# Pharmacovigilance as Scientific Discovery

## An Argument for Trans-Disciplinarity

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CURRENT OPINION

# Pharmacovigilance as Scientific Discovery: An Argument for Trans-Disciplinarity

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**Abstract**
Pharmacovigilance currently faces several unsolved challenges. Of particular importance are issues concerning how to ascertain, collect, confirm, and communicate the best evidence to assist the clinical choice for individual patients. Here, we propose that these practical challenges partially stem from deeper fundamental issues concerning the epistemology of pharmacovigilance. After reviewing some of the persistent challenges, recent measures, and suggestions in the current pharmacovigilance literature, we support the argument that the detection of potential adverse drug reactions ought to be seen as a serendipitous scientific discovery. We further take up recent innovations from the multidisciplinary field of serendipity research about the importance of networks, diversity of expertise, and plurality of methodological perspectives for cultivating serendipitous discovery. Following this discussion, we explore how pharmacovigilance could be systematized in a way that optimizes serendipitous discoveries of untargeted drug effects, emerging from the clinical application. Specifically, we argue for the promotion of a *trans-disciplinary* responsive network of scientists and stakeholders. Trans-disciplinarity includes extending the involvement of stakeholders beyond the regulatory community, integrating diverse methods and sources of evidence, and enhancing the ability of diverse groups to raise signals of harms that ought to be followed up by the network. Consequently, promoting a trans-disciplinary approach to pharmacovigilance is a long-term effort that requires structural changes in medical education, research, and enterprise. We suggest a number of such changes, discuss to what extent they are already in process, and indicate the advantages from both epistemological and ethical perspectives.

## 1 Introduction

The regulatory approval of a new drug entails the exposure of the population, including the most vulnerable groups, to unanticipated adverse reactions [1]. This problem is compounded by the increasing number of drugs coming onto the market and a growing emphasis within regulatory agencies and by the pharmaceutical industry on accelerated approvals for new drugs [2]. It is difficult, however, to formalize general criteria describing the type and amount of evidence necessary to initiate action, or even the correct

**Key Points**

Pharmacovigilance is an explorative enterprise, based on serendipitous discoveries of untargeted effects of drugs.

Serendipitous discoveries need ‘chance’ and ‘a prepared mind’, but also a responsive network of scientists and stakeholders.

Recent action and suggestions for renewal in pharmacovigilance can potentially facilitate the detection of the unexpected. However, more groundwork at the very structure of the medical community is still needed, to create a stable but flexible problem-centered and trans-disciplinary network in pharmacovigilance.

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methods for investigating causal hypotheses of harm. One persistent challenge of pharmacovigilance is determining when evidence of potential harm is significant enough to trigger a response at some level of the research and/or regulatory process (i.e., from increased vigilance to further research, warnings, or restrictions). This is not only a practical, but also a conceptual challenge, because it stems from fundamental issues concerning the epistemology of pharmacology and pharmacovigilance.

Over the last few decades, assessments of the field of drug approval and safety have resulted in a number of new insights. One such insight, arising from the philosophy of science and increasingly acknowledged by epidemiologists and regulators, is that risk assessment of drugs requires methodological approaches and standards of evidence that are different from the requirements of efficacy assessments [3–4]. Measuring the intended effect of a treatment in a population requires minimizing confounding factors via thoroughly designed randomized trials, but the same requirements do not apply to the detection of potential unintended effects. The reason for this is that, in the latter case, one needs evidence that is especially suited to identify unexpected clinical events, which point to a hypothesis of harm. Evidence of this type can be, for instance, anecdotal evidence, case reports, and case series. Indeed, such observational studies are not constricted by a rigorously pre-planned experimental design, or by inclusion and exclusion criteria and a pre-established timeframe, which might hinder the detection of unexpected outcomes [4]. Accordingly, in the field of drug safety, there is a clear trend away from the preponderant reliance on evidence from clinical trials and towards the inclusion of multiple types of observational and mechanistic evidence, for instance with the use of Bayesian tools [5].

This is directly related to a second conceptual insight in medical literature. That is, from an inferential perspective, harm detection is an explorative scientific activity, and thus should be placed within the branch of medicinal research dealing with discovery and explanation, rather than research dealing with evaluation and confirmation [4]. Further, because 'the unexpected is where discovery begins' [6] the detection of harm from pharmacological treatment needs 'prepared minds' to identify unexpected risks and risk factors [7].

