Trends in
Pharmacological Sciences

CellPress
OPEN ACCESS

Opinion

A smart hospital-driven approach to precision pharmacovigilance

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Researchers, regulatory agencies, and the pharmaceutical industry are moving towards precision pharmacovigilance as a comprehensive framework for drug safety assessment, at the service of the individual patient, by clustering specific risk groups in different databases. This article explores its implementation by focusing on: (i) designing a new data collection infrastructure, (ii) exploring new computational methods suitable for drug safety data, and (iii) providing a computer-aided framework for distributed clinical decisions with the aim of compiling a personalized information leaflet with specific reference to a drug's risks and adverse drug reactions. These goals can be achieved by using 'smart hospitals' as the principal data sources and by employing methods of precision medicine and medical statistics to supplement current public health decisions.

Highlights

Adverse drug reactions (ADRs) rank as the fifth most frequent cause of death in developed countries, with the majority of severe ADRs occurring in hospitalized patients. Some groups (notably women and children) seem to be the most affected.

Pharmacovigilance is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse drug effects. It is currently based on a fragmentary and uncoordinated process of data collection that is unfit to tackle individual decisions.

Precision pharmacovigilance is a new concept where pharmacovigilance 'meets' precision medicine to match patients' individual needs.

A more precise data collection and effective computational methods can pave the way to precision pharmacovigilance.

Smart hospitals can serve as hubs for data collection, analysis, and distribution of clinical decisions tailored for individual patients.

It is time for precision in pharmacovigilance

Some global health issues leading to hospitalization and even death have been, and still are, poorly recognized. For instance, **adverse drug reactions (ADRs)** (see Glossary) represent a silent but persistent pandemic that is ranked as the fifth most frequent cause of death in developed countries [1]. More worrisome, according to extensive surveys conducted in the United States, the majority of severe ADRs occur in hospitalized patients[i] [2] and some groups, notably women and children, seem to be the most severely affected [3]. These groups are often excluded from randomized controlled trials (RCTs) for understandable safety concerns but they do appear to experience ADRs more frequently than would be expected [4].

Pharmacovigilance is a process that aims at managing ADRs and any other drug-related problems by means of drug surveillance and risk prevention. Beyond academic and clinical research, the detection, assessment, understanding, and prevention of ADRs are implemented via a dual surveillance system involving drug regulators and pharmaceutical companies [5,6].

Information technologies should play a greater role in achieving the goals of pharmacovigilance by introducing data and knowledge engineering methods for **safety signal** detection, analysis, and management [7–16]. To this end, various data sources of potential signals are being explored both in the literature and at the operational ground level. These new approaches include: (i) voluntary reporting systems, through which observed cases, known as individual case safety reports (ICSRs), are reported by healthcare professionals to the regulatory authorities and other bodies; (ii) observational databases [e.g., electronic health records (EHRs)], which are useful in identifying causal relationships between groups of problematic clinical conditions and suspected drugs; (iii) free-text resources, for example, the scientific literature and patient self-reports, next to the growing role played by social media data [17,18].

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Due to the importance of drug safety and the limitations of each signal source (e.g., data sparsity, small samples sizes, short time horizon limiting the detection of long term ADRs), it has been argued by international authorities that there is a need for a more comprehensive **adverse drug event (ADE)** surveillance system that would be capable of handling all of these possible information sources [19]. However, the heterogeneity, fragmentation, and lack of standardized/well-defined interfaces that could characterize the available data sources and the signal detection methods complicate the implementation of this kind of synthesis. At present, there is an uncoordinated process of data collection that is unable to integrate *ab initio* a minimum package of information related to signals (especially those stemming from ICSRs) from one side with drug consumption data from the other. This appears to be the main culprit, explaining the low reliability in estimating the true incidence not only of ADRs but also of other pharmacoepidemiologic measures in patient populations. This failure to deliver affordable statistical measures has been summarized by Edwards [1], 'pharmacovigilance operates without clear objectives in relation to individual decisions, [...] with obscure materials and methods used for making decisions, with very limited reasoning and discussion, and little or no follow up and audit of the results'.

