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PHARMACOVIGILANCE: METHODS, RECENT DEVELOPMENTS AND FUTURE PERSPECTIVES

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ABSTRACT

Background Pharmacovigilance, defined by the World Health Organisation as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem' plays a key role in ensuring that patients receive safe drugs. Our knowledge of a drug's adverse reactions can be increased by various means, including spontaneous reporting, inten- sive monitoring and database studies. New processes, both at a regulatory and a scientific level, are being developed with the aim of strengthening pharmacovigilance. On a regulatory level, these include conditional approval and risk management plans; on a scientific level, transparency and increased patient involvement are two important elements. Objective To review and discuss various aspects of phar- macovigilance, including new methodological developments.

KEYWORDS: *Drug regulation Drug safety Intensive monitoring. Pharmacovigilance Spontaneous reporting Transparency*

INTRODUCTION

The field of drug safety has been receiving a great deal of attention latelv. Almost weekly, tabloids as well as scientific journals publish articles on drugs that cause unexpected adverse drug reactions (ADRs). These articles have the unfortunate result of evoking apprehension in both patients and health professionals regarding the use of these drugs. A more serious consequence may be that the patient stops taking the prescribed medication, which may lead to an even more serious situation than the ADR he was initially concerned about. Pharmacovigilance, defined by the World Health Organisation (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem' [1], plays a vital role in ensuring that doctors, together with the patient, have enough information to make an educated decision when it comes to choosing a drug for treatment.

The aim of this review is to provide a summary of the most common methods used in pharmacovigilance to guarantee the safety of a drug. Recent developments in pharmacovigilance as well as future needs are discussed. As an introduction to the sort of problems pharmaco- vigilance has to face, a few examples of recent safety concerns and the action taken are briefly described.

Safety concerns

The withdrawal of rofecoxib directed renewed attention to drug safety. The decision to withdraw rofecoxib was made after the safety monitoring board of the APPROVe trial found an increased risk of cardiovascular (CV) events in patients treated with rofecoxib compared to placebo [2]. The events leading to the withdrawal of rofecoxib, and what has happened since the withdrawal, has been discussed in numerous papers [3-6].

Another association that has been much debated the last year is the association between rosiglitazone and cardiac effects. In June 2007 a meta-analysis was published wherein the use of rosiglitazone was linked to an increased risk of myocardial infarction and death from cardiovascular causes. The results of this one meta-analysis kindled a growing debate on the safety of the drug , and new studies were rapidly published with the aim of rejecting or confirming the results of the first study. Both the US Food and Drug Administration (FDA) and the Europe- an Medicines Agency (EMEA) have now concluded that the benefits of rosiglitazone outweigh its risks within the framework of its approved indications . However, constant revision/updating of product information and a continued monitoring of this ADR are necessary.

A more recent safety concern is the association between aprotinin and increased mortality. In 2006, a study based on observational data was published by Mangano et al, in which these authors questioned the safety of aprotinin. On November 21, 2007, aprotinin was withdrawn from the market in the European Union based on data from the BART clinical trial showing increased mortality for patients receiving aprotinin. Table 1 provides an overview of recent major drug safety issues and the evidence that led to their discovery. Whenever a drug safety issue occurs, the first reaction is to search for a reason of why such a thing could happen. In the case of rofecoxib, this led to a critical evaluation

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of the current methods and mechanisms available for safeguarding the safe use of a drug.

Regulatory action after rofecoxib withdrawal In the aftermath of the withdrawal of rofecoxib, the FDA and the current system of post-marketing surveillance was heavily criticised on a number of points [18-23]. Firstly, the FDA uses only a limited number of data sources (clinical trials, spontaneous reporting) when it comes to assembling information on the safety of a drug. Secondly, the FDA has no control over the performance of post-marketing safety studies. The majority of post-marketing study commitments are never initiated, and the proportion of postmarketing safety studies (phase 4 studies) that were completed declined from 62% between 1970 and 1984 to 24% between 1998 and 2003. Thirdly, the FDA has no authority to take direct legal action against companies that do not fulfil their post-marketing commitments . Some critics also claim that the FDA has become too close to the industry that they are supposed to regulate and that a sepa- ration between regulatory duties and the post-marketing surveillance activities is desirable. In response to the criticism, the Centre for Drug Administration (CDER) at the FDA asked the Institute of Medicine (IOM) to assess the US drug safety system. In September 2006, the IOM released the committee's findings and recommendations in a report 'The future of drug safety: promoting and protecting the health of the public'. The main message in this report is that the FDA needs to follow the safety of a drug during its whole life cycle. This life-cycle approach includes identifying safety signals, designing studies to confirm them, evaluating benefits as well as risks, using risk-benefit assessments to integrate study results and communicating key findings to patients and physicians[7] .