Such arguments, which we here support and develop, not only categorize pharmacovigilance as scientific discovery, but also explicitly equate it with serendipity, a specific process of discovery [7]. Serendipity can be defined as making a discovery when one is not looking for it—or, as the quality of unexpected but valuable findings. In fact, although pharmacovigilance is increasingly based on observational studies, a crucial source of evidence for unexpected drug effects remains reports from everyday clinical experience [8]. Reports of adverse effects are made in response to evidence that no individual is purposely trying to generate. Pharmacovigilance is thus like serendipity, when an unexpected observation or event initiates a new path of research, which leads to a discovery. Unlike discoveries that are derived from an established theory (the efficacy of a drug, for instance, intentionally discovered through planned clinical trials), serendipitous discoveries as well as pharmacovigilance are unplanned and occur as observations are made, during an otherwise predictable course of clinical usage. Just as in serendipitous discoveries wise perception is necessary to catch the unexpected, in pharmacovigilance it is fundamental that a 'prepared mind' (the physician, the patient, a family member or others) perceives that an adverse drug reaction may be the cause of a patient's signs or symptoms [7].

As with serendipitous discoveries in science, however, unexpected observations and evidence of harm need to be taken up by the broader community. A relevant observation that is not followed up becomes neither a discovery nor a reason to act [9]. Consequently, pharmacovigilance ought to model itself upon patterns of practice that work to encourage serendipity in science by creating the conditions for unexpected observations to be effectively followed up.

But what does this entail, specifically? What exactly are the attributes of a pharmacovigilance prepared for the unexpected, and how can we facilitate it? Is the structure of pharmacovigilance worldwide generally encouraging serendipitous discoveries, or is there still space for improvement? Here, we address these questions, with an eye to the latest advancements in the understanding of serendipity.

## 2 Improving Pharmacovigilance: An Overview of Recent Suggestions

We begin by providing an overview of the state of the art, reviewing recent suggestions aimed at improving the processes of pharmacovigilance. We review and systematize different types of measures offered by scholars from 2007 to date. The articles we examine address diverse issues; some of the articles are only recently published, while others have made suggestions that have been already partially implemented. We grouped the issues into two categories: those related to the quality and scope of evidence, and those related to the social organization of the pharmacovigilance community.

### 2.1 Quality and Scope of Evidence

Under-reporting and incomplete reporting of drugs' secondary effects are still major obstacles to pharmacovigilance, despite decades of efforts to improve the situation. New measures are constantly suggested in the literature. Scholars urge not only that the quality of evidence should

be improved, but also that more types of evidence should be utilized [10]. Below are some of their suggestions:

- Negative or inconsistent data from research trials should be available for public scrutiny [2].
- Although in pharmacovigilance all types of evidence, including laboratory research, observational studies, and anecdotal reports are potentially crucial, the amalgamation and evaluation of different types of evidence are challenging [3]. For this purpose, researchers are currently working on unified epistemic frameworks in which different types of evidence can be combined and used for decisions on drug safety. These include probabilistic approaches based on Bayesian networks [5].
- Although anecdotal reports of side effects can potentially be important sources of signals of harm, the quality of such reports is often poor. Measures are needed to ensure a richness of potentially relevant information in the reports, to allow a proper causality assessment of the single case. For example, it has been proposed that medical journals adopt specific guidelines for the publications of adverse drug reaction case reports [11]. On another front, automated free-text analysis platforms are being developed to process patient narratives [12].
- Unintended effects of drugs might be overlooked because of inaccurate clinical evaluations; therefore, clinical cases should be systematically analyzed by a network of experts [13].
- Knowing the statistical incidence of a rare drug adverse reaction in a population has limited value in clinical practice. For the management of risk in single patients, it is important to gain a causal mechanistic understanding of particularly informative cases of adverse drug effects. We only have such deep causal knowledge for a small proportion of marketed drugs; there are still major knowledge gaps to cover [14, 15].
- Although current trends in pharmacovigilance tend to harness the potential of patient involvement through spontaneous patient reports, awareness of this possibility among patients is still low. It is not clear how patient reporting is evolving in many of the countries that introduced this practice. Moreover, research on the differences between the patients who report and those who do not is needed, to understand how to motivate participation [16].
- Tools for spontaneous patient reporting are being expanded through mobile technology and social media, and by increasing public awareness and patient commitment. At the same time, tools for more sophisticated data mining of health registries and other sources of medical information are being developed [17, 18].
- Pharmacogenomic methods should be used in pharmacovigilance as a tool for identifying co-determinants of drugs' undesired effects [14]. This would help in gaining a better mechanistic understanding of the adverse reaction.

