential link between the drug and the event, as well as the distinction between intrinsic imputability—which pertains to the case itself—and extrinsic imputability—which is related to prior knowledge of cases that are similar—are two methods that differ from one another. For a prescriber, the goal of causality may be to determine which medication in a particular patient is most likely to be the cause of the adverse reaction and needs to be stopped first. Finding any mitigating factors and determining whether any other drugs or diseases might be involved could be important to a pharmaceutical company. The identification of novel signals—that is, whether any of the patient's medications may be at play—is crucial for regulators, particularly for more recent medications about which there is scant data.

Naturally, different goals will result in different approaches to processing the same data. Differences in the outcomes produced by various methods may be explained by the use of pre-existing data [21, 25, 30, 38].

Eliminating drugs for which causality is ruled out or highly unlikely will also serve as a very helpful goal of narrowing the field of inquiry to a small number of potential suspects. When the drug is administered after the onset of the reaction, the main basis for exclusion will be chronological impossibility. This is because no clinical event can be officially ruled out as not being possibly related to a drug if the chronological sequence is compatible.

a) The timeline is the primary criterion for causality; the drug must have been taken prior to the event commencing. This suggests that in order to prevent protopathic bias, also known as reverse causality, the drug being administered for the event's early symptoms must precisely identify the event's beginning. Similar to patopathic bias, indication bias occurs when a medication is prescribed for a condition that is linked to the incident, such as pain, fever, infection, or myocardial infarction [39].

The event diminishes when the drug is stopped or the dosage is lowered (within the typical pharmacokinetics of the drug, and the natural evolution of the event), which is the secondary timeline criterion. Once more, the rationale for discontinuing the medication ought to be recorded: was it done so because the patient was improving or because the drug was stopped because an incident was suspected to be drug-related? This is an additional example of protopathic bias. Alternatively, did the treatment, whether or not the drug was stopped, cause the reaction to lessen? Rechallenge is

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commonly defined as the crucial element that validates the degree of correlation between the drug and the event in a particular patient, provided the event recurs upon the drug's administration for any given reason. If the medication is administered again for a recurrence of the event, challenge may also be connected to protopathic or indication bias. In most cases, particularly when it comes to allergic reactions, which might worsen the second time, retaliation would be unintentional. For pharmacological reactions, reintroduction might be taken into consideration at a lower dosage.

b) The criteria for the event description are less stringent: indications and symptoms, which are connected to the characteristics of the drug (such as hypokalaemia in the case of diuretics or neutropenia in the case of cytotoxic cancer treatments), may validate the pharmacological nature of the reaction. Naturally, this depends on the specific context, as new medications may have unreported direct pharmacological effects, or targeted therapies may have poorly defined targets. Therefore, a direct causal relationship is not always excluded just because a reaction has not been inferred from a drug's known effects.

c) Another common criterion for causality is the absence of a competing cause. This criterion is more arbitrary and contingent on the extent to which alternative causes are sought after; it may also be connected to the belief that drugs played a role. Furthermore, new causes might develop over time; thus, a report that only lists the drug of interest as the cause could actually be the result of a different cause that eventually surfaces.

Recommendations for datasets in published reports have compiled the data items required to evaluate individual case reports [13].

These various data items can be combined and used in a variety of ways, including feeding algorithms. One well-known example is the French Imputability model, which produces partial and global imputability scores by feeding data into a 3-way table (Table 1) [6, 15, 40].

Computer-assisted probabilities, or Bayesian scores [17–19, 29, 36, 41]. Additionally, there are event-specific causality approaches like the Roussel Uclaf causality assessment method (RUCAM) for drug-induced liver injury [33, 42–44], or comparable applications for skin reactions [45], hemolytic anemia [46], and other conditions. Lack of information is the main problem in determining causality, which typically leads to a causality that is not excluded (not impossible, but insufficient data to draw a formal conclusion).

The European ABO classification can be used to summarize this, with A denoting a reasonable or plausible association, B denoting a possibility, and O denoting insufficient information [34].

Reports for analysis have also been categorized according to causality, which is again primarily based on information content.