In Europe the withdrawal of rofecoxib led to an assessment of the pharmacovigilance system in the different European Union member states, which was published in March 2006. The report 'Assessment of the European Community System of Pharmacovigilance' highlighted the strengths and weaknesses of the European pharmacovigi- lance system. The report's recommendations focussed on the breadth and variety of data sources, the pro-active use of registration, the speed of decision-making, the impact of regulatory action and communication, compliance by marketing authorisation holders and general principles of quality management and continuous quality improvement.

Methods used in pharmacovigilance

The activities undertaken in the name of pharmacovigilance can be roughly divided into three groups: regulatory, industry, and academia. Regulatory pharmacovigilance is driven by the aim to provide drugs with a positive benefit- harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by by a a description of the methods used to detect new ADRs and a discussion of the pros and cons of each method.

Clinical trial data insufficient to evaluate drug risk The main method currently used to gather information drug in the pre-marketing phase is to conduct a clinical trial. Pre-marketing clinical trials can be divided into three phases. Phase III studies are often double blind randomised controlled trials; these are considered the rigorous approach to determining whether a causeeffect relationship exists between a treatment and an However, when it comes to monitoring the safety of a drug, this study design is not optimal. Due to the limited number of patients participating, it is generally not possible to identify ADRs that occur only rarely. The relatively short duration of clinical trials makes it difficult to detect ADRs with a long latency. Another limitation of clinical trials is the population in which a drug is tested. The characteristics of the participants do not always correspond to characteristics of the population in which it will later be used; consequently, it may be be difficult to extrapolate results obtained from clinical trials to the population at large. This is especially true for the elderly, for women wom or for people belonging to a minority ethnic group. In order to study rare ADRs, ADRs with a long latency and ADRs in specific populations, careful monitoring of the drug in the post-marketing phase is essential[8].

Post-marketing studies can be descriptive or analytical. Descriptive studies generate hypotheses and attempt to describe the occurrence of events related to drug toxicity and efficacy. Analytical studies test hypotheses and seek to determine associations or causal connections between observed effects and particular drugs, and to measure the post-marketing surveillance because they are able to generate hypotheses that will become ne starting points for analytical studies. Two forms of descriptive studies spontaneous reporting and intensive monitoring will be discussed here. Analytical studies can be conducted using a variety of approaches, including case-control studies, cohort studies and clinical trials. In order to be able to conduct retrospective cohort and case-control studies, data which have been collected in a reliable and routine manner needs to be available. To provide an example of such studies, we describe here two European databases frequently used for analytical studies, the General Practitione Research Database (GPRD) in the UK and the PHARMO Record Linkage System in the Netherlands.

Spontaneous Reporting

In 1961, a letter from the Australian physician WG McBride was published in Lancet. In this letter, he shared his observation that babies whose mothers had used thalidomide during pregnancy were born with congenital abnormalities more often than babies who had not been exposed to thalidomide in utero . In the years to come it became evident that thousands of babies had been born with limb malformations due to the maternal use thalidomide. In order to prevent a similar disaster from occurring, systems were set up all over the world with the aim of regulating and monitoring the safety of drugs.

