Chapter 3
What Is the Future of Pharmacovigilance *and How Can We Make It as Good as Possible?*

Get the ADR Phenotype "Right"

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Pharmacovigilance is a scientific discipline that is underrecognized in its importance for improving understanding of drug effects in humans. It excels as a vehicle for detecting safety concerns particularly those early in the post-market phase after prescription drug approval. This is the time in the life cycle of a drug when manufacturers are required by regulatory agencies to provide adverse drug reaction (ADR) reports and the time when clinicians are gaining experience with new agents and are more likely to report ADRs [20]. The reporting of cases of drug-induced harm and subsequent analysis of such data is a critical part of population health surveillance, given the frequency of the use of drug therapy as a medical intervention.

The limitations of pharmacovigilance activities are well understood and include faint signals for many rare but serious ADRs. As well, many causal probabilities to ADR signals exist. For example, concomitantly used medications and active disease processes can make the ability to say definitively that an observed reaction is caused by a specific drug much more difficult. However, such possible confounders are not always apparent at the time pharmacovigilance processes are under way or known to pharmacovigilance scientists and may therefore be missed. A significant limitation is the quality of the ADR case report information. Lack of critical information in submitted reports remains a serious concern in pharmacovigilance science. Collecting high-quality data for more ADR reports is just part of a positive future for this science. But to fully appreciate the power and potential of pharmacovigilance as a scientific discipline, we need to go beyond the case report and epidemiological analysis of population risk.

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3.1 Quantifying Drug-Related Harm for Patients

The future of pharmacovigilance is tied to not just finding drug-related problems (in essence, reporting ADRs) but identifying solution strategies to avoid drug harm. With solution strategies comes wider acceptance of the importance of the discipline of pharmacovigilance. Most clinicians are not particularly interested in drug-related harm because the most serious risks are infrequent and treatment decisions are already taken seriously, with some thought about the potential for harm to occur. This means that there is a level of acceptance of the risk of drug harm by clinicians before prescribing begins. Knowing that an ADR has occurred in a given patient then is not generally unexpected. However, by quantifying risk versus benefit in increasingly objective ways (e.g., ADR risk prediction modeling in specific patients), clinicians can better understand an individual patient's propensity for drug harm. This is also what patients want – better defined risk information, relevant to them specifically – before they decide to take a drug that was prescribed. Patient-specific drug risk prediction helps to define which patients are at increased risk, an important first step in finding solutions to drug-induced harm. Pharmacovigilance science, as it stands, is therefore the first critical step of drug safety solutions. Moving the central focus of pharmacovigilance from signal detection to solution finding is the future for this scientific discipline. A side benefit of this approach is that medication adherence will likely be enhanced in those patients for whom the risk of ADRs is of significant concern when the level of risk is more objectively defined.

*This drug safety **solution-finding** approach assures the future of pharmacovigilance by demonstrating to those who most need to understand its virtues and the opportunities it affords – patients, clinicians, and regulators – that it can improve the safe use of drugs in patients, not just illustrate what harms can occur from specific drugs.*

3.2 Communicating Drug Risk

Drug risk communication is focused on population risk. "Dear Health Professional" letters often encompass statements such as "In worldwide clinical trials of drug X involving 16,450 patients, reports of reaction Y have been received for 14 patients." As a clinician, such a Dear Health Professional letter is filed in the round bin under my desk. Why? Because an incidence of 0.09 % means I will likely never see this reaction in my clinical practice. It is not meaningful to clinicians to see very small numbers that reflect *population* risk and not an *individual patient's* risk. Clinicians don't treat populations of patients but instead individual patients one at a time. They need risk information that compliments this individualized approach to health care. Patients ideally need the same thing – an individual assessment of *their* risk of an adverse drug reaction – not just population estimates of risk. When

examining population risk estimates, we tend to think of what the "average" patient might experience or imagine ourselves being the average patient. But how average we are depends on things we may not know about or are beyond our control, like our genetic makeup. How, then, can we communicate the risk of drug harm to individual patients in the most meaningful way? To answer this question, we first need to understand how differently patients respond to the same drug at the same dose.

3.3 Heterogeneity of Patient Response

Heterogeneity of patient response to drug therapy is well known, but not well understood despite years of pharmacovigilance detective work. Risk factors for drug harm are almost always known. Some are obvious – for example, most ADRs are concentration (dose) dependent – but for many drugs, differential risk of ADRs between patients is not well defined. Objectively quantifying and cataloging drug response heterogeneity such that clinicians can compare and contrast therapeutic choices would help tremendously in capturing the enthusiasm of clinicians in building better pharmacovigilance systems. *Pharmacovigilance needs to give clinicians what they need.* But cataloging responses can be difficult, particularly if patient outcomes are not objectively measured in the same way or with tools of unknown validity.