## 2.2 Social Organization

Because the social organization of the medical and scientific community influences the production, processing, and communication of relevant evidence, a number of scholars suggest methods to maximize its effectiveness. Some examples are:

- Clinical insights on drug safety have the potential to support basic medical research in advancing general understanding about the causal mechanisms underlying drug action and physiological set-ups. Information about unexpected drug effects should feed back from the clinic to research more effectively than currently, and new communication channels are needed for this purpose [2, 15].
- The cooperation between regulators and patient organizations should be tighter and more systematic and comprehensive. Representatives from patient organizations urge that an official contact person for pharmacovigilance should be appointed by regulators in each patient organization [19].
- Coordination among drug regulatory authorities should be increased [1].
- Not only findings, but also the related uncertainties, should be communicated to the public, as postulated in the Erice declaration [20].
- The evaluation of hypotheses is currently often performed confidentially by stakeholders such as the pharmaceutical industry, government regulators, and donor organizations, introducing different levels of conflict of interest over pharmacovigilance outcomes. The information held confidential for this potentially long time span, although uncertain, might be useful for critical clinical considerations for specific patients [21]. Accordingly, some pharmacovigilance centers such as the Netherlands Pharmacovigilance Centre Lareb have chosen to be transparent about the signals they identify. After the signal has been shared with the Medicines Evaluation Board, the drug regulatory authorities in the Netherlands, it is also posted on the website of the Netherlands Pharmacovigilance Centre Lareb. This is before the signal of potential drug-related harm has undergone a full (regulated) evaluation and before regulatory action is taken.

Once systematized, it is apparent that the diverse suggestions and actions toward renewal offered by the recent pharmacovigilance literature constitute interconnected parts of a broader call for: (1) a simultaneous networking of different actors; (2) an openness to diverse types of evidence; and (3) the integration of scientific methods with the insights,

perspectives, and interests of diverse stakeholders (including but not limited to patients and decision makers).

Furthermore, we argue that all the suggestions listed above can potentially facilitate the detection of the unexpected. Indeed, they call for a switch from a 'pipeline' or additive process, in which each phase of investigation is somehow distinct from the others, to a 'web' or interactive process, in which information and activities are integrated in respect to time, structures, and the responsibilities held by the actors involved [2]. In the next section, we show that the benefits such a 'web' and process-based approach can bring to pharmacovigilance are also the properties of highly serendipitous communities.

## 3 Serendipitous Discoveries and Responsive Communities

Recent work on serendipity has taken up Walpole's (1754) definition that serendipity is a combination of chance and wisdom [22], with the aim to better understand how such 'happy accidents' can be cultivated, if not designed. For instance, theorists are looking closely at what type of wisdom, or skills, enable serendipity at the level of the individual [9, 23]. What many have found, however, is that serendipity is best cultivated at the level of the community, as much or more so than by individuals. Walpole's two components do not alone represent a satisfactory account of serendipity because networks play an important role in following up on unexpected observations and events [9, 24, 25].

Rather, the outcome of fortunate circumstances and individual skills also depends on the social and epistemic context in which those circumstances and skills are found [26]. What is essential in both pharmacovigilance and serendipitous discovery is that unexpected observations are incorporated into processes that lead to theory generation or an action being taken. Among the key aspects of environments that cultivate serendipity, Björneborn points to the importance of cross-contacts, where "dissimilar resources" come into contact with each other and enable new connections to be made [25]. Yaqub has shown that a key mechanism behind serendipity is what he calls "network-emergence": networks connect researchers who have made an unexpected observation with those who know its value; exploiting an unexpected observation often requires diverse skills and expertise; and belonging to a diverse network means more resources for recognizing and exploiting the potential value of the unexpected [24, 27]. What grounds serendipity events are strong lines of communication, collaboration toward common interests, and integration of diverse sets of skills.

The importance of setting up the conditions for collaboration with flexibility in response to the unexpected in pharmacovigilance as well as serendipity might be emphasized using the thalidomide example. What was missing in the pre-thalidomide era was not basic research about how chemicals could damage the fetus, nor the use of model animals for this purpose. As reported by Dally, a review [28] containing 354 references to the evidence of the effects of drugs in the fetus was published before thalidomide was marketed. What was missing, rather, was the intersection between the realms of basic research and clinical care; these were traveling in distinct parallel paths. Teratology was confined to the interest of a few laboratory researchers, while medical students were taught that "the placenta gave perfect protection from toxic substances" [29].

