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Andrew Bate *Editor*

Evidence-Based Pharmacovigilance

Clinical and Quantitative Aspects

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Evidence-Based Pharmacovigilance

Clinical and Quantitative Aspects

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Dedication

To Jenny, Agnes, and Mary
To my mum
To my dad: to whom I so wish I could have handed over a copy of this book.

Foreword

No effective medicine is without hazard. Furthermore, not all hazards can be known before a medicine is marketed. Safety monitoring of medicines in clinical use is therefore a vital activity to protect people from harm.

Such a simple summary belies the challenges and complexities of pharmacovigilance, a scientific discipline whose goal is to ensure that for all marketed medicines the benefits outweigh the risks. Pharmacovigilance is a dynamic and constantly evolving field, which is focused on the optimal utilization of data, tools, and methodologies to rapidly identify and manage risks and to monitor the effectiveness of risk minimization.

Importantly, pharmacovigilance has emerged from the early days of crisis management and sudden drug withdrawals as a specialty whose growing importance is widely recognized in its own right. Notification systems to report suspected adverse reactions were put in place after the thalidomide tragedy of the 1960s in most countries and established the value of a direct link between the healthcare professional and the authorities. But maintaining public confidence has demanded more than this: it has demanded a shift in culture from reactive firefighting to proactive, planned characterization of safety, always taking into account a medicine's therapeutic role.

Technological advances in information transmission, management, and analysis have enabled groundbreaking developments in pharmacovigilance, particularly in detecting signals of emerging harm. New data sources and ways to integrate different kinds of data have been key, for example methodologies for linking spontaneous case reports with electronic health records to contextualize signals. There is no doubt that careful evaluation and wise use of new data tools and methodologies will continue to be the springboard for improvement in pharmacovigilance.

Pharmacovigilance must also keep pace with increasingly complex medicinal products. Robust pharmacovigilance is increasingly seen as an enabler of innovation rather than a barrier. Novel medicines which are developed for small target populations require specially designed approaches to best characterize their safety profile and reduce uncertainties. Evaluating the safety of advanced therapies may extend to the process of product administration itself. Follow-up of patients may need to be lengthy, even lifelong. Unusual or previously unknown adverse effects may be anticipated.

Increasing societal expectations have posed special challenges and dilemmas for pharmacovigilance: operating best protection of individual privacy while optimizing data sharing; promoting greater transparency of signal evaluation while maintaining commercial confidentiality; increasing speed of regulatory decision-making while ensuring robust analysis of all available data. The full impact of involving patients and the public in pharmacovigilance systems is yet to be realized. These tensions, if well managed, will stimulate productive change.

The future opportunities for pharmacovigilance are exciting. The advantages of harnessing mobile technologies and social media, the use of artificial intelligence and machine learning, the potential of pharmacogenetics, and new scientific disciplines such as implementation science—these and others will all influence and shape the future of the field.

With such opportunities will come responsibilities—social as well as scientific. The same standards of safety protection should surely apply wherever in the world a medicine is taken. With this book as a compass, a road map to achieving improved public health outcomes for all can become a reality.

Director of Vigilance and Risk Management of Medicines ***June Raine***
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Preface

Background and Introduction

Pharmacovigilance is defined by the World Health Organization as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [1]. In the 1960s, in the wake of the thalidomide disaster, it was painfully apparent that there was an essential need for a systematic approach to the monitoring of marketed medicinal products, and it was out of this drive for change that the field of pharmacovigilance was born.

Interest in pharmacovigilance has never been greater than it is now: awareness and attention in pharmacovigilance have spread from being the sole preserve of the safety scientist to a subject of interest to the wider community of healthcare professionals and patients themselves around the world. There are many issues and developments that seem to be driving this heightened interest. The use of medicinal products has made such a clear contribution to increased life expectancy and general well-being that being such a core part of modern living, there is more discussion and debate about them and their benefits and risks in the lay and social media. This debate has been fueled by several high-profile medicinal product withdrawals and extensive media discussion about them [2]. In a risk-averse society with much focus on healthy living, the perception of preventable harm generates much dialogue. Also, as data associated with, or of relevance to, healthcare is more extensively collected and more readily accessible, this has to increased research possibilities within pharmacovigilance and also too much research activity to progress the science and discussions about appropriate use of such data and ensuring appropriate privacy of individual data.

As a young science in the twentieth century, the core scientific principles that underpin the field were developed. Initially as small specialized field, but with a very broad remit and plenty of opportunity for scientific development, much methodological work occurred in silos, for example, statisticians advancing quantitative thinking in pharmacovigilance; computational scientists developing better and more sophisticated approaches for collecting, storing, retrieving, and sharing data; and clinicians developing approaches for the diagnosis and prevention of adverse drug reactions. Over time, as other scientific advances (such as the development of the Internet, electronic data capture systems, diagnoses tools, and increased computational power) have occurred, these advances have been leveraged to look to improve pharmacovigilance. The field has subsequently grown in complexity as it has matured. Pharmacovigilance is now widely accepted as a broad discipline requiring input from many different fields of work, and it has become increasingly clear that a multidisciplinary approach is essential and that scientists cannot focus solely on one aspect of pharmacovigilance without a strong grasp of other elements of the field, specifically awareness of both quantitative and clinical aspects. Successful pharmacovigilance requires marrying of both perspectives into an overall holistic strategy and that accepting some amount of natural tension between these two very different perspectives is a necessity and something to be embraced rather than resisted.

This book aims to provide insights into the latest thinking and core concepts in areas of key methodological endeavor in pharmacovigilance (PV). A vast array of methods underpins the science of PV, as we strive to ever more effectively protect patients from harm while they have access to the medicines they need. This book aims to give practitioners who wish to contribute or simply to better understand the science of pharmacovigilance an awareness of key progress and challenges in methodological advances. This book covers both clinical and quantitative aspects and is intended to be accessible for all with a role to play or interest in PV. The book makes no attempt to provide an exhaustive list of all methodological development in or associated with pharmacovigilance, but rather provides a selection of some of the key areas of methodological development, whether clinical or quantitative, considered either particularly important, controversial, or areas changing rapidly.

Each book chapter tends to have a clear quantitative or clinical slant and aims to provide an overview of methodological insights within a specific topic but also provide a perspective on how the area is anticipated to develop in the future. Quantitative chapters focus more on statistical and epidemiological strategies and thinking that underpin core developments in pharmacovigilance but written with a generalist pharmacovigilance scientist in mind. Clinical chapters focus on clinical methods for detecting hypotheses for and determining side effects of medicinal products as well as misdiagnosis pitfalls: written for both the medically qualified but also those that have less clinical background.

Examples of areas of importance include signal detection, risk management, and risk benefit. Ultimately, one hopes that the reader should come away with a sense of the advances that have occurred in pharmacovigilance methods and approaches but inspired and motivated to progress the field of pharmacovigilance with a strong sense that there is much more work to be done: as we as a field do all that we can to try to ensure the safe use of medications by patients.

Tadworth, UK *Andrew Bate*

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Contents

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About the Editor

Andrew Bate is Senior Director, Epidemiology Group Lead for Analytics, Worldwide Safety and Regulatory at Pfizer. In this role he oversees the provision of methodological and analytic expertise to the Epidemiology group in support of drug development and Regulatory and Safety activities worldwide. He previously led an enterprise-wide assessment of data and analytics needs associated with Real World Data. Prior to joining Pfizer in 2009, Andrew was at the WHO Collaborating Centre for International Drug Monitoring for more than 12 years, where he was responsible for the research function.

Andrew has an extensive research record focused on the development and assessment of a range of methods and tools for the analysis of diverse types of Real World Data with a focus on Pharmacovigilance. He has over 70 publications in peer-reviewed international journals and is a regular invited presenter at international symposia. Andrew has contributed to several international initiatives and partnerships including membership of the FDA Science Board Subcommittee on Pharmacovigilance, acting as an expert adviser to the Committee for Medicinal Products for Human Use (CHMP) of EMA, and participated as a member of Council for International Organizations of Medical Sciences (CIOMS) Working Group VIII on signal detection of adverse effects of medicinal products. Andrew was on the Advisory Board of OMOP (Observational Medical Outcomes Partnership), a US Foundation for the National Institutes of Health (FNIH); coordinated public-private partnership to help improve the monitoring of drugs for safety; and was a co-PI for the IMEDS Evaluation Pilot, the first evaluative access and use of the FDA's Sentinel Data Network by a non-FDA entity. He is on the editorial board of *Therapeutic Advances in Drug Safety*, and previously *Drug Safety*.

Andrew holds a master's degree in chemistry from Oxford University and a PhD in clinical pharmacology from Umea University in Sweden. His doctorate, awarded in 2003, was on "The use of a Bayesian Confidence Propagation Neural Network in Pharmacovigilance." He was a Visiting Professor in Information Systems and Computing at Brunel University, London, UK, and is an Adjunct Associate Professor in Clinical Pharmacology at NYU School of Medicine and formerly affiliate faculty of the NYU Center for Health Informatics and Bioinformatics. He has served on both the Executive Committee of the International Society of Pharmacovigilance and the Board of the International Society of Pharmacoepidemiology.

Chapter 1

Congenital Malformations

Eugène van Puijenbroek

Abstract

Although we tend to be reluctant in exposing mother and child to drugs, treatment with medicinal products during pregnancy cannot always be avoided. In the past decades several safety issues occurred that highlighted the need for special attention for the use of medicinal products during pregnancy.

Whether or not a drug causes a potential teratogenic effect depends on several factors. Moreover, effects may be visible at birth, but may also become apparent later in life, among which developmental disorders. Before marketing of a drug the information about the safety in pregnancy is sparse and mainly limited to animal studies and scarce observational data. Clinical trials carried out before marketing, rarely include pregnant women, except when the product is specifically intended to be used in pregnancy. For the most part, effects of drug use during pregnancy can only be identified after marketing of the drug and when used by pregnant women.

The optimal method for evaluating the risk of exposure to drugs in pregnancy strongly depends on the stage of drug development. Preapproval data on risks during pregnancy is limited and most information in this phase comes from embryo-fetal toxicity studies in animals. In the post-marketing phase observational studies are preferred. Next to the clinical presentation, epidemiology, and mechanisms of congenital malformations, the most prominent study types used in the premarketing phase; case reports and case series, cohort- and case control studies, will be discussed. Subsequently, possible ways to study the safety of drugs after marketing will be highlighted as well as current regulations for monitoring drug safety during pregnancy will be addressed.

Key words Pregnancy, Congenital malformations, Developmental disorders, Teratology, Observational studies

1 Introduction

When a medicinal product is used during pregnancy not only the mother, but also the unborn child, may be exposed to the drug. Although pre- and post-marketing studies are aimed at acquiring information on efficacy and safety when medicinal products are used in daily practice, data on safety for the unborn child is usually poor or even lacking.