The lack of critical data in drug safety reports is an ever-present problem in pharmacovigilance. Clinicians are of particular value in drug safety reporting because they are generally in the best position to observe and describe patient response. But clinicians have other health-care priorities with busy schedules and little spare time. Properly quantifying drug response requires time and energy to note concomitant drug therapy, doses of all agents, comorbid conditions – all of which can and do influence therapeutic response – as well as many other factors. It is important to remember that clinicians are also rarely experts in pharmacovigilance nor see ADR reporting as a primary role.

3.4 Patient-Focused Risk Communication

Clinicians are patient focused and therefore require a patient-focused management strategy or solution for ADRs. Risk communication from pharmacovigilance professionals must increasingly fill this need if the future is to remain bright. If pharmacovigilance can provide *patient-specific risk information*, then reporting and *quality* of reporting will ensue with very little effort. Clinicians and patients will see the high value of ADR reporting when they see this information being brought back to them, formulated in a way they can use or benefit from it. For example, showing which patients are at increased risk and not just that a given drug has an

ADR risk. Clinicians, when completing ADR reports, will then begin to ask themselves, "what information do pharmacovigilance professionals need such that more patient-specific risk information reports can be generated?" instead of providing what they think pharmacovigilance experts need. There is a significant difference between these two approaches to providing drug safety information. The latter – clinicians providing ADR information based on what they think pharmacovigilance centers need – happens because they are completing the reports on the basis of what they believe will be done with it. If, for example, they imagine reports grouped by generic drug name and a broad reaction descriptor, then this is the specific information they will provide. ADR report-based literature generally focuses on ADR risk descriptions in this fashion.

The future of pharmacovigilance is based on clinicians getting what they need to make more informed treatment decisions for the patients they care for. The best advocates for pharmacovigilance are those that are served well by it.

3.5 Quality of ADR Data

Quality of the drug harm data used in epidemiological analyses is often poor and dependent on detailed cases provided mostly by "volunteer" clinicians or patients whose primary mandate is not to find solutions to these problems but only to report them. They generally see their pharmacovigilance mandate as *identifying* cases of drug harm. They can often reject the mandate to report a reaction by convincing themselves that the case is not clearly drug related and therefore not really reportable. Pharmacovigilance professionals often ask for all potential drug reaction reports precisely to prevent this filtering by health-care professionals who do not have the pharmacological background to make a proper causality assessment.

The future of pharmacovigilance depends on finding new ways to integrate clinician "volunteers" in this scientific discipline such that solutions to drug harm can be found.

The very next steps the discipline of pharmacovigilance must face are to identify how drug-induced harm should be best managed, how high-risk groups of patients can increasingly be identified before drug therapy commences, and perhaps most importantly, what therapeutic options should be considered when drug harm is likely to result in a tragic outcome. This "drug-safety-solutions-strategy" approach is best managed by pharmacovigilance professionals who are without question the best professionals to help characterize ADRs and build this solution strategy. That said, clinicians can help through the submission of better-characterized case reports which will come from them when they see more value in their reporting of ADRs. The value they see in ADR reporting comes when it helps the patients they serve. This is why finding solutions to drug safety problems needs to become the new mantra in the science of pharmacovigilance.

3.6 Active Surveillance

One important contribution of the epidemiological science of drug harm is that safety signals can be found needing regulatory or clinical action. But to ascertain the specific role of the drug to the development of an ADR (e.g., versus a concomitant disease), more than a compilation of ADR case reports is required. Detailed (and time-consuming) clinical characterization of the adverse event and temporal relationships in each case must be accomplished. Such "deep phenotyping" requires a specific type of pharmacovigilance. Active surveillance can be used to develop better-defined cases once an epidemiological signal is found, and this surveillance approach can help overcome epidemiological confounding.

Active surveillance is simply a method of pharmacovigilance but advanced by the use of trained surveillors who have standard case definitions by which to record critical data related to the ADR. As well, data are collected in real time as reactions occur or are uncovered during quality assurance initiatives, and the data can be collected over time, and treatment and management strategies to deal with the ADR are utilized. *ADR reporting is not just a point estimate for harm but an examination of the drug-induced harm over its entire course in the patient.* We need to understand harm – in whom, when it is likely to occur in treatment, and what makes patients who experience it different from those who do not. This requires that pharmacovigilance scientists collect comprehensive data on each ADR case. Active surveillance is not about collecting large amounts of data on patient drug experience, but instead collecting the right type of data and thereby creating well-phenotyped cohorts of patients from which further analyses and investigations can begin. For example, from such well-phenotyped data, pharmacogenomic determinants of drug-induced harm can be determined. This then leads to understanding genetic predisposition as well as the mechanistic basis of the ADR. This can lead to risk avoidance strategies in clinical care (e.g., not using a drug if the risk of serious harm is high) or even new therapeutic approaches to avoid ADRs or prevent them with concomitant agents to protect against harm.