Despite these criticisms, the problem has been approached by: (i) analyzing one data source at a time, mainly resorting to nonparametric statistical methods [20] (for instance, disproportionality analysis based on contingency tables built on data); (ii) linking *ex post* two or more data sources of potential signals to **reimbursed prescriptions** databases or other proxies of drug consumption [9,17,21]. An ambitious example of the latter approach is the ORDEI drug safety project[ii], launched by the French National Agency for Medicines and Health Products Safety, ANSM, which is intended to merge information coming from at least three national databases: one concerning ADEs extracted from case reports, one collecting information on reimbursed prescriptions, and one including drug safety information for a large set of authorized medicines. However, there is a major concern emerging from this kind of approach regarding the concept of therapeutic adherence: the data of prescription purchases does not guarantee *per se* that the patient has consumed the prescribed drug at all or at the correct dosage or time. Sometimes, this can be particularly problematic and have disastrous consequences, not only for his/her health but also on the soundness of database linking and on the robustness of information extraction.

As an alternative to this kind of approach, another path has been advocated by academics [22,23], drug regulators [24], and the pharmaceutical industry[iii]: precision pharmacovigilance. In this case, the goal of precision pharmacosurveillance is similar to the changes occurring in medical treatment (i.e., the development of **precision medicine)**. This strives to achieve a customization of healthcare, with medical decisions, treatments, practices, or products being tailored to each specific patient, instead of a one-drug-fits-all paradigm [25]. Whereas precision medicine is clearly on the horizon in even routine clinical practice in many diseases [26], pharmacovigilance is lacking such advances and the push towards a precision framework for this field is still at a very initial stage [27]. Nevertheless, some proposals for implementing precision pharmacovigilance have been outlined [28,29], for example, attempting to cluster specific risk groups in spontaneously reported ADE databases[iv], with the goal of mitigating children's risks in paediatric pharmacosurveillance [30,31] and with a particular focus on hospitalized patients in emergency wards [32–34]. These publications highlight our viewpoint that the hospital can be considered as a privileged observatory for precision pharmacovigilance. In this respect, the data should not be restricted to registering the medical events in emergency departments. We propose that a **smart hospital** could resemble a good laboratory where researchers could examine, at the same time, samples of patients taking drugs and subsets of those experiencing possible ADRs. This constitutes the kernel of a smart hospital-driven approach to precision pharmacovigilance: we will outline this new concept in the next section. Afterwards, we will investigate methods

Glossary

Adverse drug event (ADE): any untoward medical occurrence in a patient or individual administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment [29].
Adverse drug reaction (ADR): in postmarketing settings, a response to a drug that is noxious and unintended and which occurs at doses normally used for prophylaxis, diagnosis, or therapy of a disease or for modification of physiological function. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated by the healthcare professional or consumer as a primary source, it meets the definition of an adverse reaction [29].
Bayesian inference methods: a class of methods of statistical inference in which Bayes' theorem is used to update the probability for a hypothesis as more evidence or information becomes available [77].
Internet of Things (IoT): a network connecting any item via the internet to implement information exchange, communication, intelligent recognition, positioning, tracking, monitoring, and management, by means of radio frequency identification, infrared sensors, global position system devices, laser scanners, and other information sensing equipment [41].
Omics data: informal name for data belonging to the fields of biology that end in 'omics', such as genomics, proteomics, and metabolomics.
Precision medicine: any tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology or prognosis of those diseases they may develop, or in their response to a specific treatment [78].
Real world evidence: any observational data obtained outside the context of randomized controlled trials (RCTs) that are produced during routine clinical practice [43].

that could be worthwhile implementing in the section 'A research agenda for developing precision pharmacovigilance' and end by discussing some limitations and possible extensions of this approach in the section 'Concluding remarks and future perspectives'.

Precision pharmacovigilance: a smart hospital-driven approach

In this article, by the term precision pharmacovigilance, we mean providing a more comprehensive and interactive framework than that currently delivered by standard pharmacovigilance for drug safety assessment. Our approach stresses that pharmacovigilance should be at the service of the individual patient. This is an ambitious goal as it challenges the current viewpoint about pharmacovigilance. Nonetheless, before it can be achieved, several subtasks will have to be undertaken, the main ones being: (i) designing a new data collection infrastructure for precision pharmacovigilance; (ii) exploring new computational methods capable of analyzing and assessing data regarding drug safety; (iii) providing a computer-aided framework for distributed clinical decisions with the aim of compiling a personalized information leaflet (also known as a personalized package insert) with specific reference to a drug's contraindications, warnings, precautions, and ADRs; and (iv) integrating this framework into clinical practice. In addition to these four points, we believe that the feasibility of precision pharmacovigilance demands that two additional elements need to be considered. First, precision pharmacovigilance can be best achieved by positioning the hospital as the main center of this kind of research work, and second, by exploiting the growing role of the **secondary use of healthcare data** laws that are now in force in several nations and are expected to be more widely implemented in the future.