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

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Implicit biases in spontaneous reporting

Numerous biases exist in spontaneous reporting, including the notoriety bias, commonly referred to as the "round up the usual suspects" or Casablanca syndrome [47]. A case of protopathic bias occurs when a drug is prescribed for early signs or symptoms of an event (e.g., antibiotics for fever prior to agranulocytosis) [48, 49]. Another type of bias is indication bias, which occurs when a drug is prescribed for a condition that may cause the effects (e.g., non-steroidal anti-inflammatory drugs [NSAIDs] for acute pain, which can cause myocardial ischemia on its own) [50]. Numerous additional biases may impact causality or spontaneous reporting [39].

The purpose of determining causality:

If the goal of the causality assessment is to identify the medication that is most likely to be involved in a particular patient, then prior descriptions of the association may indicate which medication, out of all the medications taken by the patient, should be stopped first. The fact that a reaction hasn't been documented before is irrelevant if the goal is to find previously unidentified reactions because, by definition, only known reactions will be found if known reactions are the only ones looked for. Conversely, as was the case with thalidomide and phocomelia, previously unreported reactions with strong apparent causality might be of particular interest.

Diverse approaches aimed at distinct goals will yield disparate outcomes.

Approaches that take into account or give weight to past descriptions of comparable events—including labeling the reaction in the product characteristics summary—would be most helpful for prescribers managing individual patients because they would identify the medications most likely to be actually involved. Consider a horse if you are a prescriber and you hear hoofbeats in front of a patient.

However, for a pharmaceutical company, the primary goal of a causality assessment could be to discredit their product by finding alternative explanations for a patient's reaction.

Finding new signals—those cases with strong chronological causality, no other cause discovered, and no prior association between the event and the drug in question—would be a regulatory agency's primary goal. These are known as initial index cases. If you work as a regulator and hear hoofbeats, you might associate it with zebras. However, you should only come to the conclusion that a horse exists after you have confirmed that there is no zebra.

The traditional imputability methods do not address the new regulatory definitions of adverse reactions, which include medication errors, misuse, abuse, or dependence. Consequently, if one wishes to investigate the causality of these reactions, new and different methods may be needed [27].

The assessment of individual drugs is, however, limited. While it can show that a drug may likely cause a particular reaction under certain conditions (index cases, high imputability cases, "smoking gun case") [14], a single case or anecdote cannot provide sufficient information to support regulatory decisions. On the other hand, it might produce a distinct signal that will support additional research.

Disproportionality analyses and case groups

When there aren't any smoking gun cases, other factors—such as the existence of several cases—can persuade people of the association's validity and raise an alarm.

A strong indication that something is occurring (or that all the cases share the same indication or protopathic biases) may be present if the reported cases are similar to one another.

A pseudo-epidemiological method known as proportionality analysis compares the percentage of an event associated with a drug among all events associated with the drug to the same percentage for a comparator population (Fig. 2).

As long as there are at least three reports, this will provide reporting odds ratios (ROR) [51, 52], proportional reporting rate ratios (PRRR) [53, 54], or any number of other measures of disproportionality, of varying complexity, but producing similar conclusions. [55] Although this disproportionality measure is merely a potential signal or alert indicator, it has the benefit of offering quantitative analysis in the form of confidence intervals, which can be interpreted as probabilities and may even produce P-values. It is easy to forget that these are disparities in the reporting of events, not the actual occurrence of them. It's common to claim that something is more common when, in reality, it's only the relative reporting of that event that is. FDA or EMA regulatory authorities advise marketing authorization

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holders to perform disproportionality analysis on a regular basis in order to detect safety signals (refer to GVP VIII, IX).

Disproportionality is predicated on the null hypothesis, which holds that reporting is random and that any of the patient's medications could be arbitrarily linked to any particular event. In the event that a drug is linked to the incident, that drug will be discovered more frequently than would be predicted by chance. In order to prevent adding causality biases to the biases already present in reporting and disproportionality, disproportionality needs to be examined using all reports mentioning the drug, whether they are suspect or not, and without using any individual causality [56].