The first observations of the thalidomide teratogenic effect generated a common interest among previously disconnected research communities. Teratology came to be seen as a science that could serve the purpose of medical research. A significant take-home message from the thalidomide story, therefore, is the importance of a network of contributors with different types of expertise, able to react to unexpected observations.

Did such a take-home message make a difference in modern pharmacovigilance? Partially, it did. The importance of shared information and networking has largely been acknowledged, for instance by the recent reorganization of the pharmacovigilance structure in Europe. Since 2012, the evaluation of the safety management of drugs in all its aspects is centralized and shared by all European states by the Pharmacovigilance Risk Assessment Committee, which makes it much easier to circulate information and to detect signals of harm [30]. However, there are practical restrictions that limit the inter-disciplinarity of this network. Because of the General Data Protection Regulation, for instance, the direct access to the complete information provided by side-effect reports is generally restricted to health professionals and drug agencies. Other professionals and stakeholders (i.e., medical researchers, basic researchers, patients) need to file a motivated request to get access to the data. Arguably, such a system is not ideal for enhancing unexpected observations through multi-disciplinary networking. Furthermore, there are some efforts, at least within some specific safety issues, to amplify the inter-disciplinarity of the pharmacovigilance enterprise. For instance, the Drug-Induced Liver Injury Network collects expertise in hepathotoxicity, epidemiology, pharmacokinetics, and pharmacology to promptly identify and understand cases of drug hepathotoxicity (www.dilin.org). This action and similar efforts point to the right directions and should be amplified.

We are suggesting here, however, that much more groundwork at the very structure of the medical community is still needed, if we wish these emerging networks for drug safety to be genuinely *responsive* to the unexpected.

Organizing a scientific community for the purpose of optimizing serendipitous discoveries is a challenge increasingly taken up by both theoretical and empirical researchers [9, 23, 27]. We argue that many of the insights so far gained can benefit the field of pharmacovigilance.

A major challenge not only for pharmacovigilance, but also for the scientific enterprise in general is that a rigid organization might sometimes hinder, rather than benefit, serendipitous discoveries and action [31]. This is because of the very nature of serendipity: every unexpected observation needs some particular skills in place, which are difficult, or even impossible to anticipate. For instance, a physician needs not only to notice the irregularity of a symptom, but also to know enough to hypothesize its casual connection with a drug, to deem it worthy of documenting as a case report. Similarly, in cases of serendipity, the potential importance of the unexpected observation is clear because the observer can relate it to previous knowledge and theory [23, 32]. Just as many observations of adverse effects are inherently unpredictable, so it is difficult to say beforehand when a responsive network will be needed. Equally, the full spectrum of advantages and outcomes that the responsive network will yield is underdetermined. Therefore, pre-determined structures and protocols are likely to have the effect of constraining, instead of promoting, the utility of a serendipitous network in pharmacovigilance [33].

A serendipitous network, therefore, needs to be both flexible and stable, so that it can be activated promptly in response to observations of harm that may or may not lead to research hypotheses. It is responsive like the immune system is responsive: while the system as a whole is in place, ready to be activated, exactly *how* it activates cannot be predefined. Instead, it depends on the problem (the pathogen) at hand. How can such organization, at the interface between the structured and the spontaneous, be actively encouraged? As an example of how such responsiveness is enacted effectively, below are some cases of serendipity in science as well as pharmacovigilance.

## 4 Features of a Responsive Network

### 4.1 Multi-Directionality

The common element between cases of serendipitous discoveries in medicine, besides the unexpected observation, is the collaboration of researchers working on diverse projects and using different methodologies. In some cases, this collaborative diversity can take a single observation and lead to a number of significant findings. In other cases, the production of results through diverse methods can converge to formulate a single hypothesis. Often, both of these can happen at different points in the same process of discovery.