In the past decades several safety issues occurred that highlighted the need for special attention for the use of medicinal

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products during pregnancy. The most prominent example is the thalidomide disaster, which caused limb reduction malformations (phocomelia) in approximately 10,000 children [1]. Thalidomide was used since the late 1950s for mild sedation but also for the alleviation of nausea in pregnant women. It was not until 1961 that case reports in literature appeared mentioning that the drug may cause severe congenital abnormalities. Wiedemann was the first to report on a series of children with malformations in September 1961 [2]. At the end of that year Lenz issued a warning on a congress of the German Society for Paediatric Medicine [3]. Shortly hereafter, the Australian gynecologist Mc Bride published an article in the Lancet asking if other readers may have noticed similar cases [4]. Lenz subsequently described his findings in the Lancet in January 1962 [5]. In addition to phocomelia, other malformations were attributed to thalidomide, like congenital heart disorders, ocular malformations, and malformations of the inner and outer ear [6]. Nevertheless, thalidomide is currently used for the treatment of various disorders, among which multiple myeloma, leprosy, and HIV/AIDS [6, 7]. The drug has proved to be an effective treatment for these serious diseases. When appropriate risk management procedures are in place to ensure avoidance of its administration in pregnant patients the benefit of this drug outweighs its potential risks under these specific circumstances.

A second example is Diethylstilbestrol (DES), an oestrogen mimic that was used from the 1940s till the 1970s and was indicated for the prevention of miscarriages resulting from progesterone deficiency. It was also used for various other indications like break-through bleedings, inhibition of lactation, and the reduction of adult height in adolescent girls [8]. In 1970, Herbst and Scully reported a case series on vaginal clear-cell adenocarcinoma (CCA) in seven young women [9]. At least 25% of daughters, whose mother had been using DES during pregnancy, developed genital tract anomalies including vaginal- uteral- and fallopian tube anomalies and ensuing fertility problems. In addition they had an increased chance for developing vaginal adenosis and clear cell adenocarcinoma of the vagina and cervix [8]. Also in this case it took several years before the relation between DES and the congenital disorders was discovered. A complicating factor was the fact that the disorders could only be discovered 15–20 years later since they usually became apparent after puberty [10].

Both in the case of thalidomide and DES a condition that is extremely rare to occur in the population was associated with the use of a drug, which led to the discovery of these serious effects. In both situations observations by clinicians, published as cases reports, were the basis for a more detailed analysis of these signals.

Although we tend to be reluctant in exposing mother and child to drugs, the use of drugs during pregnancy cannot always be avoided. An example is epilepsy, where seizures can pose a threat

for both mother and child for instance as a result of gestational severe maternal disorders like preeclampsia, preterm labor and hemorrhage, as well as several obstetrical complications among which maternal death. An optimal control of seizures is important both for the mother and the unborn child [11, 12]. Although treatment is essential to avoid these risks for the mother and the child, some antiepileptic drugs may also be associated with an increased chance of developing congenital malformations. In children of mothers who are treated for epilepsy, the chance for developing major congenital malformations is increased as compared to the general population, whereas the chance for malformations in nontreated woman with epilepsy is comparable to controls without epilepsy [13]. Other examples where treatment during pregnancy may be indicated, are inflammatory bowel disease, asthma, depression, autoimmune disorders, and HIV/AIDS [14–16].

Taken all these considerations together, there is a strong need for reliable information on the safe use of medicinal products during pregnancy.

Before marketing of a drug the information about the safety in pregnancy usually is sparse. It is mainly limited to animal studies and rare observational data. Clinical trials rarely include pregnant women, except when the product is specifically intended to be used in pregnancy. For the most part, teratogenic effects can only be identified after marketing of the drug and when they were used by pregnant women [17]. As a result of this lack of reliable data at the time a drug is marketed, information about the safety of drugs during pregnancy is mostly undefined and many drugs will be contraindicated or not indicated for the use in pregnancy [18]. A study by Adam et al. showed that the teratogenic risk of drug treatment approved by the FDA between 2000 and 2010 was "undetermined" in 97.7% of the cases [19].

In this chapter, the clinical presentation, epidemiology, and mechanisms of congenital malformations will be discussed. Possible ways to study the safety of drugs after marketing will be highlighted as well as current regulations for monitoring drug safety during pregnancy.

2 Drugs and Pregnancy

The limited information on the safety of drug use in pregnancy requires an active approach in drug development and post-marketing surveillance. The discipline of Teratology studies the causes and biological processes leading to abnormal development and birth defects of a structural nature, but also functional effects are taken into account [2]. According to the EMA Guideline on the Exposure to Medicinal Products during Pregnancy from 2005, a number of situations require special attention as far as monitoring

drug safety during pregnancy is concerned [20]. Firstly this applies to conditions where drug therapy is essential and where omitting therapy could cause an increased risk for mother and child. This situation requires balancing the risk and benefits for treatment against the risk/benefits for no pharmacological treatment. Secondly, this applies to circumstances where drug treatment is frequently given, but not necessarily required. This is often the case when drugs are being used, available as Over The Counter (OTC) products. An example is the use of NSAIDs which may cause an early closure of the ductus arteriosus, prolong the duration of labor and the length of gestation [21, 22]. In addition, attention should be paid to those drugs which are a chemical structure or mechanism of action similar to drugs which are known to cause harmful effects. An example are the retinoids, which are aromatic analogous of vitamin A. isotretinoin has been associated with congenital malformations and also to the related drugs acitretin and etretinate, case reports of similar patterns of anomalies have been published [23–25]. A final example is lenalidomide, which is related to thalidomide. Although teratogenicity has not been reported, women of childbearing potential should have two negative pregnancy tests performed within 14 days prior to lenalidomide intake [26]. Finally, special attention should be paid to those drugs that represent a new chemical structure or have a new mode of action.

3 Epidemiology

The embryonic and fetal development is a complex process, which is reflected in the relative high number of miscarriages, stillbirth, and the occurrence of major and minor congenital malformations. Deaths due to birth defects account for more than 21% of all infants deaths [27]. Major malformations occur spontaneously with a prevalence of 3–4% [2]. These are defined as anomalies that create significant medical problems for the patient or that require specific surgical or medical management [28]. Minor anomalies can be characterized as features that vary from those most commonly seen in the normal population and as such they do not represent increased morbidity [28]. Examples are a sacral dimple, ear tag, supernumerary nipple, or rib.

Although prescribing or using medicinal products during pregnancy should be avoided when possible, the number of women using drugs at any time during pregnancy is rather high. A study in the Netherlands in 2004 showed 86% of pregnant women using medication at one moment during pregnancy. If iron-preparations, folic acid, and vitamins are excluded, this is still 69% [29]. Studies in other countries revealed similar percentages. A study by Mitchell et al. in 2011 showed that approximately half of the pregnant women in the United States used prescribed medicinal products

in pregnancy [30]. A retrospective, population-based study of all women who gave birth between 2002 and 2011 in British Columbia showed that approximately two-thirds of women filled a prescription during pregnancy, gradually increasing from 60% in 2002 to 66% in 2011 [31].

Given the background incidence of certain congenital malformations, studying the relation between drug exposure and congenital malformations can be bothersome if the difference in incidence between those exposed and those unexposed is rather small and the condition under study is rare. In those circumstances, relatively high numbers of patients are needed to be able to find a statistically significant association between the drug and a specific malformation. For instance, suppose a specific type of cardiac malformation which is associated with the use of a drug occurs in the control population with an incidence of 0.5% and the risk of similar malformations in the exposed population is 1.5%. There is one control per case, the Type I error probability is 0.05, the power is 0.8 and a Fisher's exact test will be used to test the hypothesis. In these circumstances we will need to study 1747 cases and a similar number of control patients to be able to reject the null hypothesis. In the event the incidence in the exposed population would only be 1%, the study size needed would be 5066 cases and a similar number of controls [32].

4 Pathophysiology

Congenital malformations may occur for a variety of reasons and may be due to for instance exposure to environmental agents, exposure to drugs, chromosomal abnormalities, single gene defects or they may have a multifactorial cause [27]. It is estimated that between one and two-thirds of all congenital anomalies are of unknown aetiology [2]. For the majority of birth defects however, the aetiology has not been elucidated [33]. Whether or not a drug causes a potential teratogenic effect is determined by several factors as described by Wilson in 1977 [34]. These factors give guidance in assessing the causal relationship both on a population level and on a case by case level for instance when counselling patients on drug treatment.

1. The susceptibility for developing congenital malformations depends on the genotype. Sensitivity may vary among species, so a drug may cause a malformation in one species whereas the other one will not be affected. An example is thalidomide, which does not cause phocomelia in rodents, whereas rabbits are affected [35]. In animal studies, exposure of juvenile Beagle dogs shows damage to the developing cartilage when exposed to fluoroquinolones, but this effect is not present in human

studies when exposed in similar time frame, i.e., during pregnancy [36, 37]. Within the same species, the sensitivity may vary among individuals as well and these genetic differences may be further modified by environmental factors [2].

2. The susceptibility may vary with the developmental stage at the time of exposure. Depending on the period of exposure, various effects may occur. When conducting studies detailed information on timing is needed, since the timeframe in which malformations can occur is often limited and imprecise exposure time can reduce the power of the study and bias all estimates to unity [38]. When the development of tissues/organs in the early stages of pregnancy is disturbed, congenital malformations may occur. Depending on the developmental stage, drugs may exert different effects. In the first 2 weeks after conception (third and fourth gestational weeks), exposure to a teratogen may either cause death or may lead to the development of a normal embryo (all-or-none phenomenon). In this stage, damage to the omnipotent stem cells may cause the death of the pre-embryo [39]. Less damaged embryos can still survive due to the ability of the stem cell to regenerate. Structural malformations are less likely to occur in this stage. Later on in the development, after the fourth gestational week, during organogenesis, specific damage to the development of the various organs may lead to structural abnormalities [2]. The development of various organs is often limited to specific time frames. Information on the moment of exposure is therefore important. Effects occurring at this time are usually visible at birth, but may also become apparent later in life. An example is exposure to valproic acid in the first trimester which may result in an increased risk of neural tube defects between 2 and 5% [40]. Whereas exposure in the first trimester may generally result in a loss of the embryo or severe structural malformations or intrauterine death, exposure in the second and third trimesters results in functional defects, adverse effects on the maturation of the organs, or retardation of growth. An example is prenatal exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists which may cause renal failure, arterial hypotension, or intrauterine growth retardation [41]. At the end of pregnancy or during labor, pharmacological effects on the neonate may occur. Functions affected by prenatal exposure include behavior, reproduction, endocrine function and development, and various other physiological functions [2]. Sometimes, the effects on the newborn are not visible at birth, but are only to be detected later in life. An example is the occurrence of structural abnormalities in the genital tract in the offspring of women who used diethylstilboestrol (DES) during pregnancy.