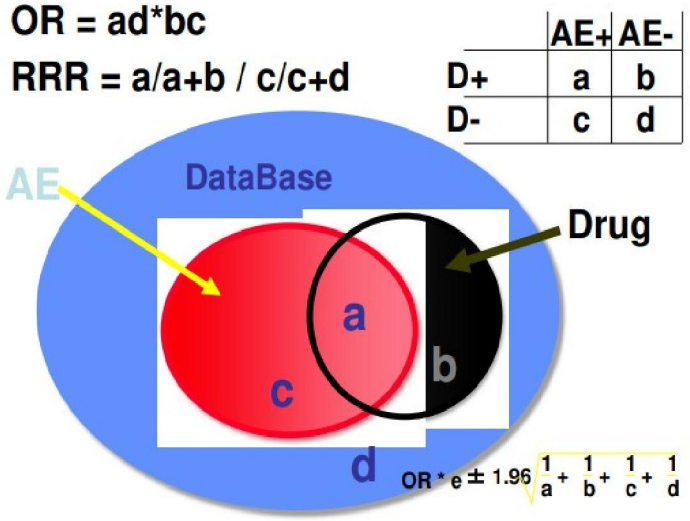

Fig. 2. Disproportionality analysis. a) are the reactions of interest (ROI) in which the drug of interest (DOI) is present; b) are other reports with the same DOI; c) are the ROI associated with other drugs, and d) are all the cases that have neither the ROI nor the DOI.

Disproportionality analysis biases

Beyond the reporting of the individual cases that feed the analysis (protopathic, indication, and notoriety), there are numerous potential biases due to the declarative and non-systematic nature of the data [56]. There have been numerous reports of factors that could erroneously impact disproportionality analyses [57–65].

One way to improve a reporting ratio is to report the event of interest more often while reporting the other events less frequently. A medication with excellent tolerability and few other reports will produce a far stronger signal than a medication with the exact same risk but many more reports of adverse reactions due to poor tolerability. The Weber effect describes how these shift with time in reporting. A well-publicized adverse event that could prompt regulatory action could also raise signals about the same event in other drug families or in drugs belonging to the same family [63]. Common drug associations have the potential to produce signals involving two drugs when only one should be of concern [62]. Even in the lack of interactions, event masking by other drug-event associations has been documented [58].

Selecting the right comparator can also be very important. This could be the entire database, which is probably inappropriate if the population's risk factors for the event are not distributed equally. Alternatively, the comparators could be medications used for related indications or other medications in the same family. In the event that there is no discernible alert pertaining to the drug of interest or the comparator, these drugs should ideally be marketed concurrently to prevent distortion due to the Weber effect [56]. These biases are manipulable and should be carefully considered. For example, reporting more non-specific (even serious) or well-known reactions will increase "b," which will obscure the appearance of new signals. One surefire way to hide new alerts is to report more trivial events.

Disproportionality is highly susceptible to reporting biases, particularly those related to notoriety, which can lead to spurious alarms or, conversely, false alerts. Disproportionality measurements of the events should ideally be examined

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prior to the publication of any alerts or cases. Analysis of spontaneous reporting stops having any value as soon as an alert is discovered and made public [60–64].

In the absence of obvious biases, individual case reports with strong causality and disproportionality analyses may suggest that there is a signal—possibly even an alert—that requires further examination. Numerous regulatory decisions were made in situations where the only information available was spontaneous reporting. Additionally, this could still be the case if a single new drug entity is closely linked to a wave of uncommon, serious events that are known to be drug-related.

In other situations, no decision should be taken without carefully analyzing population data and pharmacoepidemiology if the events are uncommon, may have multiple causes, and the drugs have been on the market for a long time.

The management of issues that have been identified falls under the risk management chapter. This chapter emphasizes the need for systematic evaluation using population analytics resources rather than relying solely on the spontaneous reporting of individual reactions.

Pharmacoepidemiology

Potentially the most effective means of producing novel drug safety signals is probably spontaneous reporting of unexpected or serious reactions. Safety signals can also originate from issues specific to an indication, from knowledge of drug pharmacology, or from the known effects of similar drugs. They could also result from pre-marketing clinical trials, particularly if it's unclear how representative the trials were. These may have been known when the drug was marketed, and they will lead to requests for post-authorization safety studies from the regulatory authorities. They could also show up in alerts for other medications that share the same pharmacological, chemical, or therapeutic properties [66]. These warnings usually call for comprehensive research, which ought to be planned even before the medication is released onto the market [66, 67].

Sources of Data in Pharmacoepidemiology

Pharmacoepidemiological research may use primary data collection methods (field studies) or secondary data collection methods (claims databases, electronic health records) [68].