An example in the field of pharmacovigilance is the emergence of multiple pathways of research, all stemming from the observation of the effects of thalidomide, in particular its teratogenicity and anti-leprosy effects. More than 30 separate theories about the mechanism behind these effects have been proposed over time [34]. This considerable body of research has contributed to understanding the mechanisms underlying angiogenesis and limb development, as well as discovering an anti-carcinogenic effect of thalidomide [35]. Similarly, in modern pharmacovigilance, observations of adverse drug reactions have led to a general advance of medical understanding beyond the strict boundaries of drug safety. For instance, a study collected data from the side effects of a large number of marketed drugs, and used the information to gain understanding of the mechanism by which drugs interact with human molecules [36]. The emergence of new general knowledge from pharmacovigilance, however, is sporadic, or at least not systematic. Pharmacovigilance remains, to a large extent, an isolated discipline, despite the fact that unexpected side effects could potentially reveal much about the causal mechanisms underlying pharmacological and, even more generally, physiological functions [15]. Such potential is still waiting to be fully and systematically harnessed.

### 4.2 Problem Centeredness

By working in a problem-centered manner, experts can influence their respective means of reasoning around the problem. An example can be found in the biological field stations that were enlisted in response to outbreaks of hanta virus and West Nile virus in USA [37]. Biological field stations are “sites of serendipity”, at which evidence databases can be created and later accessed and applied by researchers and stakeholders, such as federal agents, local doctors, ecologists, and naturalists. When these groups were united in a network in response to a hanta virus outbreak, they shared the perspective that the problem needs urgent intervention. Crucially, experts worked together by combining a plurality of methods and interests: new shared reasoning was applied to conventional tools from each discipline, and new methods were generated from this interaction, for this specific purpose [37]. This unique network was *responsive* not only in the sense that it worked once, but as a result of this precedence, was able to quickly mobilize in response to a similar problem, West Nile virus outbreaks in the same region [37].

Problem centeredness is often difficult in drug safety networks, even when databases, evidence, and skills are in

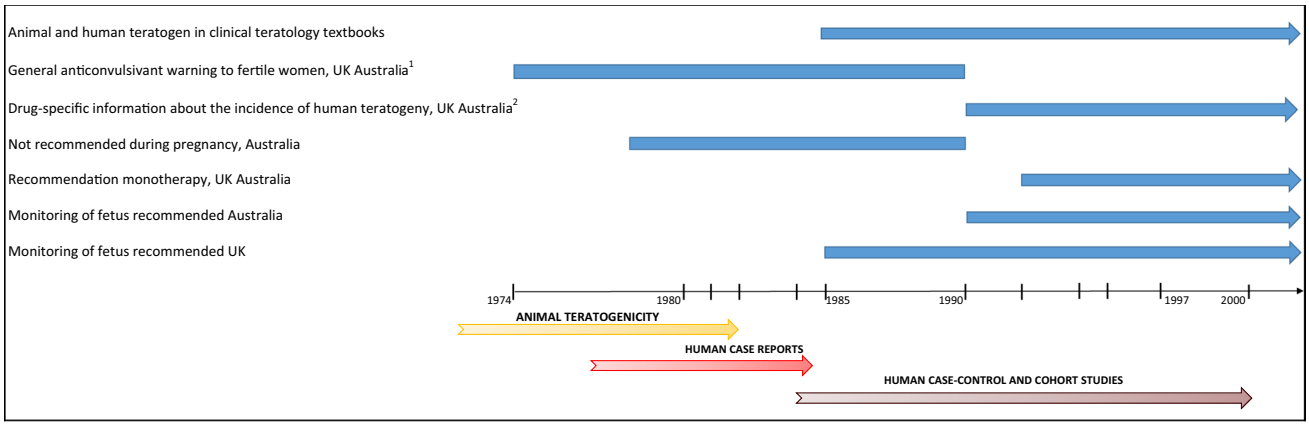


**Fig. 1** Analysis of the evolution of information about valproate teratogenicity in clinical textbooks and Epilim (sodium valproate) data sheets in UK and Australia, and a comparison with the progression of available evidence. Figure 2 summarizes our findings in a temporal perspective. Interestingly, the three analyzed sources have a different metric for 'enough evidence'. For instance, while textbook authors list valproic acid as human teratogen already in 1985, on the basis of animal studies and human case reports, data sheets both in the UK and Australia switch from unspecific warning to specific risk and incidence communication only 5 years later. For comparison, two examples of complete statements in the data sheet are reported below.