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Spontaneous reporting systems (SRS) were created, and these have become the primary mary method of collecting post marketing information on the safety of drugs. The main ction of SRS early detection of signals of new, rare and serious ADRs. A spontaneous reporting system enables physicians and, increasingly more often, pharmacists and patients to report suspected ADRs to a pharmacovigilance centre. The task of the pharmacovigilance The centre is to collect and analyse the reports and to inform stakeholders of the potential risk when signals of new ADRs arise. Spontaneous reporting is also used by the pharmaceutical industry to collect information about their drugs. By means of a SRS it is possible to monitor all drugs on the market throughout their entire life cycle at a relatively low cost. The main criticism of this approach is the potential for selective reporting and underreporting . In a review article, Hazell and Shakir investigated the magnitude of underreporting in SRS and determined that more than 94% of all ADRs remain unreported. Underreporting can lead to the false conclusion that a real risk is absent, while selected reporting of suspected risks may give a false impression of a risk that does not exist. However, underreporting and selective reporting can also been seen as advantages. Because only the most severe and signals of ADRs because the person reporting the reaction has already pinpointed what may be a new safety issue. Against this background, the system should perhaps be called 'concerned reporting' instead of spontaneous reporting, seeing as those reporting the issues are highly selective of what they are reporting. With a SRS, it is not possible to establish cause-effect relationships or accurate incidence rates; it is also not possible to understand risk factors or elucidate patterns of use. Although critics say that spontaneous reporting is not the ideal method for monitoring the safety of drugs, it has proven its value throughout the years. Eleven products were withdrawn from the UK and U.S. markets between 1999 and 2001. Randomised trial evidence was cited for two products (18%) and comparative observational studies for two products (18%). Evidence from spontaneous reports supported the withdrawal of eight products (73%), with four products (36%) apparently withdrawn on the basis of spontaneous reports only. For two products, the evidence used to support their withdrawal could not be found in any of the identified documentation . Of nine recent significant drug safety issues handled in the European Union since 1995[9,10], six were detected by spontaneous reports (Table 1), which demonstrates the strength of spontaneous reporting in detecting new safety issues.

Data mining in spontaneous reporting

In the past, signal detection in spontaneous reporting has mainly occurred on the basis of caseby-case analyses of reports. In recent years, however, data mining techniques have become more important. The term 'data mining' refers to the principle of analysing data from different perspectives and extracting the relevant information. Algorithms are often used to determine hidden patterns of associations or unexpected occurrences-i.e. signals in large data- bases. Although the methodology of the various data mining methods applied in pharmacovigilance differ, they all share the characteristic that thev express to what extent the number of observed cases differs from the number of expected cases.

Several approaches of data mining are currently in use. Proportional reporting ratios (PPRs), compare the pro- portion of reports for a specific ADR reported for a drug with the proportion for that ADR in all other drugs. The calculation is analogous to that of relative risk. Using the same information, it is also possible to calculate a 'reporting odds ratio'.

The Bayesian confidence propagation neural network (BCPNN) method is used to highlight dependencies in a data set. This approach uses Bayesian statistics imple- mented in a neural network architecture to analyse all reported ADR combinations. Quantitatively unexpectedly strong relationships in the data are highlighted relative to general reporting of suspected adverse effects. The WHO Collaborating Centre for International Drug Monitoring uses this method for data mining. A related approach is the Multi-Item Gamma Poisson Shrinker (MGPS) used by the FDA for data mining of their spontaneous report's database. The MGPS algorithm computes signal scores for pairs, and for higher-order (e.g. triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict. All data-mining approaches currently cannot distinguish between associations that are already known and new associations. Moreover, clinical information described in the case reports is not taken into account; consequently, there is still the need for a 4/10 analyse these events[11].

Intensive Monitoring

In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (the Intensive Medicines Monitoring Programme) and the UK (Prescription Event Monitoring)[12]. These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored. These data are collected and analysed for new signals. The methodology of these intensive monitoring systems have been described in depth elsewhere. The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spon- taneous reporting because the former only monitors selected drugs during a certain period of time. Through its non-interventional character, intensive monitoring provides real world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. It is unaffected by the kind of selection and exclusion criteria that characterise clinical trials, thereby eliminating selection bias. Another strength of the methodology is that it is based upon event monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs of the drug being studied. Intensive monitoring programmes also enable the incidence of adverse events to be estimated, thus enabling quantification of the risk of certain ADRs[13,14]. This approach, however, also has recognised limitations. The proportion of adverse effects that go unreported to doctors is unknown. The studies also produce reported event

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rates rather than true incident rates. This is the same for all studies based on medical record data, including computer databases and record linkage. There is no control group in standard intensive monitoring studies, and the true background incidence for events is therefore not known strong relationships in the data are highlighted relative to general reporting of suspected adverse effects. The WHO Collaborating Centre for International Drug Monitoring uses this method for data mining [43]. A related approach is the Multi-Item Gamma Poisson Shrinker (MGPS) used by the FDA for data mining of their spontaneous report's database. The MGPS algorithm computes signal scores for pairs, and for higher-order (e.g. triplet, quadruplet) combinations of drugs and events that are significantly more frequent than their pair-wise associations would predict [44]. All data-mining approaches currently cannot distinguish between associations that are already known and new associations. Moreover, clinical information described in the case reports is not taken into account; consequently, there is still the need for a 4/10 analyse these events. Although the intensive monitoring methodology was developed more than 20 years ago, this methodology has received renewed interest in the last years. In the European Commission consultation 'Strategy to better protect public health by strengthening and rationalising EU pharmacovigilance intensive monitoring is mentioned as one tool that can improve the pharmacovigilance system .