Primary Gathering of Data

Similar to clinical trials, studies are designed on the fly during primary data collection. Specific data can be obtained, including quality of life, blood samples for drug concentrations, and deoxyribonucleic acid (DNA) samples. Field studies might be required when the information required—such as the side effects of an ocular injection, the existence of lifestyle traits, or the potential reasons for stopping a medication—is not available in the claims or EHR databases. These studies are governed by informed consent and patient safety regulations because they involve patient interaction and the collection of primary data. Additionally, there will be differences in the regulations for reporting adverse events and secondary data (EMA good pharmacovigilance practices chapter 6, www.encepp.eu).

Ad hoc field studies and claims databases can also be combined in studies. This can happen directly, when patients are found, described, and enrolled by prescribers and are then tracked in claims databases [69–72], or indirectly, when potential confounder associations with prescribing are confirmed in the field study. When there is no correlation (for example, when a medication is not prescribed more often to smokers), the potential confounder is merely a risk modifier and can be disregarded in database research.

Secondary data sources

Although new advancements in clinical data repositories may soon change this, in secondary data sources, all the data is already present at the time of the study and it would typically not be possible to enrich the dataset. These information sources could be

Claims databases, such as Medicare, the système national des données de santé (SNDS), the French national health data system, [73]

All medical encounters that are paid for by the insurance company or the healthcare system are documented in claims databases. In addition to hospital admissions with diagnosis and treatments, this may also include outpatient medical

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consultations, medication or device dispensing, lab testing or imaging, and paramedical interventions. There are records of chronic conditions or outpatient diagnoses in some countries. The information gathered for each patient covered by the healthcare system is stored in claims databases and is gathered prospectively. This may limit the usefulness or representativeness of such claims databases [74, 75]. It may also be lifelong for the entire population, as in the case of France or the Nordic countries, or restricted to particular areas, as in the case of Germany, Italy, or Canada, or to specific ages, social status, and resources, as in the case of the US.

These records may be connected to particular registries, such as those for diabetes, cancer, or other uncommon diseases, or to registries of deaths, whether or not the cause was listed.

The benefit of the claims databases is that they prevent a number of potential biases because the data are gathered methodically and prospectively, apart from any particular study.

Depending on the data sources, they might include a wide range of information that makes it possible to pinpoint specifics about different possible confounders. For example, even if they don't include lifestyle details like smoking or body mass index (BMI), they do include information on the medical consequences of those behaviors, like chronic bronchitis, sinus infections, using antibiotics, peripheral arterial disease, using devices or aids to quit smoking, seeing a specialist, etc. BMI can also be linked to diabetes (either directly or indirectly), osteoarthritis, knee or hip replacements, using medications for these conditions, bariatric surgery, and other obesity-related interventions. Modern statistical analyses, like those that use high-dimensional propensity scores and disease risk scores, can incorporate all of these variables [76, 77].

Electronic health records

Clinical practice research datalink (CPRD) and other databases rely on participating physicians voluntarily entering clinical details of the patients they monitor. This will include lifestyle factors, laboratory test and other exam results (if entered), results of specialist visits, discharge summaries from hospitals, and outpatient diagnoses and prescriptions (not dispensing). The health care professional's input determines the data's quality and completeness. A healthcare records management program will ideally handle this, sending the anonymized data to the database. In this instance, patient management will truly make use of the data. Regular verification is necessary to ensure the accuracy and completeness of the data, and missing data could be a problem. The accuracy of the data may also be a problem and will rely on the medical system. The data may be deemed complete if the general practitioner (GP) is in charge of overseeing all aspects of the patient's healthcare; however, not all hospital records and some specialist visits may have been fully transcribed [78].

Chart reviews, which are a third method of using data for secondary purposes, involve looking through patient files to see if there are any specific events—like signs of cancer progression—that aren't typically included in the claims data [79–81]. Chart reviews may address patients receiving particular medication treatments or documented drug exposure prior to liver transplantation [82, 83].

Lastly, various data sources can be merged into datahubs, which would include information from clinical records—in-hospital or outpatient—claims databases, data from registries, including test results and DNA sequencing descriptions or target information, and information from newly developed wearable technology [84].