[1] From the Epilim UK data sheet, 1983: 'Valproic acid or sodium valproate, like certain other anti-convulsivants, have been shown to be teratogenic in animals. In women of childbearing age, the benefits of these compounds should be weighed against the possible hazards suggested by these findings.' [2] From the Epilim, UK data sheet, 1990:'An increased incidence of congenital abnormalities in offspring born to mothers with epilepsy both untreated and treated has been demonstrated. There have been reports of foetal abnormalities including neural tube defects in women receiving valproate during the first trimester. This incidence has been estimated to be in the region of 1%.'

place. A move from suspicion to action in pharmacovigilance often requires researchers, clinicians, manufacturers, and decision makers to work together on a problem they all perceive equally worthy of resolving. That is, they need to share an overlapping judgment: that the available evidence is potentially indicative of a causal relationship, and of the urgency of the discovery at stake. This is not always the case. Consider for instance valproic acid, which by the early 1980s was known to be teratogenic in laboratory animals, and within the first few years after commercialization was implicated in some clinical case reports [38]. The potential significance of this evidence was evaluated differently by basic medical researchers, drug agencies, and the pharmaceutical industry. For instance, clinical teratologists followed up these data by listing the drug as a human teratogen as early as 1985, although the available evidence was only indicative of a possible hazard [39]. On the contrary, despite the common evidence available, the drug's datasheets were not updated before the mid-1990s, and the information was reported at different time-points in different countries, as summarized in Fig. 1. This example and similar cases suggest that building a problem-centered network is a particularly difficult task for pharmacovigilance, which includes complex risk-benefit judgments not only on the therapeutic vs. harmful potential of the drug, but also on the distribution of resources for studying chemicals with relatively rare exposure profiles.

### 4.3 Trans-Disciplinarity

We have said that a responsive network needs to function in a multi-directional manner (Sect. 4.1) and to make shared judgments that a problem is worth pursuing (Sect. 4.2). These features of a responsive network are shared by communities that are genuinely trans-disciplinary. A trans-disciplinary network or community is one in which cross-disciplinary interactions are a part of its very culture, to the point where the ideas and methods in use represent contributions from multiple (scientific and other) fields, and could not be traced back to a particular field [40, 41]. For instance, patient involvement works best when researchers and patients work together on research questions, design, and outcome. This in turn, "fundamentally change[s] the way research work is conceptualized, conducted, and disseminated" [42], meaning that a new common praxis is established. Therefore, trans-disciplinarity goes beyond multi-disciplinarity, in which different scientific disciplines collaborate but without creating a shared praxis, and without the inclusion of non-scientific insights. Pharmacovigilance, as a field of research, already involves multiple disciplinary approaches, practices, and fields of expertise. For instance, clinical practice, clinical research, epidemiology, data science, toxicology, pharmacology, and decision making are all constitutive parts of pharmacovigilance. As highlighted above, it also requires the continuing involvement of non-scientific insights, from

patients to policy makers. Yet, the network of stakeholders concerned with pharmacovigilance has a specific common goal, which goes beyond disciplinary or class boundaries and therefore requires the establishment of a shared praxis, or interactive reasoning. For this reason, we argue that pharmacovigilance is best conceived as a trans-disciplinary enterprise.

Several features of trans-disciplinarity hold for the type of network we envisage for pharmacovigilance, one that would allow for unanticipated discoveries and encourage them to be taken up more effectively:

- Trans-disciplinarity begins with a common perception of a complex societal problem, as does pharmacovigilance [43].
- Trans-disciplinary approaches may go beyond disciplinary methods and expertise, but they do not forgo them. Likewise, pharmacovigilance, through a shared goal, requires otherwise independent disciplines to work together to go beyond their own interests and resolve a shared problem [43].
- In applying trans-disciplinarity to the field of epidemiology, Ciesielski et al. argue that such approaches allow for the generation of better hypotheses [33]. Generating better hypotheses is a key step toward increasing efficiency in pharmacovigilance as well.
- Trans-disciplinarity provides the means by which heterogeneous methods and interests can be juxtaposed in a manner that is "likely to stimulate the emergence of new knowledge" [43].

Therefore, we argue that trans-disciplinarity provides the best model for understanding the nature of the network that must exist for effective and efficient pharmacovigilance.

## 5 Creating a Responsive Network

To promote an effective responsive network in pharmacovigilance, the best approach is to promote a culture of trans-disciplinarity during education and training, and as a normal feature of both research and practice. That is, if we create a culture of trans-disciplinary medical thinking, a responsive network-based pharmacovigilance will be easier to promote. Further, it gives each node equal expertise and authority in asserting that follow-up is needed for itself and other nodes in the network. In this type of culture, it would also be easier to fully and more easily implement the measures reviewed in Sect. 2.