Database Studies

In order to test a hypothesis, a study has to be performed. The study can be conducted using a variety of methods, including case-control studies and cohort studies. The limitations of these methods include power considerations and study design. In order to be able to conduct retro- spective cohort and case-control studies, data which have been collected in a reliable and routine fashion needs to be available. The General Practice Research Database (GPRD) and the PHARMO Record Linkage System, which will be described in further detail in the following sections, were chosen here because they represent two different types of European databases. Other database- and record linkage systems are available for research purposes in both Europe and in North America.

General Practice Research Database

Virtually all patient care in the UK is coordinated by the general practitioner (GP), and data from this source provide an almost complete picture of a patient, his illnesses and treatment. In any given year, GPs, who are members of the GPRD. collect data from about 3 million patients (about 5% of the UK population). These patients are broadly representative of the general UK population in terms of age, sex and geographic distribution. The data collected include demo- graphics (age and sex), medical diagnoses that are part of routine care or resulting from hospitalisations, consultations or emergency care, along with the date and location of the event. There is also an option of adding free text, referral to hospitals and specialists, all prescriptions, including date of prescrip- tion, formulation strength, quantity and dosing instructions, indication for treatment for all new prescriptions and events leading to withdrawal of a drug or a treatment. Data on vaccinations and miscellaneous information, such as smoking, height, weight, immunisations, pregnancy, birth, death, date entering the practice, date leaving the practice and laboratory results, are also collected.

A recent review of protocols using GPRD data showed that the database is used for pharmacoepidemiology (56%), disease epidemiology (30%) and, to a lesser degree, drug utilisation, pharmacoeconomics and environmental hazards. There have been over 250 publications in peer-reviewed journals using the GPRD [15]

In the early 1990s, the PHARMO system of record linkage was developed in The Netherlands. PHARMO links community pharmacy and hospital data within a specific region on the basis of patient birth date, gender and GP code. The system now includes drug-dispensing records from community pharmacies and hospital discharge records of about 2 million people in the Netherlands. The data collection is longitudinal and goes back to 1987. More recently, PHARMO has also been linked to other data, such as primary care data, population surveys, laboratory and genetic data, cancer and accident registries, mortality data and economic outcomes. The system has well-defined denominator information that allows incidence and preva- lence estimates and is relatively cheap because existing databases are used and linked. The PHARMO database is used for follow-up studies, case-control studies and other analytical epidemiological studies for evaluating drug- induced effects. In the past the database has been used for studies on drug utilisation, persistence with treatment, economic impact and ADRs.

Developments

Pharmacovigilance and the methods used need to continue to develop in order to keep up with the demands of society. In recent years, three publications have been of utmost importance in terms of providing guidance on the future of pharmacovigilance. The first is the Erice Declaration on transparency, which was published in 1997. In this declaration, pharmacovigilance experts from all over the world, representing different sectors, emphasise the role of communication in drug safety with the following statements:

1.Drug safety information must serve the health of the public
2.Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for health care providers All the evidence needed to assess and understand risks and benefits must be openly available
3.Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated and made accessible to all
4.Innovation in drug safety monitoring needs to ensure that emerging problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated

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It is believed that these factors will help risks and benefits to be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust. This declaration was followed in 2007 by the Erice Manifesto for global reform of the safety of medicines in patient care [58]. The Erice Manifesto specifies the chal- lenges which must be addressed to ensure the continuing development and usefulness of the science, in particular:

1.The active involvement of patients and the public in the core debate about the risks and benefits of medicines. and in decisions about their own treatment and health The development of new ways of collecting, analysing and communicating information about the safety and effectiveness of medicines; open discussion about it and the decisions which arise from it
2.The pursuit of learning from other disciplines about how phamacovigilance methods can be improved, alongside wide-ranging professional, official and public collaboration
3.The creation of purposeful, coordinated, worldwide support amongst politicians, officials, scientists, clini- cians, patients and the general public, based on the demonstrable benefits of pharmacovigilance to public health and patient safety
The third article that has had a profound impact on how pharmacovigilance should work in the future is the article published in 2002 by Waller and Evans in which they give their view on the future conduct of pharmacovigilance. The key values that should underpin pharmacovigilance are excellence (defined as the best possible result), the scientific method and transparency. The paper defines five elements that are considered to be essential for achieving excellence. Three of these are: process-oriented best evidence, robust scientific decision-making and effective tools to deliver protection of public health. The other two elements, scientific development and audit, underpin these processes, recognising that excellence cannot be achieved merely by process .