3. Teratogenic agents act in specific ways on developing cells and tissues to initiate abnormal embryogenesis. Knowledge of these mechanisms will enable predicting the occurrence of malformations in medicinal products that will be developed. For instance, valproate has been associated with the development of neural tube defects. Supplementation of folic is associated with a reduction of these neural tube defects in the population [42]. It is possible that noncompetitive inhibition of the folate receptors by valproate may lower the bioavailable folates in mothers treated with valproate and may disrupt the normal development of the neural tube [43].
4. The final manifestations of teratogenic effects are death, malformation, growth retardation, or functional disorders, although other effects like fertility disorders, transplacental carcinogenesis, and pharmacological effects in the new born may occur as well [8, 44].
5. The effect on embryo or fetus strongly depends on the dosage and ranges from "no effect" to "lethal" and is characterized by a dose-effect relationship. For nearly all medicinal product there is a threshold, under which no effect occurs [2].
6. Several factors affect the ability of a teratogen to reach a developing embryo or fetus, such as the agent itself, route of administration, degree of maternal exposure, rate of placental transfer and systemic absorption. The total dose of a chemical reaching the embryo or fetus therefore depends on various variables [34].

5 Methods for Studying Congenital Malformations

Various methods can be used to detect and evaluate the risk of exposure to drugs in pregnancy. Each method has its own advantages and disadvantages. The optimal method to be used strongly depends on the stage of drug development. In the premarketing phase human data on exposure of drugs during pregnancy are rarely available. Prospective randomized controlled trials are usually not carried out, unless the drug is meant to be used during pregnancy. Moreover, clinical trials are generally not considered to be ethically acceptable. For this reason, preapproval data is limited on risks during pregnancy and most information in the premarketing phase comes from embryo-fetal toxicity studies in animals. In these studies rodents like rats, but also mammals, like rabbits, are mostly used. The route of administration and dose should be similar to the route that will be used for administration in humans. In addition, extrapolation of the pharmacokinetic profile from animals to humans should be feasible [18]. Nevertheless, because of inter-species variations, studies in animals are limited in their ability to predict teratogenesis [17].

In the post-marketing phase observational studies are preferred. Cohort studies and case-control studies are the primary types of observational studies to evaluate the relation between exposure and outcome in pregnancy. The most important study types used in this phase; case reports and case series, cohort- and case control studies, will be discussed in this section.

Case reports and case series can provide valuable information on the effects of exposure of medicinal products. A first indication for a malformative effect can be based on one or more case reports [18]. For the evaluation of case reports, elements comparable with the evaluation of reports of adverse drug reactions in the postmarketing setting may be used. A consistent pattern of malformations, plausible time relationship, and possible mechanism may be suggestive for the existence of an association. It is obvious that case reports and case series can only be applied to highlight a potential association between drug and malformation. Additional studies are usually needed for substantiation and confirmation of the association.

An important source of case studies are Teratology Information Services (TIS) that provide information on (intended) exposure to drugs during pregnancy and lactation to healthcare professionals or the general public and which advise on optimal treatment options. Detailed information on additional exposures and other possible risk factors can be retrieved when a TIS is contacted, enabling a detailed description of exposure and outcome. Information is not limited to medicinal products, but may also apply to for instance chemicals, physical agents, or diseases. Usually, information on the outcome does not only concern congenital anomalies, but also comprises spontaneous abortions, stillbirth, perinatal complications, and the development of the child in the first period of life. Studies from TIS, among which case reports and case series, have shown to be an important source of information, since they often provide the first information on human pregnancy exposure, especially in the case of newly marketed drugs [38, 45]. TIS collaborate in two networks to coordinate the activities of the various centers and to collect and evaluate data on exposure of drugs during pregnancy: the European Network of Teratology Information Services (ENTIS) and the North American Organization of Teratogen Information Specialists (OTIS) [46].

Cohort studies can provide information about the relation of exposure to a medicinal product and outcome over time. In these studies cohorts of pregnant women are created that can be followed longitudinally to study the outcome of the pregnancy. Cohort studies can either be retrospective of prospective in nature. Although exposure can be precisely defined in most cases, ascertainment of the outcome can be difficult, since interviews or questionnaires may be needed to obtain information. Accordingly, the comparison between observed and expected outcomes may be

difficult [38]. Since exposure data are collected prospectively in cohort studies, recall or interview-bias is usually absent. A drawback is that the power of these studies is often limited, as far as exposure to medicinal products during pregnancy is concerned. This hampers the possibility to detect new signals or confirm absence of effects. For establishing cohort studies, various approaches can be used for the collection of data, like pregnancy registries, Teratology Information Services, and record-linkage of miscellaneous data-sources.

Pregnancy exposure registries can be used to identify specific teratogens and estimate their risks. These registries may follow either a single drug or disease specific group of product, and can be set up by the pharmaceutical industry or academia, either country specific of international [47]. Given the background incidence of congenital malformations in the population, the number of patients to be included in the register should be relatively high. Registries are expensive to establish and the voluntary enrolment and risk for loss of follow-up may limit their statistical power and validity [47, 48]. An example is the Swedish Medical Birth Registry where information on ante- and perinatal factors is collected prospectively and the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) [13, 49].

Based on the information collected by Teratology Information Services retrospective and prospective observational cohort studies can be carried out in which the birth prevalence of major congenital malformations and other adverse pregnancy outcomes between those exposed and non-exposed can be compared [45]. Similar to other prospective cohort studies, disadvantages of TIS studies are the limited sample size and the lack of information to what extent results can be generalized, since it is unknown to what extent the enrolled pregnant women represent the population due to selection bias. Congenital anomalies or developmental disorders cannot be monitored for an extended period of time, so disorders with a long time to onset or discovery after birth cannot be studied [45].

In record-linkage studies, information of women who were exposed to drugs during pregnancy is linked with data from various data sources, including data derived for non-research purposes, on certain outcome of pregnancies. In this way rather large cohorts can be established and this approach can be useful for monitoring long term effects. Examples are linking information from health care databases such as claim databases from insurance companies, electronic medical records, or population registers [50, 51]. However, data on the actual exposure are not always certain, information may be incomplete and over-the-counter drugs may not be taken into account. In respect to drugs used for chronic diseases, adherence is probably better as compared to drugs that are used more temporarily [38].

5.1 Case-Control Studies

The case-control design is used to compare exposure among those with and without a specific outcome [17]. In this design, the antenatal exposure to medicinal products among cases is compared to that of controls [38]. Multiple studies can be conducted in case-control surveillance once the infrastructure is established. [17]. For the ascertainment of cases, existing registries or reporting systems can be used, like birth defect registries. An example is the National Birth Defects Prevention Study in Atlanta, designed to identify associations between major birth defects and genetic or environmental factors associated with the occurrence of birth defects, the population-based congenital anomaly register EUROCAT, and the Sloane Epidemiology Center Birth Defect Study [52–54]. For the identification of exposure, mothers can be interviewed after birth or when identification is done later, other approaches, like questionnaires, interviews, or using medication history of pharmacists can be used.

5.2 Validity

All types of studies can be subject to various sources of bias, confounding, and misclassification. An important topic to consider is the time of exposure, which may differ between the various data sources, but determines the ability of the study to detect differences in outcomes in embryogenesis when a specific time window is required for an effect to develop.

Selection bias may occur when women voluntary enrolling prospective cohort studies have different characteristics compared to those who are not enrolled in respect to risk factors or outcome [45, 55]. In the event mainly healthy women enrol the registry they may also diverge in respect to the use of smoking or use of alcohol which may subsequently reduce the chance for disorders associated with these risk factors. In ideal circumstances, enrolment in pregnancy registries should take place before the prenatal screening in order to avoid selection bias [47].

Also in the case control setting selection bias may occur in the event cases or controls are selected on criteria that are related to the exposure. An example is the selection of cases from a cohort of women with an underlying condition known to be associated with the occurrence of congenital disorders, like epilepsy, asthma, or psychiatric disorders.

Recall bias refers to the situation where information on drug use is interpreted in another way or remembered in a more detailed or erroneous way by cases as compared to controls where these problems did not appear. The presence of recall bias may increase when the time between questionnaire and birth is longer [38]. Interviewer bias may happen when the interviewer is informed about the fact whether the women did take the suspected drug or not. This may especially pose a problem in retrospective

studies where small increases in risk are studied [38]. Recall bias and interviewer bias especially pose a threat in retrospective studies.

When enrolment of pregnant women in studies relies on whether a pregnancy is planned or not, this may result in ascertainment bias, since some members of the population are less likely to be included than other parts of the population. This may hamper generalizability of the results. This may for instance be dependent on the social status, access to medical and prenatal care [56].

Confounding may occur when the factor under study both interacts with exposure and outcome. Because pregnant women in observational studies were not randomized to their treatment, the differences and impact of various characteristics across treatment groups on the observed associations should be analyzed. Examples are year of birth, maternal age and parity, health status of the mother, smoking, alcohol use and exposure to folic acid and underlying condition (confounding by indication) [38, 47].

5.3 Evaluation of Study Outcomes

Observational studies can reveal correlations between exposure and outcome, but will not enable the definitive establishment of a causal relationship. To make a proper risk assessment epidemiological information should be combined with nonclinical toxicity studies, clinical and biological data [56].

Detecting malformations is most effective when there is an increase in a previously rare condition [38]. Differences in the background rate of major and minor congenital disorders, compared to incidence of congenital malformations associated with the use of drugs, may be small. In these circumstances, the power needed for these studies is high as well and therefore observational studies may not provide the final answer about the existence or absence of a true relationship between drug exposure and congenital disorder.

Some defects may not be detected directly after birth, but may be detected later in life, like cardiac disorders, renal disorders (like unilateral renal agenesis or dysplastic kidneys), and congenital malformations of the intestinal tract. The extent of antenatal diagnostic procedures carried out may influence the amount of induced abortions and as a consequence the number of congenital malformations among live births [20]. This especially holds for severe malformations like anencephaly and spina bifida aperta. In these circumstances, the results of case control studies may show an underestimation of the effect. Also spontaneous abortion and stillbirth in early pregnancy may not be registered and an increased risk may not be noticed, even when associated with the drug exposed.