This is obviously a long-term challenge. The difficulty of educating trans-disciplinary individuals and forming trans-disciplinary teams has been discussed [44], and clearly any solution that does not imply profound institutional changes appears naïve. However, the training involved for trans-disciplinary individuals for this purpose does not necessarily mean that each person must be an expert on more than one discipline. Rather, he/she needs to have the tools to understand the arguments, basic assumptions, and value judgments of other disciplines [45, 46]. A critical attitude toward the tools and approaches offered by an individual's own expertise must be also cultivated. Hypotheses of harm need to be commonly discussed. The context in which a safety issue arises needs to be clearly understood, as do the motivations and aims of various stakeholders for their differing needs and responsibilities.

Measures in this direction might include (but not be limited to) those listed in Fig. 2. Note that we are focused on the conceptual aspects that are peculiar for pharmacovigilance—not an approach driven by scientific experimentation, with the ideal of controls and predictability, but an approach driven by scientific serendipity instead. Our practical suggestions, therefore, are what we think are the best methods for foregrounding this conceptual peculiarity of pharmacovigilance on the grandest possible scale.

Our conclusions do indeed have other practical consequences. One important issue is the role of the manufacturing industries that introduce potential conflicts of interest, but also hold the majority of the information as well as the legal responsibility for the safety of their product. Can one assume that the pharmaceutical industry will engage in efforts to build a serendipitous network for delineating the full profile of their drugs, even when this collides with commercial interest?

Although we should not be naïve about the ethical and policy issues in pharmacovigilance, we need to highlight that some examples do exist, in which the industry not only takes part, but also promotes and coordinates inter-disciplinary safety networks. One example is the Chinese Chipscreen Bioscience, the first Chinese pharmaceutical company who gained, for the drug Chidamide, marketing authorization by conditional approval from the Chinese Food and Drug Administration (now National Medical Products Administration) in 2014. At the time, China was not a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and there was no experience in drug safety and risk management for a local company. In the face of this challenge, Chipscreen funded and established, in collaboration with national authorities, a pharmacovigilance network for the safety management of its own product. This involved company members, pharmacists, nurses, physicians, patients, and medical researchers (information from private correspondence with Xinhao Wang, Chipscreen director of the Drug Safety Department). This and similar examples indicate how the value of an improved drug safety service might be acknowledged by


**Fig. 2** Suggestions for institutional changes in medical training and research, which could promote the emergence of a transdisciplinary network for pharmacovigilance

the manufacturer, as the pharmaceutical industry is willing to fund and establish a pharmacovigilance network when required.

However, we maintain that the trans-disciplinary body should be autonomous in its operation. We believe this is an ambitious yet not impossible vision. There are several other examples of autonomous bodies such as the National Institute for Health and Care Excellence, the Uppsala Monitoring Centre, the Council for International Organizations of Medical Sciences, and the International Organization for

Standardization, among others, which provide critical services in support of drug safety. These and other organizations should be involved in creating a global network that operates in this manner.

## 6 Conclusions

In this article, by drawing a parallel with the features of serendipitous discoveries in science, we highlighted that, for the purpose of accelerating the process of pharmacovigilance, we need to ensure that unexpected observations are met by a responsive network. We qualified this as a problem-centered network in which information can travel in a multi-directional manner. We argued that trans-disciplinarity is a key feature of such a network, and we indicated why existing networks, such as the Pharmacovigilance Risk Assessment Committee and the Drug-Induced Liver Injury Network, point in the right direction but still diverge considerably from the ideal that we envisage for pharmacovigilance. In particular, seeing that currently *inter*-disciplinarity itself is often still a challenge, the possibility of a truly *trans*-disciplinary network, as described in Sect. 5, seems currently out of reach. We believe such a goal will not be met without deep structural changes in the organization of medical education and research as a whole (Fig. 2).

We have thus argued that serendipity, as described, is a major initiator in science and that a 'signal' in pharmacovigilance should be considered as serendipity. The time from the first hint of an unusual effect of a treatment being seen, through to its evaluation and understanding of how it might affect patient care is likely to be lessened by using a network of trans-disciplinary scientists. The fact that such a network will exist and is truly transparent about its results and their limitations should help to support public confidence and is in keeping with other, widely accepted system-based approaches to the analysis of failure[1].

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[1] The air transport industry might be an example of such a system.

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