International developments

In the past, pharmacovigilance has been most concerned with finding new ADRs, but Waller and Evans suggest that pharmacovigilance should be less focused on finding harm and more focused on extending knowledge of safety. In recent years, regulatory agencies have been reforming their systems in order to keep pace with the developments in pharmacovigilance, with the focus on being more pro-active.

Europe

In 2005, a document was drafted by the Heads of the Medicines Agencies called 'Implementation of the Action Plan to Further Progress the European Risk Management Strategy'. In July 2007, the EMEA published a document in which they discussed the achievements booked to date. These achievements included the implementation of legal tools for monitoring the safety of medicines and for regulatory actions. Particular emphasis was placed on:

1.Systematic implementation of risk management plans
2.Strengthening the spontaneous reporting scheme through improvements of the EudraVigilance database
3. Launching the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project to strengthen the monitoring of medicinal products
4. The conduct of multi-centre post authorisation safety studies
5. Strengthening the organisation and the operation of the EU Pharmacovigilance system

In the course of the next 2 years, two main areas will be covered by the European Risk Management Strategy: further improving of the operation of the EU Pharmaco- vigilance System and strengthening the science that underpins the safety monitoring for medicines for human use.

In December 2007, a public consultation 'Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance' was published on behalf of the European Commission. This document contains legislative strategy and key proposals for legislative changes within the European Union. Areas where legislative changes are needed include: fast and robust decision-making on safety issues, clarification of roles and responsibilities for industry and regulators, strengthening of the role of risk-management planning, improvement of the quality if of non-interventional safety studies, simplification of ADR reporting, including introducing patient reporting, strengthening of medicine safety, transparency and communication, including clearer safety warnings in the prod- uct information to improve the safe use of medicines.

The USA

In the USA. the FDA has had a difficult time since the withdrawal of rofecoxib. The main concern is that the FDA is not able to protect the public from drug risks as efficiently as it might. In February 2007, on the basis of the IOM report, the FDA announced several initiatives designed to improve the safety of prescription drugs. These initiatives fall into four main categories. The first is increasing the resources for drug safety activities. Perceiving the agency as being overly dependent on industry funding, some observers propose eliminating user fees. The second category of proposed reform is new authority for the FDA; the agency needs regulatory tools to help assure drug safety. This authority would be exercised through a required risk evaluation and mitigation strategy, including measures such as prescribing restrictions, limits on direct consumer marketing and requirements for post-marketing studies. The FDA could impose monetary penalties for non-compliance. A third aspect of the reform is the improvement of post- marketing surveillance. A routine systematic approach to active population-based drug surveillance that could identify potential safety problems is needed. Finally, changes in the FDA management practices and safety supervision necessary[16].

In May 2007, the U.S. senate passed its version of reform for the FDA. The senate proposed that the Prescription Drug User Fee

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Act, which allows the pharmaceutical industry to pay money directly to the FDA, should increase their payments to the FDA by close to U.S. 400 million dollars. Furthermore, this reform would give the FDA new authority to order companies to undertake formal safety studies of drugs that are being marketed and to fine those who do not honour their post-marketing commitments, However when it came to changing the structure of the FDA, the proposal to create an independent office for the monitoring of the safety of drugs was rejected by a majority of one vote.

Methodological developments

Transparency

The Erice Declaration , as well as Waller and Evans , stated that transparency is important for the future of pharmacovigilance. In the last few years transparency around ADRs has increased. The registration of clinical trials will allow the necessary tracking of trials to ensure full and unbiased reporting for public benefit [17]. A number of countries, including Canada (http://www.hc-sc. gc.ca), the Netherlands (http://www.lareb.nl) and the UK (http://www.mhra.gov.uk), have made their databases con taining the data from the spontaneous reporting system freely available to the public.