We need a method to improve the quality of pharmacovigilance data. Active surveillance can help. Much of current epidemiological methods are to overcome the data quality problem with larger datasets. *"Small data" – data which are well constructed around a specific question – are likely better than "big data" in getting us to an understanding of what determinants are important in improving the safe use of drugs.*

3.7 Utilizing Pharmacogenomic Methods in Pharmacovigilance

Pharmacogenomic methods can also be employed to find genetic causes of drug harm, create risk prediction models to inform patients, and overall avoid harm in patients for whom therapeutic alternatives exist. Only expert-conducted pharmacovigilance can provide the appropriate background data surrounding the adverse

event upon which to build the genetic analyses and risk-of-drug-reaction prediction models. Some examples are the following.

Codeine, a weak analgesic, is commonly used for the treatment of mild pain. Interindividual variability in codeine analgesia is in large part related to functional polymorphisms in the CYP2D6, with resultant morphine formation ranging from 0 to 75 % of total codeine metabolism [5]. There are currently over 150 allelic variants and subvariants of varying functional activity identified for CYP2D6 (CYP2D6 allele nomenclature committee webpage: http://www.cypalleles.ki.se/cyp2d6.htm [4]). Traditionally, CYP2D6 enzymatic activity has been determined by the urinary metabolic ratio of a specific CYP2D6 substrate to its *O*-demethylated metabolite. Subsequently, genotyping methods have classified the population into four phenotypic groups: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultra-rapid metabolizer (UM) [11]. Presently, *CYP2D6* genotype cannot fully predict phenotype. Concomitant use of a CYP2D6 inhibitor that may mimic a poor metabolizer phenotype leads to discordance between the genotype-to-phenotype predictions [11]. The majority of codeine-related deaths have concomitant drugs detected on the toxicological screen, making it difficult to determine if the death is attributed to codeine alone or multidrug use [9]. Understanding the combined role of genetic factors and drug-drug interactions contributing to these mortalities is likely to provide valuable information for the interpretation of circumstances around death, may help toxicologists and coroners decipher the cause of death, and may prevent future codeine-related fatalities from occurring.

Cisplatin is an effective chemotherapeutic agent used for a variety of solid organ malignancies in children and adults. Ten to twenty percent of all cancer patients receive cisplatin [17]. However, its use is limited by the high incidence of adverse drug reactions, including irreversible ototoxicity, peripheral neuropathy, and nephrotoxicity [2, 12, 21]. Cisplatin-induced hearing loss is an especially pervasive problem as it affects 40–60 % of pediatric patients and hearing loss at an early developmental age and can hamper the speech, cognitive, and social development of a child [6]. Strikingly, cisplatin-induced hearing loss shows significant interindividual variation; some patients are susceptible at any dose, while others do not experience toxicity at very high doses. Such wide variability implies a genetic basis underlying the ADR, and some genetic findings have been published [13, 15], but more work remains to be done to understand how these identified variants influence both cisplatin toxicity and its effectiveness as a chemotherapeutic agent.

Anthracyclines are highly effective and commonly used chemotherapeutic agents to treat adult and childhood leukemia and various solid tumors. Sixty percent of all childhood malignancies and more than 50 % of breast cancer patients each year receive anthracyclines [3, 14]. Their clinical utility is primarily limited by an individually variable, cumulative dose-dependent cardiac toxicity, manifesting as asymptomatic cardiac dysfunction in up to 57 % of treated patients and restrictive or dilated cardiomyopathy resulting in congestive heart failure in 16–20 % of treated patients [7, 8, 10, 18, 19]. The development of a predictive clinical and genetic risk model would aid in the screening, prevention, monitoring, and management of this serious adverse reaction. At least 21 genes associated with anthracycline-induced

cardiotoxicity have been identified [1]. Knowledge of these genes would improve our understanding of the mechanistic basis of the pathogenetic mechanisms for anthracycline-induced cardiotoxicity and could significantly improve our ability to predict in whom cardiotoxicity will occur.