Pharmacoepidemiology approaches and designs for medication safety

In pharmacoepidemiology, there are two primary methods for assessing drug safety: methods that are exposure- or event-driven

Methods based on events

With this strategy, the event serves as the primary motivator, and case-based techniques are used. The standard procedure involves identifying cases of a particular event of interest, noting exposures before that event, and comparing those exposures to exposures in comparator patients who do not have an event. In case-crossover methods or self-controlled case series, the comparators could be the patients themselves; in classical case-control methods, cases are matched to a subset of controls, with matching that can be relatively complex and involve (high-dimensional) disease risk scores, or at the most basic level, casepopulation approaches, which take the entire source population as the control

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population. Nonetheless, this necessitates the identification of every case within a specific population. When repeatedly monitoring all exposures linked to a specific event—such as hospital admissions for acute liver injury or liver transplantation—this kind of approach could prove helpful. These occurrences are simple to locate using the national transplantation networks or the national claims databases. One can compare drug exposure to the national exposure to drugs identified prior to the event (sometimes restricted to the age group that might be transplanted) because all events within a given territory are recorded.

Exposures in cases are compared to exposures in controls in the majority of case-control methodologies.

	Cases	control
Exposed	a	c
unexposed	b	d
	a+b	c+d

In this case, the odds ratio (ad/bc) is typically used to measure association.

Exposure in cases and controls is most frequently contrasted with non-exposure (i.e., users versus nonusers). But this assumes that exposure is random and unrelated to the event, whereas drug exposure is determined by a disease that results in the prescription and may be connected to the event. For example, it is reasonable to assume that patients taking NSAIDs will experience more pain or inflammation than those who are not. Inflammation and pain may be signs of a hidden illness. As a result, one would anticipate that NSAIDS users would be sicker and, consequently, die at a rate higher than non-users, which is in fact the case. All medications that are prescribed to treat illnesses and are believed to be curative will share this bias. Comparing drug users with non-users may be valid when the drugs are administered to healthy patients in an effort to prevent disease. In other situations, it would undoubtedly be better to employ active controls or medications with similar indications. Simply changing the nature of the controls is all that is required to go from self-controlled case series to case-population approaches. Full matching in self-controlled methods is replaced with more or less tight matching in case-control methods, and little to no matching in case-population approaches.

When there is a suspicion or indication of a drug's connection to an event, case-based approaches could be helpful in a pharmacovigilance setting. In this situation, the first step would be to confirm how the association compares to similar drugs with similar indications. They could also be employed for systematic monitoring of recognized markers of drug-related hazards, like the essential terms lists maintained by the World Health Organization (WHO) or the more typical grounds for drug withdrawals from distribution. These could include, as a first approximation, cytopenia, myocardial infarction, liver damage, renal failure, and gastrointestinal bleeding. Automated surveillance could be one such method.

Exposure-based techniques

This method involves adding new drug users to a cohort and keeping an eye out for unexpected events. Traditionally, phase-IV studies or field studies using purported registries—which are not—would be used for this. New users of a new drug are identified, profiled, and followed for factors related to the prescription, including lifestyle factors, and followed for common events, like drug cessation and the reasons behind it, or common adverse reactions in such primary data collection studies. The event rates for serious events in these small-scale studies would be too low to allow quantification, unless the patients were very high-risk, as in the case of cancer patients. Nonetheless, they might offer priceless information on less serious frequent occurrences that wouldn't require hospitalization and wouldn't show up in claims databases.

However, by utilizing the enormous claim databases, it will be possible to identify and track down the drug's initial users, provide a description of them, and track changes in their use over time.

Using prescription symmetry analysis, they will provide event rates for events leading to hospital admissions (serious adverse reactions) or that might have therapeutic markers (e.g., using antidepressant drugs to identify depression) [85-87].

These cohort studies will yield unbiased whole population event rates and have the potential to be very large [88]. These event rates can be compared to those recorded with other drugs that have the same indication, or they can be taken as absolutes, for example, in the absence of non-drug related occurrences of the event. Then, you can use the same techniques that are used in studies of comparative effectiveness. These will compare two or more marketed drugs

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using a "new user" cohort design, mitigating comparison biases through the use of adapted methods. To prevent selection biases or depletion of susceptibles—a situation in which patients who continue on a medication (prevalent users) are those who tolerate it or benefit from it—only new users must be included in all comparison groups [89].

Additionally, the use of a new medication may signal poor tolerability of an older medication or the failure of a previous medication. Alternatively, it may signal that the new medication is indicated in a particular subset of the population with a different baseline risk. The only patients who are equally at risk of positive or negative events are new users in the same indication and patient groups. In chronic diseases where there is a low incidence of new cases and most patients have had previous treatments for a long time, it may be challenging to find new users.