6 Rules and Regulations

The lack of information on the potential risks associated with the use of medicinal products or its absence once a drug is available on the market, contrasts with the strong need for this information from the perspective of patient and healthcare professional. This strengthens the need for clear rules and regulations to obtain reliable exhaustive observational data in the postmarketing phase. In 2005, EMA published the Guideline "Exposure to Medicinal Products during Pregnancy: Need for Post-authorisation Data," aimed at providing criteria for selecting products for which active surveillance in pregnancy is necessary [20]. In 2008 the European Medicines Agency (EMA) guideline "Risk Assessment of Medicinal Products on Human Reproduction and Lactation" was introduced, describing the way nonclinical and clinical data should be integrated. Various guidelines on Good Pharmacovigilance Practices (GVP) were published by EMA, addressing the way the European Pharmacovigilance Legislation of 2009 should be implemented. In GVP module VI the need for collecting data on drug use during pregnancy from spontaneous reports is described. When exposure during pregnancy takes place, this information should be forwarded to the regulatory authorities in the event of an abnormal outcome. In the absence of an adverse reaction, these spontaneous reports should be discussed in the Periodic Safety Update Report (PSUR) [57] All cases known to marketing registration holders or pharmacovigilance centers, in which embryo or fetus are exposed to a medicinal product should be followed in order to get a clear picture of the outcome of the pregnancy and the development of the child. According to the CIOMS criteria, all reports in which a medicinal product is associated with a congenital malformation should be considered a serious report [58]. This also refers to developmental disorders, reports of fetal death and spontaneous abortion and reports in which the newborn suffers from complaints. Pharmacovigilance centers and Marketing Authorization Holders should also make reasonable efforts to retrieve information needed for a proper assessment.

For drugs for which it is known that they might cause potential harm, actions to reduce potential risks should be specified in the Risk Management and Risk Minimisation Plan. Which method should be applied for monitoring the safety depends on the identified risk, such as congenital abnormalities or psychomotor retardation later on in life, the frequency of use and the magnitude of the risk [20]. Generally, the possibilities for prevention congenital disorders are limited and should focus on the environmentally determined and modifiable teratogens [27]. Once a drug is associated with a potential risk during pregnancy, risk minimization measures focussed on reducing the burden should be in place. These

measures may vary from communicating potential risks to measures that are actually aimed at preventing pregnancy when a medicinal product is used. An example is the Pregnancy Prevention Programme (PPP) to avoid the risk of fetal malformation with oral retinoids. The risk for congenital malformation in this class of drugs is high, even when they are used at a low dose. Malformations associated with the use of retinoids are craniofacial, cardiac, thymic, and central nervous system defects [59]. Every oral retinoid has a dedicated and specific Pregnancy Prevention Programme (PPP), which includes an educational programme in which all women should be made aware of the teratogenic risks and before starting treatment pregnancy must be excluded. Women should be on at least one, but preferably two, complementary forms of contraception [60]. However, despite all efforts, pregnancy on oral retinoids still occurs [59].

7 Conclusion

More than 50 years after the thalidomide disaster the attention for the potential risk for congenital malformations associated with the use of drugs during pregnancy is high. Healthcare professionals and patients are aware of potential risks of using drugs in pregnancy, but also of the risk of not using medication to treat the underlying condition. The downside of this cautiousness is that the experiences before a drug comes on the market are still limited, since in preclinical trials pregnant women are excluded.

Studying the safe use of drugs during pregnancy is challenging and sorely needed to treat mother and child in a safe way. Since information about the preclinical phase is hardly available, information heavily relies on sparse data from the post registration phase. It is only until after marketing that the majority of information on potential teratogenic risks becomes known [17].

The potential risk for developing congenital disorders associated with the use of medicinal products is well known, but withholding treatment to a pregnant woman is not always feasible and may not be in the best interest for the expectant mother and child. Although safety monitoring is primarily aimed at collecting information on possible negative outcomes on both mother and child, knowledge on their absence is also needed to facilitate balanced decisions whether or not patients can be treated with medicinal products.

Due to the increased awareness for potential risks, it is more likely that strong effects will be picked up once a drug is marketed as compared to the situation decades ago. However, less outspoken effects and those that will only become apparent during the development of the child or even in later generations, like in the case of DES, are still difficult to detect. Data used for signaling and

estimation of the potential risk rely strongly on observational data. The establishment of registries that enable prospective monitoring of potential effects is an important step forward. Miscellaneous data sources have complementary characteristics to be considered in studying medicinal products associated with pregnancy outcomes. Methodological approaches should be integrated in order to get a detailed overview on potential risks or assumed safety when using medicinal products during pregnancy.

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Chapter 2

Pharmacovigilance and the Eye

Anthony P. Grillo and Frederick W. Fraunfelder

Abstract

The eye has a unique biology that offers relative protection from the systemic administration of most drugs. Despite this, the eye can still be affected by numerous systemic medications as well as topically administered medications. The eye is often overlooked when thinking of pharmacovigilance because of this relative protection from systemic agents as well as the unfamiliar nature of the eye to many clinicians who are not eye-care providers. This presents a unique challenge to pharmacovigilance with respect to the eye as the incidence of ocular side effects is low in general; this makes identification of adverse drug events (ADEs) difficult to recognize and determine causality. As with other parts of the body, one's age, genetics, state of health, and several other factors all play a role in how a drug interacts with the eye. This chapter begins with some of the basic anatomy and physiology of the eye and how that affects the pharmacology and subsequent toxicity of systemic medications that reach the eye, and then provides a few well-documented and specific examples for reference and understanding of the principles of drug-induced ocular toxicology. This chapter will also address topically administered medications intended for the eye and their systemic ramifications. Recently, in an attempt to capture those uncommon ocular drug side effects, steps have been taken to report these cases online in an attempt to capture in a single comprehensive database known as the National Registry of Drug-Induced Side Effects (www.eyedrugregistry.com).

Key words Ocular toxicology, Ocular adverse drug event, Ocular side effects

1 Ocular Side Effects of Systemic Medications

1.1 Ocular Blood Supply and the Blood-Ocular Barrier

The blood supply to the eye is derived from the central retinal artery and the ciliary or uveal arteries, all of which are branches of the ophthalmic artery. The blood supply to the eye is no different than anywhere else in the body, but once it reaches the capillary beds that supply the eye, there are unique endothelial cells and tight junctions that comprise the blood-ocular barrier, which is formed at two primary locations: (1) the blood-retinal barrier created by the tight junctions of the endothelial cells of the retinal arteries and the tight junctions of the retinal pigment epithelium, and (2) the blood-aqueous barrier created by the endothelium of the iris vessels and the non-pigmented ciliary epithelium. It is similar to the more well-publicized blood-brain-barrier, and likely serves a similar

Andrew Bate (ed.), *Evidence-Based Pharmacovigilance: Clinical and Quantitative Aspects*, Methods in Pharmacology and Toxicology, https://doi.org/10.1007/978-1-4939-8818-1_2,

purpose—to ensure that no foreign particles enter the sensitive areas of the eye and to reduce the possibility of inflammation within the eye as this can lead to irreversible vision loss. This barrier ensures that the eye is relatively well protected from pathogens, enzymes, and large molecules in general and gives the eye relative "immune privilege." This is obviously beneficial for vision, but also makes pharmacovigilance for the eye more difficult as the incidence of eye-related adverse events is inherently low. Despite this protection, however, the blood-ocular barrier can be altered by medications as well as in states of disease. For example, in diabetes, chronic hyperglycemia leads microvascular ischemia of the retina. The compensatory mechanisms of the retinal vasculature to combat this ischemia are complex, but eventually there is vascular dilatation and subsequent loss of endothelial cell integrity. This leads to "leaky" vessels and a compromise in the blood-retinal barrier. This example is useful for understanding as it is easy to conceptualize, but the mechanisms by which medications can bypass the blood-ocular barrier are numerous and complex. The tight fenestrations of the retinal endothelial cells prevent hydrophilic molecules and most drugs that are bound to carrier proteins from entering the eye. In states of disease, such as diabetes, medications that may be normally filtered by the blood-ocular barrier may be able to penetrate the eye and produce toxic effects [1]. Drugs that are lipophilic, however, can pass through the lipid-based cell walls of the endothelium and migrate past the barrier into the eye directly. Some therapies, such as blood-brain-barrier disruption therapy for tumors of the central nervous system, are intended to break up these types of junctions and have unintended side effects within the eye [2]. Carrier transport molecules have also been developed to bypass the blood-ocular barrier for the purpose of delivering drugs, and these have potential for therapeutic purposes as well [3]. Additionally, some medications are secreted within the tears, which continually bathe the eye and this can lead to toxic effects of the anterior segment of the eye [4]. As such, it is important to understand the pharmacology of the medications we prescribe.

1.2 The Role of Pharmacology

The pharmacology of a drug also plays a large part into whether or not it will have the ability to produce toxic effects in the eye. Concentration, pH, presence of buffers, duration of treatment etc all play a part into whether or not a drug will reach the types of cells within the eye that may be sensitive to its presence. There are numerous examples of well-documented prescription, over-the-counter, herbal, and homeopathic medications that can produce toxic and sometimes severe effects in the eye. As the liver and kidneys are responsible for the majority of drug clearance, it is understandable that many of the toxic effects of medications will be seen there first. It is important, however, to understand that a

large amount of injury must be sustained to these organs in order to produce detectable toxic effects. The eye is, by comparison, a delicate organ and even a small amount of injury may result in severe effects/symptoms. It is the responsibility of the prescribing clinician to have a high degree of suspicion and familiarity with the pharmacology, mechanisms, and known side effects of the medications they are prescribing.

1.3 Classification and Reporting of Adverse Events of the Eye

In recent years, there have been numerous medications that have been found to have significant ocular side effects. In 2008, the World Health Organization (WHO) defined the terms to be used in causality assessment of suspected adverse drug reactions (ADRs) and this is outlined below (Tables 1 and 2).

1.4 Systemic Medications with Ocular Side Effects

The next few examples will highlight some commonly used systemic drugs with more clinically significant (Certain and Probable only) side effects, but it is beyond the scope of this chapter to present an exhaustive list of medications with ocular side effects. The two most definitive texts addressing this topic are Grant and Schuman's *Toxicology of the Eye*, Fourth edition (1993) and Fraunfelder's *Drug-Induced Ocular Side Effects*, Seventh edition (2015).

2 Clinically Significant Side Effects of Commonly Used Systemic Medications

2.1 Anti-bacterial Agents

1. Tetracycline family:
   - Generic and proprietary names: (1) demeclocycline (Declomycin), (2) doxycycline (Adoxa, Atridox, Doryx, Doxy 200, Monodox, Pracea, PerioStat, Vibra-Tabs, Vibramycin), (3) minocycline (Arestin, Dynacin, Minocin, Solodyn, Ximino), (4) Oxytetracycline (Terramycin), (5) tetracycline (Achromycin, Actisite, Sumicin).
   - Primary use: Derived from polycyclic naphthacene caboximide, these antibiotics are bacteriostatic and effective against a wide range of both Gram-negative and Gram-positive organisms. Also effective against mycoplasma and psittacosis members.
   - Ocular side effects: (1) Certain: Myopia, Photophobia, Blurred vision, Yellow or green deposits within the eyelids and conjunctiva, Blue-gray discoloration of the sclera (*see* Fig. 1), Enlarged blind spots, Visual hallucinations, and aggravates dry eyes and decreases contact-lens tolerance. (2) Probable: Intracranial hypertension (pupil abnormalities, papilledema, etc.) and aggravation of Myasthenia Gravis (diplopia, ptosis, etc.).
   - Ocular teratogenic effects: Probable: Permanent scleral and corneal pigmentation (crosses placenta).