Despite substantial evidence supporting a pharmacogenetic approach to warfarin therapy in adults, evidence on the importance of genetics in warfarin therapy in children is limited. The contribution of *CYP2C9/VKORC1/CYP4F2* genotypes and variation in other genes involved in vitamin K and coagulation pathways to warfarin dose and related outcomes in children have recently been published [16]. Associations between *CYP2C9/VKORC1/CYP4F2* genotypes and therapeutic dose, time to therapeutic international normalized ratio (INR), time to over-anticoagulation, and incidence of adverse drug reactions have been found [16]. Evidence to date shows an increased sensitivity to warfarin in *VKORC1* and *CYP2C9* variant allele carriers, emphasizing the diagnostic significance of predictive genotyping.

3.8 Linking Pharmacovigilance with Pharmacogenomics

The work of pharmacogenomics science depends entirely on the work of pharmacovigilance science. Without proper phenotyping of a patients' ADR, careful, detailed characterization of the adverse drug reaction (also known as "deep" phenotyping), identifying genetic variants of relevance to clinicians, is unlikely to occur. Drug biotransformation is a complex process of multiple pathways and in some cases saturable ones, whereby other pharmacokinetic pathways are used in part or in full. This makes the future of pharmacovigilance very bright. The decoding of the human genome holds great promise, but the use of genomic data to decode human drug response relies entirely on the quality of the drug use and outcome data that underlies such associations. A number of things can alter gene expression (e.g., diet, age, which would be captured with rigorous pharmacovigilance), but these are likely to have milder effects on drug response compared to genetic mutations. The value of pharmacogenomic information can only be found if rigorous pharmacovigilance precedes it.

3.9 New Drug Development or Drug Repurposing

One principal reason that pharmacovigilance science has not had the impact in patient care that it could have is the lack of a specific focus on finding solutions to drug-induced harm. If the mechanistic basis of ADRs can be found, then drugs developed that preserve efficacy and reduce toxicity are at least hypothetically possible to produce by avoiding these mechanistic pathways. As well, existing drugs that, for example, target key pathways of drug toxicity may be able to be successfully used to prevent toxicity of existing agents that are effective and produce positive drug outcomes but significant harm in some.

3.10 Assuring Pharmacovigilance's Positive Future

What is needed for the positive future of pharmacovigilance science is to move from considering it an independent science into one that is only really valuable if it is a part of achieving the most important outcome – a better way to predict and prevent ADRs in susceptible patients.

One model to accomplish this is to link the work of pharmacovigilance with the work of pharmacogenomics (Fig. 3.1). This model has four distinct phases:

1. The *discovery* of genetic variants that put patients at risk of specific ADRs or protect them from drug-related harm
2. The *replication* of these discoveries to ensure generalizability of findings and *validation* of why the identified variants mechanistically lead to an ADR or reduce its chance of occurring
3. The *translation* of findings into clinical practice
4. The creation of a sustainability plan to allow the process to work in perpetuity

Commercialization of the research allows the findings to be brought into widespread use. The profits from which are then fed back into the model to support the next pharmacovigilance work that leads to the next genetic discoveries, and so on.

The training of highly qualified personnel is at the center of this model, whereby personnel are trained in all relevant domains of the wheel to ensure drug safety solutions are developed. This is distinct from accomplishing just one task, such as developing pharmacovigilance activities that stand alone. Importantly, the model begins with patient- and clinician-recognized ADRs of interest and returns back to

Fig. 3.1 The Canadian Pharmacogenomics Network for Drug Safety wheel model for developing solutions to drug safety problems

them better ways to predict and prevent the ADRs they are most concerned about. This circular approach helps ensure that patient and clinician interests are addressed – an important determinant to ensuring uptake of the resulting research into clinical care.

3.11 Concluding Thoughts

Get the phenotype "right" for ADRs. This requires far more than meeting minimum ADR reporting requirements but a fundamental rethinking of the reason for pharmacovigilance in the first instance. Is it to record and report ADRs or find solutions to drug-induced harm? The latter has staying power for pharmacovigilance science – clinicians and institutions want solutions, most importantly, so do patients.

If dedicated pharmacovigilance professionals are employed to do the important work of properly phenotyping adverse drug reactions, we can find solutions to drug safety problems through new genomic technologies that can help us characterize patients based on risk and develop predictive models of drug harm. Armed with such genomic data, the mechanistic basis of these ADRs can be found, and new therapeutic approaches can be explored to minimize harm through drug development or drug repurposing.

The future of pharmacovigilance is bright as long as we meet the needs of the patients, clinicians, and institutions that we serve.

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