Hospitals as ADE observatories

Some recent reports have highlighted how hospitals can be considered as privileged local observatories for understanding the temporal features and causal links behind the onset of ADEs [32,35]. While hospital ADEs clearly account for only a fraction of all possible events, it is evident that the most severe ADEs occur in hospitals (see earlier). Furthermore, signals stemming from hospital medications are not the only ones to be tracked in a clinic, since even over-the-counter drugs may cause ADEs and lead to hospitalization. Therefore, an assessment of ADEs as a result of hospital prescriptions and prescriptions given before the start of hospital care has to be considered. However, even with these caveats, the data quality of hospital ADEs may be viewed as superior to the average pharmacovigilance signals originating from other sources. In fact in a hospital setting, therapeutic adherence problems generally affecting patients and their own data should be minimized by properly recording drug administration/dosing, a task generally fulfilled by physicians and nurses with the assistance of the available technology.

Hospital data sources

The idea of using hospitals as the main data sources of signals for computer-aided pharmacovigilance purposes has its roots in the late 1980s, when the first proposals were outlined about the concept of hospital pharmacoepidemiology and how this could be underpinned by the automated data management systems then becoming widely available [36,37]. Nowadays, next to the already up and running computerized systems (e.g., claim databases, insurance databases, e-prescription systems, EHRs, computerized physician order entry systems, laboratory information systems, to name a few), the growing implementation of sensors [38–40] and the **Internet of Things (IoT)** [41,42] in smart hospitals could pave the way to an even more robust and widespread data collection, leading to a much more fine-tuned representation of in-patient and out-patient states. In this scenario, a much richer picture would be acquired for each individual patient depicting the profiles of the disease path and the effects of interventions (i.e., with a higher time resolution and longer duration) allowing better opportunities to provide personalized therapies, even in

Reimbursed prescriptions: any drug prescription, usually dispensed in community- and hospital-based outpatient pharmacies, the data of which are collected with the purpose of reimbursement to be redeemed from state or private insurances. They represent a rich source of information regarding patients and their related drug usage.

Safety signal: any reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously [79].

Secondary use of healthcare data: the use of a patient's health information for purposes other than his or her direct care. The secondary use of health information has significant implications for basic and clinical research, public health surveillance and management, quality improvement, and safety monitoring [48].

Smart hospital: a new kind of hospital, integrating the function of diagnosis, treatment, management, and decision. The features of IoT, such as comprehensive perception, reliable transmission, and intelligent processing, provide a critical support for its construction and implementation [41].

real time. Furthermore, since data collected in a smart hospital would be accurate, this would help to identify the subset of patients experiencing ADEs out of the total number receiving some particular drug.

Towards patient stratification in pharmacovigilance

To supplement this minimal setting, several covariates like the genomic background of patients/other **omics data**, drug dosage, polypharmacy, comorbidities, and **real world evidence** could also represent a more in-depth level of patient stratification (the division of one patient group into subgroups, each one representing a particular subsection of the potential patient population). This would involve the application of a wide spectrum of data analysis, based on standard and new computational methods specially devised for pharmacovigilance. In particular, **Bayesian inference methods** [19,43] could be employed, since they represent a natural framework for aggregating diverse types of evidence and, importantly, for updating the reliability of a working hypothesis as more evidence or information becomes available. Ultimately, the previous data infrastructure and data analysis could be beneficial in a retrospective manner, aiding in clinical decision-making, by helping to generate a personalized information leaflet with specific reference to a drug's contraindications, warnings, precautions, and ADRs for each individual patient. According to some of the recent literature in the field [44–47], this would be moving in the same direction as many pharmacogenetic approaches and not focusing solely on selecting the dose with optimal efficacy. Instead it should be appreciated that this is too simplistic; optimal dose should also consider the patient's risk of avoiding drug–drug interactions and/or ADRs. Figure 1 presents what this personalized information leaflet may look like and how it differs from the current leaflets used in clinical practice.