Conditional Approval

Both the FDA report and the report from the European Union described earlier emphasise that compliance by marketing authorisation holders needs to be improved when it comes to additional post-marketing studies. A possible solution to this problem would be a time-limited conditional approval, which would place pressure on the manufacturers to conduct and report additional safety studies.

Within the European Union, the EMEA has introduced a conditional marketing authorisation. The Committee for Medicinal Products for Human Use (CHMP) delivers a conditional marketing authorisation for products where The benefit of the immediate availability of the medicinal product to public health outweighing the risk inherent in the absence of additional data there is a specific patient need. Examples include products for seriously debilitating or r lifethreatening life-threatening diseases, medic inal products to be used in emergency situations in response to public threats and products designated as orphan medicinal products. A conditional marketing authorisation is granted in the absence of comprehensive clinical data referring to the safety and efficacy of the medicinal product. However, a number of criteria have to be met including:

1. A positive risk-benefit balance of the product
2. Likeliness that the applicant will be in a position to provide the comprehensive clinical data 3. Unmet medical needs being fulfilled

Conditional marketing authorisations are valid for year, on a renewable basis. The holder is required to complete ongoing studies or to conduct new studies with the objective of of confirming that the risk-benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data. The authorisation is not intended to remain conditional indefinitely. Rather, once the missing data are provided, it should be possible to replace it with a formal marketing authorisation. The granting of a conditional marketing authorisation will allow medicines to reach patients with unmet medical needs earlier than might otherwise be the and will ensure that additional data on a product are generated, submitted, assessed and acted upon.

Risk Management Plans

Another step in a more pro-active post-marketing surveillance is the introduction of risk management plans (RMPs) [68]. Such RMPs are being set up in order to identify, characterise, prevent or minimise risk relating to medicinal products, including the assessment of the effectiveness of those interventions. A RMP mav need to be submitted at any time in a product's life cycle, for example, during both the pre-authorisation and post-authorisation phases. A RMP is required for all new active substances, significant changes in established products (e.g. new form/route of administration), established products introduced to new populations, significant new indications or when an unexpected hazard is identified. The EU Risk Management Plan consists of two parts: the first part contains a 'safety specification vigilance plan' and the the second part conta 7/ 10 of the need for risk minimisation act necessary, a risk minimization plan. The safety specifica- tion contains a summary of what is known and what is not known about the safety of the product. This specification encompasses the important identified risk and any infor- mation and outstanding safety questions which warrant further investigation in order to refine the understanding of benefit-risk during the post-authorisation period.

A risk minimization plan is only required in circum- stances where the standard information provision, by means of a medicine's summary of product characteristics, is considered inadequate. Insufficient patient information leaf- lets or inadequate labelling of the medicine are additional reasons for drawing up a risk minimization plan. Where a risk minimization plan is considered necessary, both routine and additional activities are to be included. Some safety concerns may have more than one risk minimisa isation activity, each of which should be evaluated for effectiveness.

Many RMPs have already been established; however, to date, no quantitative or qualitative reports have been released by the EMEA. Information to the public about RMPs has also been scarce. If RMPs are to take an important place in pharmacovigilance, they need to be made public and easily accessible to scientists, professionals and patients.

Involvement of patients

Another important development is the recognition of the patient as an important player in pharmacovigilance. Patients are the users of drugs, and it is their use of a drug in a safe manner is the ultimate goal of pharmaco- vigilance activities. In an increasing number of countries patients are now allowed to report ADRs to

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the spontaneous reporting system. The European Commission acknowledges the role of the patient in spontaneous reporting [50]. Patients and patient organisations are becoming increasingly more involved in pharmacovigilance, especially when it comes to risk communication.

After introducing patient reporting in the spontaneous in the spontaneo reporting scheme in 2004, the Netherlands Pharmacovigilance Centre Lareb took patient reporting one step further and introduced, in 2006, an intensive monitoring programme using patients as a source of information. The Lareb intensive monitoring programme (LIM)[18], follows the prescriptionevent monitoring methodology in that patients are identified on the basis of prescriptions. Eligible patients are identified in their pharmacies when they come and pick up for the first time the drug under study. Patients can register at the LIM website, and during a certain period of time they will receive questionnaires asking them about adverse events. The system is totally web-based; consequently, questionnaires can be sent mail to participating patients at different points, allowing the collection of longitudinal data. The high level of automation also allows a rapid collection and analysis of data.