The comparator

In real life, it is irrelevant to compare drug use to non-use; if a drug is used, there is usually a reason for it, and that reason may have negative effects that are specific to treated (ill) individuals and not untreated (healthy) individuals. Most medications carry a higher risk of illness when taken by sick people. For example, individuals who take low doses of aspirin are far more likely to experience cardiovascular events than those who do not [90]. The death rate for NSAID users will be higher than that of non-users. This is a common bias in indications. Since every patient starts a clinical trial with the same disease state, the indication bias will be eliminated, for example, by using placebo. 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. For this reason, it is essential that all pharmacoepidemiological research employ active comparators. Ideally a comparator would be another new drug marketed within the same timeframe, and sharing pharmacological characteristics and indications.

Matching

Matching on variables linked to the use of the relevant drugs and known to be predictive of the outcome may improve the comparability of cohort groups. These variables have the highest probability of either being confounding variables themselves or of being related to them.

High-dimensional propensity scores (hdPS), which are calculated using several hundred variables out of the thousands in the datasets, are currently used in the most extreme matching techniques.

They produce groups that, for every variable measured, including those not included in the hdPS itself, are identical or very similar [76, 77, 91-93].

The ability to compare outcomes found in these trials, such as efficacy outcomes, with pivotal clinical trials is one of the advantages of these new users cohort studies. This allows one to understand the applicability and representativeness of these trials [94].

Another advantage is that these studies will make it possible to assess the potential advantages and risks of the medications, particularly with regard to the ultimate arbiter, all-cause death. This will help in determining the benefit-risk analysis of medications used to treat severe illnesses or avoid catastrophic consequences.

Analysis

Cohort studies are typically analyzed to determine relative risk by comparing event rates between comparator and exposed groups:

	Events	Noevents	All
Treated	a	b	a+c
control	c	d	c+d

It is a/(a+b)/c/(c+d) for relative risk.

Any comparative analysis in these studies would focus on the treatment as it is exposed. In clinical trials, where the majority of treatment will be continued until the end of the study, meaning that the off-treatment period will be but a very small part of the total study period, intent to treat (ITT) analyses may be justified. When a disease is spontaneously reversible, the main goal is the timing of outcomes (most patients will eventually die), the initial treatment period is short compared to potentially unlimited observation time, or stopping treatment materially alters outcomes, using ITT is

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essentially meaningless. However, when the follow-up period is constrained to the anticipated length of treatment, ITT may be utilized.

Time-dependent variables are frequently used in survival analysis techniques, such as Cox proportional hazards analyses and Kaplan-Meier curves. Particular analyses, such as the Fine and Gray competing risk model, should be used for the other, non-fatal outcomes when death is a frequent occurrence that could operate as a competing risk [95].

Cohort studies can offer additional and absolute risks, which may be crucial information for regulatory decision-making.

Many other methodological approaches and considerations are covered in detail each year at the ICPE annual meeting (www.pharmacoepi.org). These include the use of big data and the enrichment of claims data with information from patient data warehouses or new data sources that include clinical, pathology, genetic, and clinical information in addition to health expenditures.

In summary

For many years, the cornerstone of drug safety or pharmacovigilance has been the spontaneous reporting of medical drug-related anecdotes, with derived analyses like disproportionality or causality (imputology) analyses. In the lack of alternative information sources, it has aided in numerous regulatory decisions to limit or remove medications from the market.

Large population databases, like electronic health records or claims databases, have made it possible to use methods that have been validated by science to more precisely evaluate the relationship between exposure to drugs of interest and particular events of interest. These ought to take precedence over other information sources when making regulatory decisions.

An alert or hypothesis-generating system would be the ideal application for spontaneous reporting. After the alarm has gone out, additional techniques can be employed to gauge the alert's strength and reality, comprehend its mechanism, and identify potential risk factors. These techniques include exposure-based assessment of comparative real-life risk-effectiveness and case-based analysis of specific events of interest, all of which will support more data-driven decision-making [96].

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Abbreviations
ADRs: adverse drug reactions
BMI: body mass index
CPRD: clinical practice research datalink

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DNA: deoxyribonucleic acid
E2B: clinical safety data management: data elements for transmission of individual case safety reports
EMA: European Medicines Agency
EnCEPP: Network of Centers for Pharmacoepidemiology and Pharmacovigilance in Europe
FDA: Food and Drug Administration
GP: general practitioner
ICH:The International Council for Harmonization of Technical Standards for the Use of Medicinal Products
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