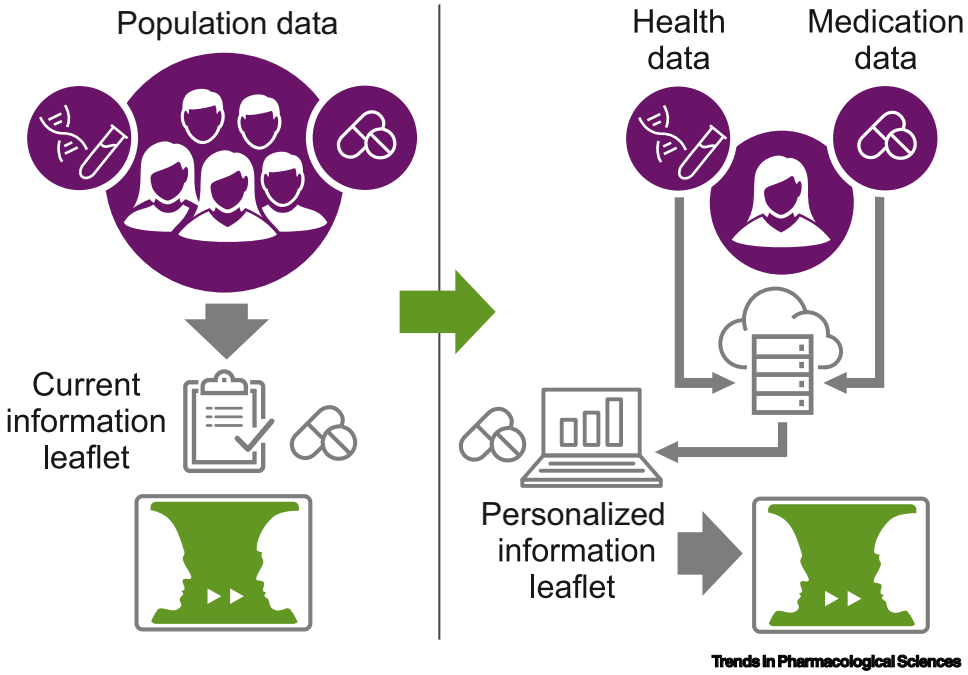

Figure 1. A comparison between current and personalized information leaflets. On the left side, population data of various sources form the basis of the current information leaflet, whose critical information is conveyed during a medical doctor–patient consultation. On the right side, both population and individual data (e.g., health and medication data) are processed to create a personalized information leaflet. The latter is produced in digital format (see section 'Concluding remarks and future perspectives') and its critical information would be implemented during the medical doctor–patient consultation.

Secondary use of healthcare data

In addition to smart hospitals, the secondary use of healthcare data laws represents the foundation for the concept of precision pharmacovigilance. For more than a decade, the shift to the collection of data for secondary use has been forecast and encouraged [48] and several international organizations and national states have now launched programs and projects to meet such a challenge (see, e.g., the directions provided by the Organisation for Economic Co-operation and Development [49]). In this respect, Finland represents one of the forerunners, with a specific national legislation passed by its parliament in 2019[v]. This Finnish act mainly aims at facilitating the effective and safe processing and access to the personal social and health data for steering, supervision, research, statistical purposes, and development in the health and social sector. A second objective is to guarantee an individual's legitimate expectations as well as their rights when processing personal data. This legislation was the result of a long reform process that has shaped the new 'secondary use'-friendly environment [50]. Alongside this process, some preparatory work, both in terms of sketching and prototyping how data should be gathered and exploited within this kind of system, has been carried out [51] with the clear intention of taking advantage of the opportunities evident in this new framework. In the next section, we will provide more details regarding the methods to be employed within a secondary use healthcare data environment.

A research agenda for developing precision pharmacovigilance

The concept of precision pharmacovigilance will have to be based on three strands of research: data collection, data analysis, and data exploitation. Both theoretical and applied research will be needed to match abstract modeling to a boots-on-the-ground approach, where statistical-based models will have to handle real world evidence and cope with the clinical constraints present in a hospital setting, as detailed later. Figure 2 shows a graphical representation of this entire process taking place in a hospital.

Data collection

The methods concerning data collection will be mainly borrowed from health informatics [52] and information engineering [53] on one side and hospital pharmacoepidemiology [54] on the other. The task of tracking one patient (administered a drug treatment) from the very first moment he/she is admitted to a hospital, till the moment he/she is discharged, will require the design and realization of a data management system based on the best scientific data [39,55]. This system will have to be integrated with the current data management systems and practices used by the hospital (especially those for data sharing with the local regulatory agencies) and be matchable in real time and in a scalable way with the drug consumption data stored in the hospital pharmacy, the information coming from the patient's EHRs, and the reports and codifications of possible ADRs entered by physicians, drawing on current standard classifications for drug safety [56]. Smart ways of data collection (e.g., through IoT devices for physicians, nurses, and patients [38,57]) will represent the backbone of such a system, and attention will have to be given to its possible implementation on both a national and international scale, following previous experiences in the field [58]. Particular care will be paid to data privacy, to ensure the maximum security of the information either locally acquired [59] or shared among hospitals, but with the goal of including enough cases and patients [58]. The validation of this kind of system will adhere to the approaches currently applied in digital medicine [60–62].