Table 1
Factors in determining causality

• ***Temporal association*—**Timing of symptom onset with relation to timing of administration of medication
– The coincidence of symptoms with administration does not alone demonstrate causality, nor does the delay in symptoms rule out the medication as the cause of the symptoms
• ***Medication dosing:*** *strength,* etc.
• ***Positive de-challenge*—**Effect disappears when medication is discontinued
• ***Positive re-challenge*—**Effect reappears when medication is restarted
• ***Mechanism*—**A plausible scientific explanation of the mechanism of action
• ***Class similarity*—**Similar symptoms or effects from other drugs of the same class or family

Table 2
Definitions of causality

• ***Certain causality*—**When a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to medicine administration and cannot be explained by concurrent disease or other medicines or chemicals; readministration of the medicine causes a similar reaction
• ***Probable or likely causality*—**When a clinical event occurs with a reasonable time sequence to medicine administration and is unlikely to be due to any concurrent disease or other medicine administration
• ***Possible causality*—**When a clinical event occurs with a reasonable time sequence to medicine administration, but which could be explained by concurrent disease or other medicine administration
• ***Unlikely causality*—**When a clinical event (including laboratory test abnormality) occurs in temporal relationship to medicine administration that makes a causal relationship improbable, and when other medicines, chemicals, or underlying disease provide plausible explanations
• ***Unclassified*—**When a clinical event (including laboratory test abnormality), reported as an adverse event, about which more data are required for proper assessment or the additional data are under examination
• ***Not appraisable*—**When a report suggesting an adverse event which cannot be judged because information is sufficient or contradictory and which cannot be supplemented or verified

– Clinical significance: The routine use of members of the tetracycline family is only rarely associated with ocular side effects, and when present are usually reversible with removal of the offending agent. Minocycline has a greater lipid solubility than other members of the family. This results in greater permeability of the blood-ocular barrier and can lead to pigment changes of the conjunctiva, sclera, and the cornea [5]. This family of medications is also a photosensitizing agent, with doxycycline being perhaps the worst. Severe photosensitivity can lead to corneal burns with even normal amounts of sun exposure, some even look like arc-welding

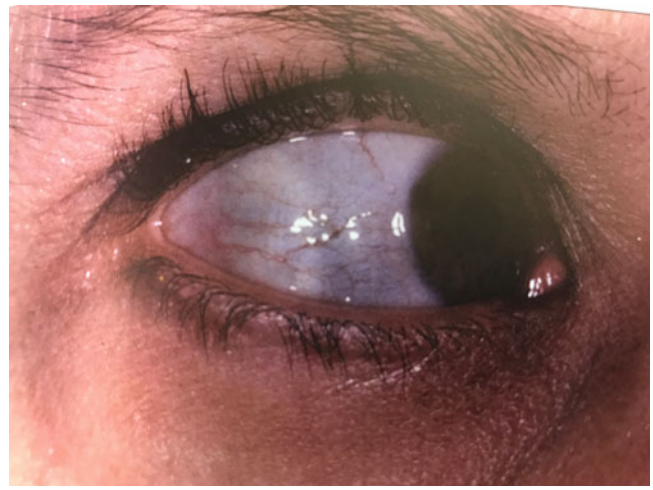

Fig. 1 Image of Minocycline related scleral hyperpigmentation

burns. Several members of the tetracycline family are also known to cause intracranial hypertension, which can manifest itself as papilledema within the eye [6].

- Recommendations: The majority of the ocular side effects related to use of agents of the tetracycline family are reversible. Their detection may require a high degree of suspicion from the prescribing physician, but no additional alterations to practice patterns are necessary.

2.2 Anti-tubercular Agents

1. Generic and proprietary name: Ethambutol (Myambutol).
   - Primary use: Bacteriostatic drug used against *M. tuberculosis.*
   - Ocular side effects: (1) Certain: Decreased color vision, decreased contrast sensitivity, decreased visual evoked potential, ERG changes, Visual field abnormalities, and optic nerve atrophy (*see* Fig. 2). (2) Probable: Optic nerve hyperemia and hemorrhage, Photophobia, Retinitis, Retinal vascular disorders and subsequent edema.
   - Clinical significance: This is one of the core agents used in multidrug therapy for the treatment of tuberculosis, and its use is on the rise with more resistant strains becoming more prevalent. Additionally, world travel is now easier than ever and cases of tuberculosis are showing up in areas that are traditionally not endemic. The ophthalmic manifestations of ethambutol use can be quite severe, with optic neuritis leading to permanent optic nerve atrophy being the most severe. This typically occurs in the first few months after beginning the medication, and characteristic features of optic nerve atrophy may not be visible for months after that. It is likely to first present with loss of color, acuity, or

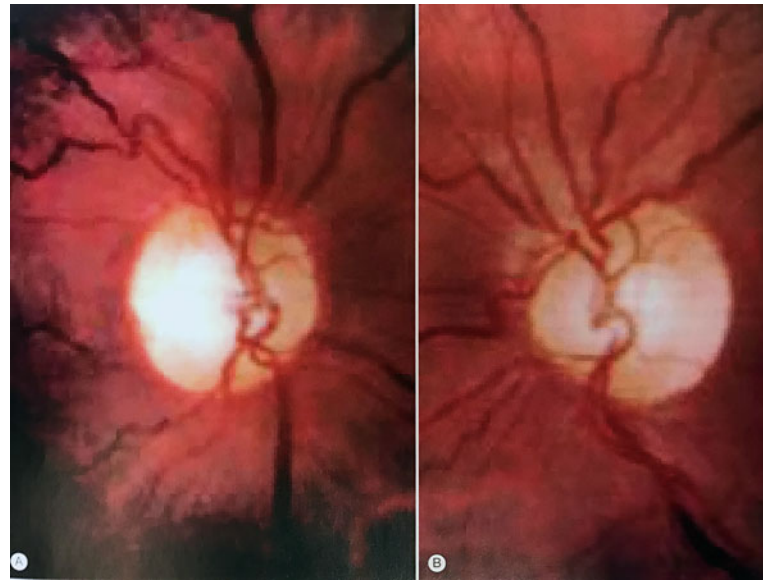

Fig. 2 Image of Ethambutol related optic nerve atrophy of right and left eye. Note the pallor of the nerve temporally from 7-10 o'clock in picture A, as well as similar pallor temporally in picture B from 2-5 o'clock

loss of parts of the visual field before any physical changes are present.

- Recommendations: It is important that proper informed consent be obtained prior to initiating ethambutol as optic neuropathy can occur at any dose and the vision changes that result are likely permanent, as there are no treatment options that have proven benefit at this time. It is recommended that a baseline ophthalmic exam with color vision and visual field be performed at the initiation of treatment as well as monthly exams for anyone taking as dose higher than 15 mg/kg/day or for any of the following high-risk situations: (1) diabetes mellitus, (2) chronic renal failure, (3) alcoholism, (4) young or old, (5) ethambutol-induced peripheral neuropathy.

2.3 Anti-convulsants

1. Generic and proprietary name: Topiramate (Topamax).
   - Primary use: Used primarily in the treatment of migraine headaches, but also used as an anti-epileptic medication. Also used in bipolar disorder and depression.
   - Ocular side effects: Certain: Bilateral suprachoroidal effusions causing bilateral angle-closure glaucoma, ocular hyperemia, myopia, nystagmus. Probable: Blepharospasm and myokymia.
   - Clinical significance: First reported in 2001, the bilateral angle-closure glaucoma associated with topiramate use is now well described [7] (Fig. 3). This complication

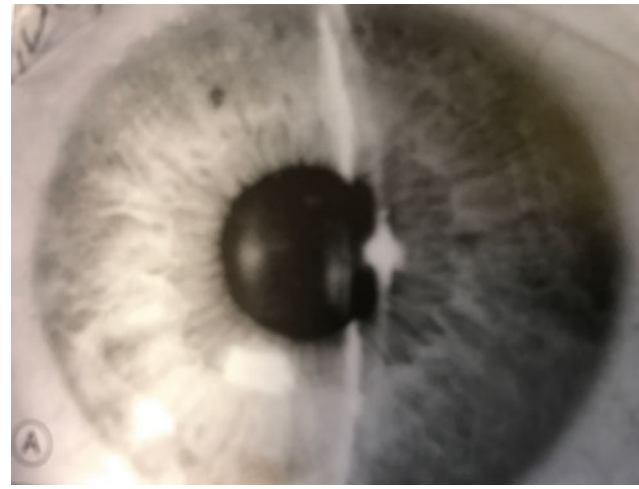

Fig. 3 Image of Topiramate related anterior chamber shallowing and angle closure glaucoma. Note the shallowing of the slit beam as it crosses from the pupil margin to the periphery

frequently occurs during the initiation phase of the medication when the dose is being increased. The findings of this condition are typical of angle-closure glaucoma, except that it is bilateral.

- Recommendations: The medication should be stopped, but this should be done in a graduated fashion, as stopping the medication altogether can exacerbate the condition for which it was prescribed. The therapy for this angle closure should include maximal medical therapy, including oral carbonic anhydrase inhibitors, but should not include laser peripheral iridotomy (LPI) or miotics as the mechanism for this angle-closure is forward displacement of the ciliary body caused by the suprachoroidal effusions, and this will not be relieved with these methods.

2.4 Anti–arrhythmic Agents

1. Generic and proprietary name: Amiodarone (Cordarone, Nexterone, Pacerone).
   - Primary use: Used to treat various forms of arrhythmias.
   - Ocular side effects: Certain: Photophobia and glare, vortex keratopathy within the cornea, decreased corneal sensation, yellow-brown discoloration of the conjunctiva, lids, and a brownish discoloration to surgically placed intraocular lenses. Probable: Optic neuropathy, loss of eyelashes, exacerbation of thyroid eye disease, and papilledema from intracranial hypertension.
   - Clinical significance: This medication has been used clinically for more than half a century. The ocular changes related to amiodarone are well described [8] (Figs. 4 and 5). The changes within the cornea are time and dose-dependent.