Future Perspectives

On a regulatory level, progress has been made during the past few years. However, the results of these changes have yet to become apparent and, therefore, it has not yet been proven if these developments have contributed to better pharmacovigilance conduct. In order to further prove pharmacovigilance as a science, it is essential that academia develops new methods which can strengthen the current system.

Pharmacovigilance as we know it today has been about detecting new ADRs and, if necessary, taking regulatory actions needed to protect public health-for example, by changing the summary of product characteristics (SPCs) or withdrawing the drug from the market. Little emphasis has been put into generating information that can assist a healthcare professional or a patient in the decision-making process of whether of not to use a drug. The gathering and communication of this information is an important goal of pharmacovigilance.

Active surveillance is necessary to receive information about the safety of a drug at an early stage. When developing new methods for active post-marketing surveil- lance, one has to bear in mind the importance of being able to gather information in a timely manner. Spontaneous reporting has indeed been shown to be a useful tool in generating signals, but the relatively low number of reports received for a specific association makes it less useful in identifying patient characteristics and risk factors that will contribute to the occurrence of an ADR in a certain person. This information is essential when it comes to a healthcare provider recommending whether or not a particular patient should use the drug in question. Furthermore, when facing an ADR, questions that patients as well as the treating physician can ask are: will this ADR disappear?; how long will it take before it does?; what treatment is needed? None of the main methods used today in post-marketing surveillance can provide an answer to these questions. It is therefore important to develop methods that can follow a patient using a particular drug over time, as the information gathered using such methods will enable such questions to be answered. Pharmacogenetics could play a role in identifying individual risk factors for the occurrence of certain ADRs[19].

The role of the patient is gradually changing. From being a person with little knowledge and little power, the present- day patient is highly informed about his disease and wants to participate actively in his treatment. As mentioned earlier, in some countries the importance of patients source of information about ADRs has bee In these countries, patients have the opt 8/ 10 ADRs via the spontaneous reporting system. Ihis patent empowerment will continue and, in the future, pharmacovigilance has nitrate on this group as a sour information in addition to the more traditional groups, such as the health professionals[20].

The field of pharmacovigilance has made a tremendous journey since it was recognised in the early 1960s after the thalidomide disaster. Recent events, such as the withdrawal of aprotinin and the questioning of the safety of rosiglitazone, show that it is a topic that lies close to people's hearts. In the past few years there has been a major push in trying to change the existing pharmacovigilance systems in order to meet the demands of the future. Scientific underpinning of pharmaco-vigilance is needed to ensure that it will develop as a scientific discipline and thereby contribute to the innovation needed in this field. The pharmacovigilance of tomorrow must be able to identify new safety issues without delav. If we succeed herein. patient's confidence in drugs will return. Furthermore, pharacovigilance methods must also be able to describe which patients are at risk of developing an ADR and what the course of the ADR is. One approach to doing this would be to use patients -more than has been done up to now-as a source of information; this approach would be consistent with the growing patient involvement in drug safety.

Result

Pharmacovigilance plays an important role in ensuring the safety,efficacy, and proper use of medicines after they are marketed. Different pharmacovigilance methods such as spontaneous reporting systems, cohort studies, case-control studies, electronic health records, and active surveillance help in detecting adverse drug reactions (ADRs) and improving patient safety. Recent developments including artificial intelligence, big data analytics, machine learning, mobile health applications, and global safety databases have improved the speed and accuracy of signal detection and risk assessment.

The integration of digital technologies and international collaboration among regulatory agencies has strengthened drug monitoring systems worldwide. Pharmacovigilance programs also help healthcare professionals and pharmaceutical industries

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in identifying rare and serious side effects, reducing medication errors, and ensuring safer therapeutic outcomes.

Conclusion

Pharmacovigilance is a vital part of healthcare that ensures the safety and effectiveness of medicines by monitoring and preventing adverse drug reactions. Various methods such as spontaneous reporting, active surveillance, cohort studies, and data analysis systems help in identifying drug-related risks and improving patient care. Recent developments including artificial intelligence, electronic health records, big data analytics, and global safety databases have made pharmacovigilance more accurate and efficient.

In the future, pharmacovigilance is expected to become more technology-driven with the use of machine learning, real-world evidence, and personalized medicine approaches. Strong collaboration between healthcare professionals, regulatory authorities, and pharmaceutical industries will further improve drug safety monitoring and public health protection.

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