Data analysis

The possibility of relying on more fine-grained statistics provided by a more robust data collection system will open novel horizons for pharmacovigilance. Along with the standard computational methods currently used in the field, like those already introduced in the section 'It is time for precision in pharmacovigilance' [7,9,15,17,20], new methods better fitted to this new precision

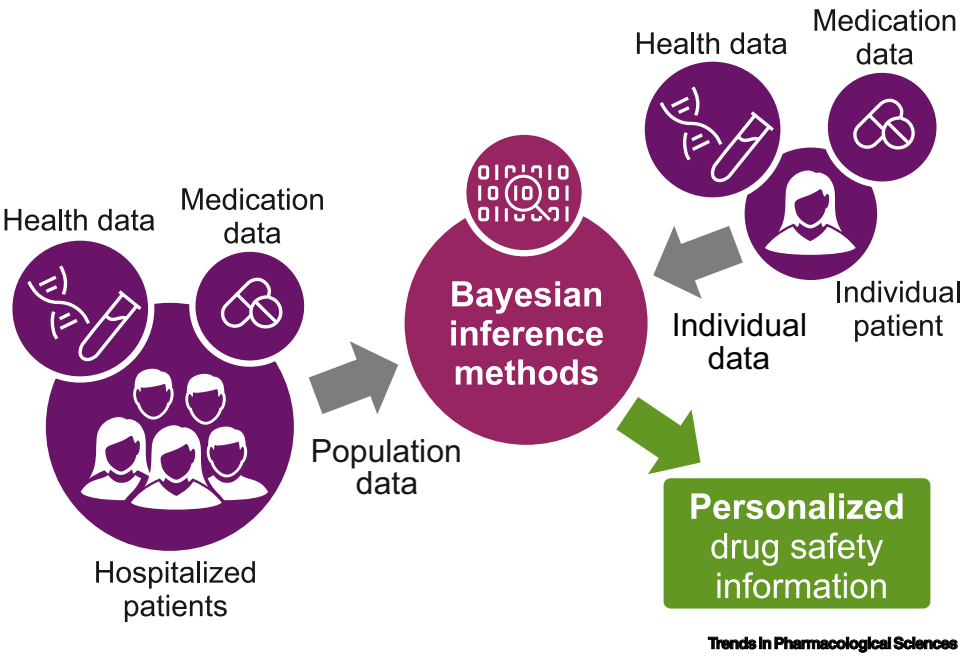

Figure 2. The process behind the provision of personalized drug safety information. This picture depicts the main premises and structure behind a smart hospital-driven approach to precision pharmacovigilance. On the left side, a population sample of treated patients have their health and medication data gathered during hospitalization. In the middle, data inputs are mainly processed through Bayesian inference methods and returned as outputs for purposes of personalized drug safety information. On the right side, one patient, whose health and medication data are also acquired as inputs, receives a personalized, digital information leaflet as the output.

framework will have to be devised. We briefly outline three of the most promising methods: (i) Bayesian inference [63], since this is very flexible in incorporating evidence from various sources while updating previous information [43]; (ii) knowledge engineering, which has high reliability in extracting, connecting, and exploiting critical information for drug safety [14,64,65]; and (iii) artificial intelligence (AI), that is, methods that can be employed for identifying, extracting, synthesizing, and interpreting relevant information, converting this into knowledge that can answer complex questions about causal associations. This is an approach becoming increasingly popular also in pharmacovigilance [13,19,66,67]. Combinations of these methods could be validated in agreement with the existing literature [20,68,69].