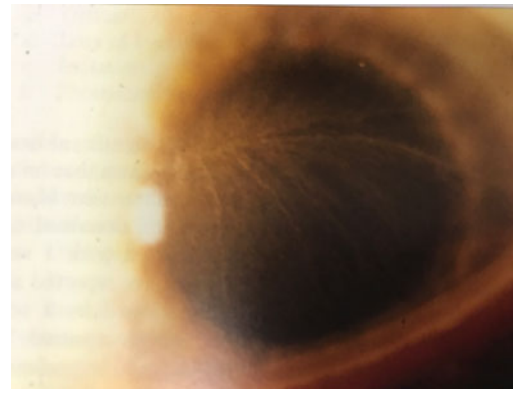

Fig. 4 Image of Amiodarone related corneal verticillata

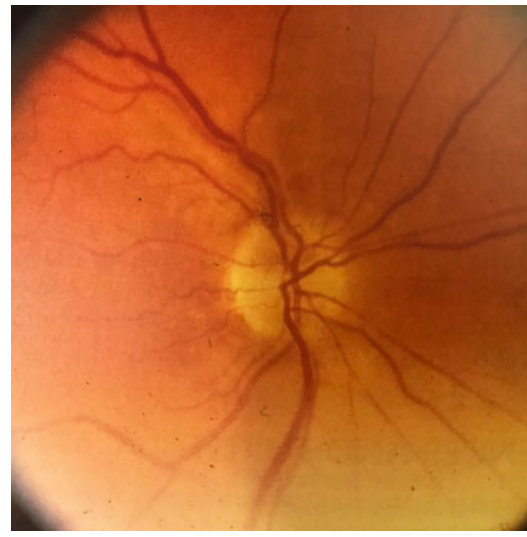

Fig. 5 Image of optic nerve atrophy

The medication is found in the tears, and it deposits into the cornea over time. Interestingly, patients who wear soft contact lenses have a reduced incidence of vortex keratopathy as the contact lenses keep the medication from reaching the surface of the cornea. As a result of the keratopathy, patients may experience glare and photophobia. Discontinuation of the medication will result in resolution of the corneal deposits, but this can take up to 2 years to completely resolve. More importantly, amiodarone has been linked to non-arteritic anterior optic neuropathy (NAION) in a number of cases. It is not definitive whether or not amiodarone is an independent risk factor for NAION, but it has been linked in numerous cases and is currently listed as "probable" by the FDA. Of note, the NAION believed to be associated with amiodarone

use typically has a slower, more insidious, and unfortunately bilateral onset than routine NAION.

– Recommendations: Recommend a baseline ophthalmic examination at initiation of therapy with annual exams thereafter; good informed consent and instructions to see an ophthalmologist if any visual changes are noticed. If exam suggests possible NAION, there should be a discussion with the prescribing physician concerning continuation of the medication.

2.5 Vascular Agents

1. Generic and proprietary name: tamsulosin, doxazosin, terazosin (Flomax, Cardura, Hytrin).
   – Primary use: Alpha-adrenergic antagonists used to treat both hypertension and benign prostatic hyperplasia.
   – Ocular side effects: Certain: Floppy iris syndrome, decreased thickness of iris dilator muscle, decreased pupil size.
   – Clinical significance: The FDA has described the association between tamsulosin and intraoperative floppy iris syndrome (IFIS) as a class drug effect (Fig. 6). It has been known for the last 10 years that even short-term use of tamsulosin can result in an increased risk for IFIS for the remainder of one's life. The risk of serious complication from cataract surgery is increased 2.3-fold in patients who have taken tamsulosin, but that effect has not been observed for the other members of this class [9].
   – Recommendations: Stopping tamsulosin prior to cataract surgery has no effect on the rate of IFIS, so this is not recommended as it will likely not help the surgery and will likely create worsening of symptoms related to BPH perioperatively. It has been recommended by some ophthalmologists that in the absence of other contraindications, other agents be used first for the control of BPH-related symptoms unless the patient has already undergone cataract surgery.

2.6 Hormone Affecting Agents

1. Adrenal corticosteroids: Generic names: beclomethasone, betamethasone, budosenide, cortisone, dexamethasone, fluticasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone.
   – Primary use: Adrenal insufficiency, numerous inflammatory and allergic disorders topically and systemically.
   – Ocular side effects: Certain: Decreased vision, posterior subcapsular cataracts, increased intraocular pressure, decreased resistance to infection, myopia, exophthalmos, diplopia, color vision changes, delayed wound healing,

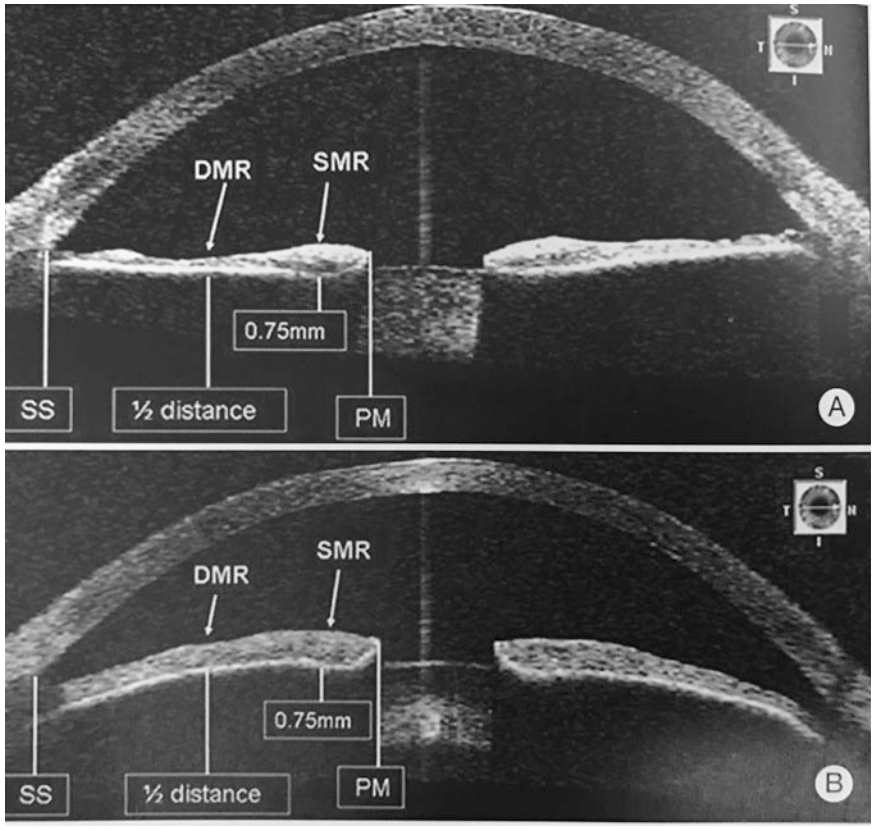

Fig. 6 (**a**) Iris with pupillary dilator atrophy and (**b**) anterior segment OCT of normal iris

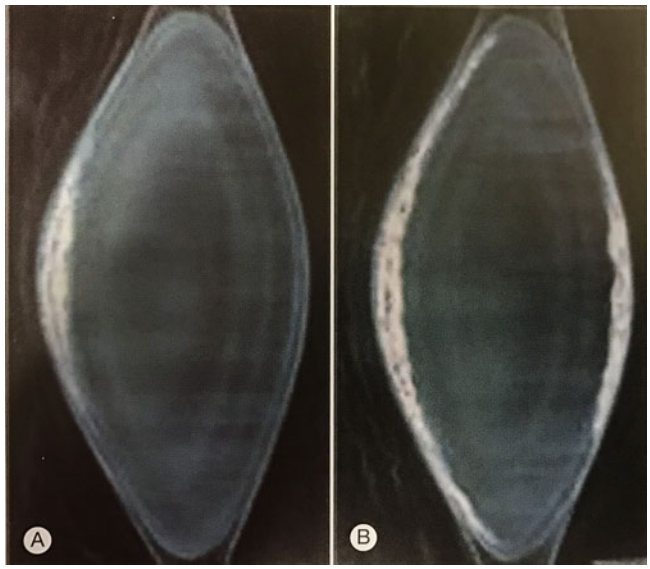

Fig. 7 Posterior (**a**) and anterior and posterior (**b**) subcapsular cataract

visual hallucinations, central serous retinopathy, blue sclera. Probable: Eyelid angioedema, subconjunctival hemorrhage, toxic amblyopia, worsening of retinopathy of prematurity.

- Clinical significance: These medications are used for countless medical conditions, both systemically and topically. The complications and adverse reactions to the use of corticosteroids are nearly as numerous, and some are quite severe. An entire chapter could be devoted to discuss the complications related to corticosteroid use. Here we will review only some of the more common, and more severe ocular complications only. It is well known that corticosteroids can lead to cataract formation, specifically a form of cataract known as a posterior subcapsular cataract [10] (Fig. 7). However, numerous studies have shown that there is an increase in cataract formation in all layers of the lens with both systemic, and topical administration of steroids. Another well-known ocular complication of steroid use is the induction of glaucoma. After a few weeks of topical use, almost everyone will develop an elevation in intraocular pressure. Inhaled steroids can exacerbate pre-existing glaucoma as well. The intraocular pressure will usually normalize once the steroid has been removed, but any damage to the optic nerve during the time of elevated pressure will be permanent. Another well-described entity associated with steroid use is central serous retinopathy [11]. This condition results when the choroidal blood vessels leak fluid into the central macula resulting in decreased vision. The majority of the time this will resolve with removal of the steroid, but roughly 10% of patients have refractory cases that can lead to permanently reduced visual acuity.
- Recommendations: In many cases the use of corticosteroids is unavoidable. It is the responsibility of the prescribing physician to be aware of some of the ocular side effects of these medications and refer the patients appropriately.

2.7 Oncolytic Agents

1. Generic and proprietary name: tamoxifen (Nolvadex, Soltamox).
   - Primary use: Estrogen receptor inhibitor used in the treatment of breast cancer, ovarian cancer, pancreatic cancer, and melanoma.
   - Ocular side effects: Certain: Decreased vision, corneal deposits, tamoxifen retinopathy, retinal edema, posterior subcapsular cataracts, and decreased color vision. Probable: Visual field constriction.
   - Clinical significance: Tamoxifen has been available and used in the fight against cancer since the 1970s, and only recently did we begin to understand the ocular side effect profile. It is

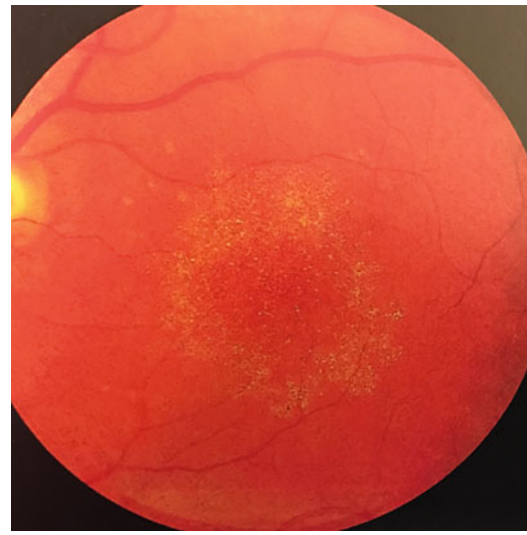

Fig. 8 Image of tamoxifen retinopathy

now known that roughly 13% of patients experience ocular side effects, but fortunately the more serious side effects are not frequently seen and usually only at higher doses (above 10 g today). The rate of tamoxifen retinopathy (white/refractile opacities deposited within the retina that lead to macular edema and subsequent decreased vision) is roughly 1–2% [12] (Fig. 8).