Data exploitation

As outlined earlier, we foresee the creation of a personalized information leaflet with specific reference to a drug's contraindications, warnings, precautions, and ADRs as the key deliverable of precision pharmacovigilance. In its compilation, the adoption of computational methods currently used in precision medicine will be beneficial, especially drawing on the experience achieved in oncology [70,71], where the advances have been rather notable. This personalized information leaflet will be mainly based on individual pharmacogenomic information on one side (extracted from EHRs or after conducting explicit laboratory tests) and on a patient stratification approach on the other. In the latter aspect, both supervised and unsupervised machine learning techniques will be employed in comparing individual data with a sample of patients. The personalized information leaflet should be released in a digital format, with its design being in line with the current advances in dematerializing medication information [e.g., as recommended by the European Medicines Agency (EMA)][vi]. It will also draw on existing research in proximity fields, like personalized

prescribing [72] and personalized medication management [73], including those decision-support tools that strive to assess the cumulative effect of a patient's genetics and entire drug regimens. In this way, it should be possible to achieve positive outcomes in various sectors of the healthcare system [74]. Validation of these methods will take place in compliance with recent research work carried out in developing and validating information leaflets [75,76]. The very dynamic and data-intensive nature of this work may also act as an impetus for using AI systems in the validation procedure [19]. Ultimately, they need to be based on clinicians' final judgment since they will be responsible for the validation and retesting of such tools. This approach is in line with the protocols applied in decision-support systems in healthcare (e.g., image analysis tools, electrocardiogram, vital support systems).

Concluding remarks and future perspectives

As a response to the challenges confronted nowadays by standard pharmacovigilance, precision pharmacovigilance aims at reducing hospitalizations and deaths due to ADRs and better protecting those groups that are usually excluded from RCTs but nonetheless experience harm from medications. Rather than being satisfied with the *status quo*, this new perspective of pharmacovigilance seeks to be a game changer in the field of drug safety by providing more precise drug safety assessments and preventing serious ADRs. It is based on a smart and efficient collection of information within hospitals (following a 'no more data thrown away' concept) by exploiting a rigorous and innovative data analysis for creating a personalized information leaflet with specific reference to a drug's contraindications, warnings, precautions, and ADRs for each individual patient, in contrast to the current one-leaflet-fits-all concept. However, while a personalized information leaflet may have many advantages, it may also represent a challenge for patient risk management in the event of erroneous or even malicious personalizing. For instance, these could derive from erroneous or old personal information encoded in medical records, leading to an unreliable patient profiling for low or high risk of ADRs associated with the usage of certain drugs. Therefore, the administration of a personalized information leaflet will need to be under strict medical control and generally comply with the standard approved drug information. Any particular deviation from standard approved drug information should be processed as an off-label use.

Next to these expected outcomes, precision pharmacovigilance also takes on a special significance during these pandemic years. For example, many patients have experienced poor or delayed medical checks; people infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been treated with several experimental medications. These challenges clearly emphasize the importance of the development of precision pharmacovigilance to lessen the risks to those patients. From another viewpoint, a more precise and detailed pharmacovigilance would also make the general population more confident to undergo safe and necessary treatments. In order to overcome all of these challenges (see Outstanding questions), precision pharmacovigilance needs to be designed in a scalable way to be easily implemented into both national and global pharmacosurveillance networks. Only in this way can all its benefits be realized by national public health authorities and the international organizations supervising health and drug safety.

Outstanding questions

How are national legislations on secondary use of health data shaping the future of pharmacovigilance?

How can research advances in precision medicine be exploited in the development of precision pharmacovigilance?

How should pharmacovigilance respond to the individual needs of the patient?

How should the global pharmacosurveillance network be adapted to receive and share precision pharmacovigilance data?

What are the best methods and practices for improving data collection for precision pharmacovigilance?

What are the minimum steps when progressing from a one-drug-fits-all pharmacovigilance to precision pharmacovigilance?

What can be done with the current state-of-the-art of research and novel technologies to move pharmacovigilance towards a precision framework?

What is the role that smart hospitals could have in collecting and processing data for pharmacovigilance purposes with respect to traditional channels of drug safety assessment?

What should the drug safety assessment process look like when tailored to the creation of a personalized information leaflet and what should a personalized information leaflet look like?

Which computational methods are best suited for precision pharmacovigilance?

Acknowledgments

Research reported in this publication was supported by the European Research Consortium for Informatics and Mathematics. We thank Dr Ewen MacDonald for valuable comments and revising the language.

Declaration of interests

The authors have no interests to declare.

Resources

[i]www.cdc.gov/medicationsafety/basics.html

[ii]www.health-data-hub.fr/partenariats/ordei

[iii]www.ema.europa.eu/en/documents/presentation/presentation-pharmacovigilance-next-5-years-industry-vision-v-edwards_en.pdf

[iv]www.uppsalareports.org/articles/towards-precision-pharmacovigilance/

[v]https://stm.fi/en/secondary-use-of-health-and-social-data

[vi]www.ema.europa.eu/en/documents/regulatory-procedural-guideline/electronic-product-information-human-medicines-european-union-key-principles_en.pdf

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