- Recommendations: Current guidelines by the American Academy of Ophthalmology suggest that a complete ophthalmic examination every 2 years, in the absence of symptoms, is warranted. Additionally, the patient should be educated in the signs and symptoms related to tamoxifen toxicity. Additionally, the risk/benefit of drug continuation must be assessed if abnormalities are detected. For example, a limited number of retinal crystals in the absence of macular edema or decreased vision may not warrant discontinuing the medication given the likely benefit of continuation in the setting of known breast cancer, but many people are on tamoxifen prophylactically and significant color vision loss or decreased visual acuity from tamoxifen may warrant discontinuation. Each case is unique, but it is important that all parties involved be a part of the risk/benefit evaluation so that the most appropriate decision be made for each case.

2.8 Anti-rheumatologic Agents

1. Generic and proprietary name: Hydroxychloroquine (Plaquenil).
   - Primary use: used in the treatment of systemic lupus erythematosus, rheumatoid arthritis, as well as an anti-malarial agent.

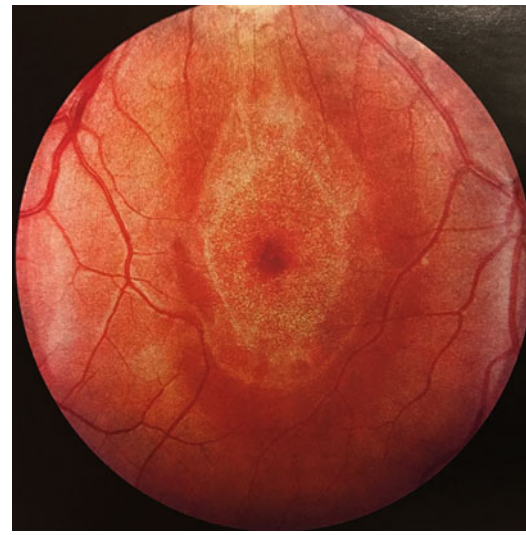

Fig. 9 Image of hydroxychloroquine-associated Bull's-eye maculopathy

- Ocular side effects: Certain: Corneal opacities, decreased sensitivity, granulations of the retinal pigment epithelium (early disease), Bull's-eye maculopathy (late disease) (Fig. 9), abnormalities of electroretinography, visual field stomata, color vision defects. Probable: Oculogyric crisis and aggravation of myasthenia gravis.
- Clinical significance: This medication is widely used throughout the world for rheumatologic disease and as an anti-malarial agent. The corneal deposits may appear rapidly after initiation of treatment, but they do not typically have visual sequelae (although they can cause halos and glare) and are reversible upon discontinuing the medication. Their presence, however is a marker for deposition within the eye and makes it imperative to diligently screen for the presence of posterior segment disease, which causes irreversible vision loss. This medication is toxic to the retina in a dose-dependent manner. The risk increases when a patient is taking more than 6.5 mg/kg/day of their ideal body weight or after the cumulative dose of more than 1000 g, if the medication has been taken for greater than 5 years consecutively, or if the patient has concomitant retinal disease such as macular degeneration [13].
- Recommendations: Currently the American Academy of Ophthalmology recommends an eye exam at the time of initiating the medication, as well as an annual medical eye exam. Additionally, a Humphrey 10–2 visual field examination in addition to one of the following tests: Spectral domain OCT(SDOCT), fundus autofluorescence(FAF), or

multifocal electroretinogram (mfERG). If an abnormality is detected, it is very important that a very serious discussion is held that involves the patient and the prescribing practitioner as the risk/benefit of continuing the medication must be scrutinized, with the majority of patients choosing to stop treatment.

This is by no means an exhaustive list of systemic medications with known ocular side effects; it is meant to highlight some of the better known examples of how medications administered systemically can have detrimental and in some cases permanent vision loss without proper monitoring. Each of the examples provided have been verified and accepted by the FDA as having ocular side effects that are defined as "certain," and as such it is the responsibility of prescribing physicians to understand that these side effects are present and counsel their patients properly regarding their use and monitoring.

3 Clinically Significant Systemic Side Effects of Commonly Used Ophthalmic Medications

3.1 Topical Pharmacology

When administering medications topically to the eye, it is important to remember that a large percentage of topical medications administered will not reach the eye as they are absorbed by the nasal mucosa. This means that these medications will bypass the first-order pass effect of the liver and will be distributed systemically. The eye is well designed to keep foreign materials out of the eye while maintaining the clarity necessary for vision. Working from the outside-in, the first barrier to absorption into the eye is the corneal epithelium. This is the outer-most layer of the cornea and is composed of a layer of stratified, non-keratinized, squamous epithelial cells. Adjacent cells are connected by dense junctional complexes (desmosomes, hemi-desmosomes, and tight junctions) that function to prevent foreign substances from penetrating the surface of the eye, and this layer is lipophilic. Most topically administered ocular medications contain compounds, such as benzalkonium chloride, which act as both a preservative to increase shelf-life as well as act to disrupt the corneal epithelium and increase absorption through the cornea. The corneal stroma, lying directly beneath the epithelium, is hydrophilic. Once most topically administered medications reach this level, they can be quickly absorbed through the stroma, the endothelial layer, and into the eye. The conjunctiva and sclera are also relatively hydrophilic and can absorb medications quickly, but the fornix of the lower lid/conjunctival sac can only contain a volume of roughly 7–10 μl [14]. The average commercial eye drop will contain 30–50 μl of fluid. As such, much of this medication will immediately overflow to the lacrimal drainage

system. Roughly 90% of the active ingredient of topically administered ocular medications will drain down the lacrimal drainage system to the nasal mucosa where it is absorbed fully and intact [15]. This then ultimately drains into the superior vena cava and is subsequently ejected to the rest of the body via the left ventricle. This gives topical ocular medications a direct path to be absorbed into the systemic circulation, and along with it the chance for adverse drug events.

3.2 Topical Ocular Medications with Systemic Side Effects

The next two examples will highlight commonly used topical medications with more clinically significant (Certain and Probable only) systemic side effects, but it is beyond the scope of this chapter to present an exhaustive list of ocular medications with systemic side effects. Again, for complete reference the two most definitive texts addressing this topic are Grant and Schuman's *Toxicology of the Eye*, Fourth edition(1993) and Fraunfelder's *Drug-Induced Ocular Side Effects*, Seventh edition (2015).

3.3 Vascular Agents

1. Generic and proprietary name: phenylephrine (Ak-Dilate, Mydfrin, Neo-Synephrine, Neofrin, Ocu-phrin, Phenoptic, Prefin)
   - Primary use: Topical sympathomimetic amine used primarily as a mydriatic, but also used for local vasoconstriction for surgical purposes.
   - Systemic side effects: Certain: dermatitis (eyelids), hypertension, myocardial infarction, tachycardia, subarachnoid hemorrhage, cardiac arrest, arrhythmia, headache, syncope, pulmonary edema, death. Probable: pulmonary edema (premature infants).
   - Clinical significance: In 2015, a meta-analysis of the cardiovascular adverse events associated with the topical administration of phenylephrine was published stating that there was no clinically relevant increase in either heart rate or systolic blood pressure [16]. This is true in the majority of cases, but there have been numerous cases of serious adverse events reported with the administration of topical phenylephrine. This is most true for 10% phenylephrine in a pledget form, for which 11 deaths have been reported. It is unclear whether these events were idiosyncratic reactions to the medications or whether this represented overdose, but the amount of phenylephrine contained within a single drop of 10% phenylephrine is 5 mg. This amount of medication is quite significant and is in the range of standard IV injection formulations that are used to combat hypotension during anesthesia.
   - Recommendations: This medication is occasionally necessary for appropriate diagnosis and treatment in the eye

clinic, but it is important to exercise good judgment and care in the use of topical phenylephrine; it should likely be avoided completely in patients who may still be using monoamine oxidase inhibitors and tricyclic antidepressants.

2. Generic and proprietary name: timolol (Betoptic, Betoptic S, Betimol, Timoptic, Timoptic-XE).
   - Primary use: Topical beta-blocker used primarily in the management of ocular hypertension and glaucoma.
   - Systemic side effects: Certain: Asthma and/or chronic obstructive pulmonary disease (COPD) exacerbation, bronchospasm, bradycardia, arrhythmia, hypotension, impotence, dizziness, syncope, emotional lability (elderly), vivid dreams, apnea (children), increased high-density lipoprotein (HDL), hyperkalemia, respiratory failure, hypoglycemia, nail pigmentation, and myasthenia-like syndrome.
   - Clinical significance: The systemic side effects of this medication are the same as for the systemic effects of other beta-blockers in the same class. The effects of topical timolol administration may be felt within minutes of administration, but may also develop later. The topical side effects of timolol are usually well tolerated and are very rarely used as a reason for discontinuation; however, the systemic effects of this medication can be quite profound [17]. Pre-existing pulmonary or arrhythmias are contraindications to use.
   - Recommendations: Thorough review of past medical history must be reviewed with the patient prior to the administration of topical beta-blockers. Additionally, the common adverse events should be reviewed with the patient as some ADEs, such as impotence, are not likely to be readily obvious to the patient just beginning therapy. It is important, as with any medication administered by the patient, that the patient be properly instructed on how to administer the drug themselves to ensure that the proper dose is being given. Punctal occlusion and closing the eyes can aid in reducing the amount of medication that reaches the systemic circulation.

4 Future Directions

The online database of information related to pharmacovigilance is expanding daily. Utilizing the capabilities of the internet is likely one of the most practical and cost-effective ways to manage/evaluate pharmacovigilance in the foreseeable future. One of the most difficult aspects of collecting data regarding ADEs is the heterogeneity in reporting the events. Some reports are very detailed and

include challenge/re-challenge data while others simply report the event and suspected mechanism. Additionally, the information is not reported in one location, it is scattered across the electronic universe. At this time, it is up to those who are concerned with this topic to consolidate the information into meaningful data. To this end, the National Registry of Drug-Induced Side Effects (www.eyedrugregistry.com) was created. It is an online resource that is readily available for the busy clinician to aid in the diagnosis of drug-induced ocular side effects. The goals of the registry are:

- To provide the clinician with data on any drug which has a significant visual side effect or an ocular medication with systemic side effect.
- To provide references of the latest articles regarding a particular drug.
- To provide a forum in which to present a case, cases, or suspicions.
- To add this database to those collected by the Food and Drug Administration (Rockville, MD, USA) and the WHO (Uppsala, Sweden).

Eventually, the wealth of information available now to providers and investigators will be coupled with more seamless data collection and analysis. This, coupled with rapidly advancing diagnostic technology, will allow for more rapid diagnosis of known ADEs and most assuredly the additional recognition of ADEs of which we are currently unaware. The inherently low incidence of ocular ADEs creates a diagnostic conundrum and mandates that we are extremely diligent to identify these events whenever possible; as was demonstrated in the previous examples, some of the ADEs from the administration of systemic medications can have profound ocular side effects and can even cause irreversible vision loss. Adding to the difficulty is the wide range of timing of onset of the variable ocular ADEs. For example, bisphosphonate-associated uveitis typically presents soon after administration of the drug, but plaquenil toxicity may not become clinically detectable until the patient has profound vision loss years after starting the medication, and by that time it is too late to stop the process. Too often patients present to the ophthalmologist long after the onset of symptoms because, depending on the specific entity, the timing of the ADE does not necessarily correlate with the initiation of the medication. This makes monitoring and detection of new ocular ADEs quite challenging. The vast majority of reported cases are either spontaneous reports based on signal detection/causality assessment and a few post-marketing surveillance reports. Rarely does an ocular ADE have a high enough incidence to be part of pre-marketing awareness or have the practical and/or financial merit to be part of formal hypothesis testing.

At this time, the relatively small number of known ocular side effects of systemic medications is not well reported throughout much of the developing world. This makes commenting on topics such as pharmacogenomic interactions difficult. Genomic variance for many primary ocular conditions is well described in the ophthalmology literature and it is reasonable to assume that there would be regional differences in the incidence and severity of ocular side effects as well. At this time, any regional or genomic variations in drug-induced ocular side effects would be challenging to prove based on such small numbers and the fact that many of the drugs responsible for these side effects are largely limited to first world countries due to cost (blood-ocular barrier retinopathy, bisphosphonate-associated uveitis, tamoxifen retinopathy, etc.). Additionally, the reporting of these ADEs is highly variable by country. The Eye Drug Registry is attempting to bring together some of these different reporting databases. Countries such as India and Japan have their own reporting system and all these databases do not currently communicate with each other for the purpose of reporting. It is through the development of global online and other easily accessible reporting resources that we will finally be able to better understand and categorize these events and comment on the importation regional variations that are most certainly present, but at this time there is still fragmented reporting and this is a major problem facing the immediate future of monitoring ocular ADEs. The continual advancement in the armamentarium of medical therapeutics is an exciting area of which we are a part, and it is our duty to be vigilant in monitoring for potentially devastating ocular side effects.

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Chapter 3

Pharmacovigilance of Herbal and Traditional Medicines

Li Zhang

Abstract

This chapter first differentiates the concepts of traditional/complementary medicine and their products. It then briefly introduces the supervision and management systems of the China Food and Drug Administration and the differences between conventional medicine and traditional/complementary medicine products, taking drugs used in traditional Chinese medicine as an example. The chapter analyzes and discusses the global use of and regulatory environment for complementary and integrated medicine, and reviews the current methodological approaches to pharmacovigilance for herbal drugs and traditional medicines. Therefore throughout this chapter are showcased the challenges associated with such products and their rational uses, and the imperfections in the global supervision of such medicines in terms of both the methodology behind monitoring by the spontaneous reporting system (SRS) and additional pharmacovigilance. Finally, suggestions are proposed for measures to enhance pharmacovigilance of herbal and traditional medicines.

Key words Pharmocovigilance, Herbal and traditional medicine (H&TM), Traditional Chinese medicine (TCM) , Spontaneous reporting system (SRS), Active surveillance, Post-authorization safety study (PASS)

1 Introduction

With the increasing acceptance of traditional and complementary medicinal therapies—including herbal and dietary supplements (HDSs), natural health products (NHPs) and traditional Chinese medicines (TCMs)—the role of traditional and complementary medicine in global health is being increasingly recognized throughout healthcare fields. As herbal and traditional medicines (H&TMs) are used extensively worldwide, more and more new products and preparations are being researched, developed, and marketed. In addition to increased use, safety issues concerning H&TMs are also becoming recognized. Pharmacovigilance of H&TMs is facing major challenges for a few particular reasons: (1) Because of differences in medical systems and drug administration systems, and in the naming and categorization approaches of these product types,

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among countries, the concepts of traditional and complementary medicines vary, which creates confusion in the literature. (2) In countries without much experience with traditional medicine use and systems for monitoring such use, knowledge and information of potential adverse effects are extremely limited. (3) Promoting rational use of H&TMs is difficult, as academic guidance on use varies greatly across countries and H&TMs are frequently used in conjunction with other medicines, whose use also varies enormously between countries with different healthcare systems and of course treated populations. (4) Most countries lack regional and national pharmacovigilance systems and risk controls for H&TMs [1]. Countries with a pharmacovigilance system for TCM, such as China, normally use the same voluntary reporting system as that used for conventional Western medicinal products. Although spontaneous reporting systems (SRSs) have recently played an important role in risk management of TCM, they cannot capture all factors that affect the safety of TCM drugs. Specific and appropriate monitoring models should be established in accordance with all the particularities of H&TMs. Against this background, this chapter provides a brief introduction to concepts related to traditional and complementary medicine, global applications, and the regulatory environment, and reviews the current situation, successes, and challenges of H&TM pharmacovigilance. It argues strongly for safety monitoring research to detect signals, verification of factors affecting safety, and the development of appropriate monitoring methods and effective risk management of H&TMs as increasingly important tasks for both scientific researchers and regulatory authorities in countries worldwide.

2 Definitions and Explanations of Terms Related to Traditional and Complementary Medicines

2.1 Differentiation of Concepts of Traditional Medicine and Pharmacology

Correctly understanding concepts related to traditional medicine (TM) and successfully differentiating them from those related to conventional/Western medicine (WM) is a key element in an objective evaluation of H&TMs. Because medical systems and pharmacy administration systems differ among countries, so do the nomenclature for and categorization of these medical practices and products. In the following sections we review and summarize key definitions relating to the use of H&TMs according to the latest definition by the World Health Organization (WHO) [1] and government regulations.

2.1.1 Differentiation of Concepts of TM and Pharmacology in Europe and North America

TM has a long history. It is the sum total of knowledge, skills, and practices applied on the basis of theories, beliefs, and experiences indigenous to different cultures, whether readily explicable or not, and used to maintain health and to prevent, diagnose, improve, or treat physical and mental illness [2, 3]. "Complementary medicine," or "alternative medicine" (AM), refers to a broad set of healthcare practices that are not part of a country's own TM or conventional medicine and are not fully integrated into the dominant healthcare system. The term "alternative medicine" is used interchangeably with "traditional medicine" in some countries [2]. WHO merges the terms as traditional and complementary medicine (T&CM), which encompasses three parts: practices, practitioners, and products [1]. Products used in traditional and complementary medical practice mainly derive from herbs and herbal preparations from natural plants. In some countries "traditional use" also includes medicines derived from animals, minerals, and synthetic medicines [3, 4].

Traditional and Complementary Medicine

Herbs or Herbal Medicinal Products

A name commonly used by WHO [1] and in the European Union [5], this category is taken to include herbal original plants, herbal materials, herbal prefabricated products, and finished herbal products [6]:

- Herbal original plants: original plant materials, such as an entire plant, leaves, flowers or pollen, fruits, seeds, roots and rhizomes, bark and root bark, and resin and fluid from plants.
- Herbal materials: materials produced in some countries where medicinal plants undergo primary processing, including selection, purification, grinding, and cutting.
- Herbal prefabricated products: the ingredients of herbal medicines and patented medicines; such products include.
  - Sections of the medicinal material (sliced, segmented, julienned, or diced), with honey, alcohol, or other materials added as excipients, and the use of methods such as steaming, boiling, frying, and grilling to obtain parts of TCM decoctions [4], which can then be used as clinical prescriptions by physicians either as they are or as raw materials for finished herbal products.
  - Medicine concentrates, tinctures, and extracts; herbal extracts created through extraction, division, purification, concentration, and other physical or biological procedures.
- Finished herbal products: herbal preparations made from one (single preparation) or various (compound preparation) herbal medicines. Herbal medicines as single or compound preparations in prescriptions and excipients are included in this group.

Herbals and Dietary Supplements (HDSs)

The US Food and Drug Administration (FDA) uses this name for T&CM products and includes in it related management systems. The US Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act of 1994 (DSHEA). A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet. The dietary ingredients in these products may include vitamins, minerals, herbs, amino acids, and enzymes. Dietary supplements are marketed in forms such as tablets, capsules, softgels, gelcaps, powders, and liquids [7]. The statement confirms that herbals and dietary supplements used as complementary therapies should be filed and that quality will vary, although Good Manufacturing Practice (GMP) requirements were issued by the FDA in 2007 [8]. Consumers and industries gain safety information and submit adverse events associated with the use of dietary supplements through the Safety Reporting Portal, an electronic version of the MedWatch 3500, 3500A, and 3500B forms tailored specifically for dietary supplements [9]. DSHEA requires manufacturers ensure that their dietary supplement products are safe; however, they need not prove the safety and effectiveness of the product for the intended use before marketing, nor does the law include provisions for the FDA to "approve" dietary supplements for safety or effectiveness before they reach consumers. Rather, once a product is marketed, the FDA must show that a dietary supplement is "unsafe" before it can take action to restrict the product's use or remove it from the market [7]. This would most commonly be done as a consequence of evaluation of submitted reports and any other available relevant data that are subsequently discovered. The manufacturers and distributors of dietary supplements must record, investigate, and forward to the FDA any direct reports they receive of serious adverse events associated with the use of their products [7]. In contrast to dietary supplements, herbal drugs must be approved under the FDA drug registration system.

Natural Health Products (NHPs)

This is the name for T&CM products used by Health Canada. Under the Natural Health Products Regulations, which came into effect on January 1, 2004, NHPs are defined as vitamins and minerals, herbal remedies, homeopathic medicines and 'TMs' such as traditional Chinese medicines, probiotics, as well as other products like amino acids and essential fatty acids. NHPs must be safe to use as over-the-counter products and do not require a prescription for sale. Any product requiring a prescription is regulated as a drug under the *Food and Drug Regulations* [10]. In May 2015 the Natural Health Products Directorate changed its name to the Natural and Non-prescription Health Products Directorate, subsequent to its recently expanded mandate to include the oversight of nonprescription and disinfectant drugs in addition to NHPs [11].

With the wide use of herbal preparations around the world, global regulation of herbal products has been improving in order to ensure their quality, safety, and efficacy. Health authorities in some countries have strengthened registration regulations. For instance, since May 1, 2011, herbal preparations must be registered according to the EU Directive on Traditional Herbal Medicinal Products (2004/24/EC) before being marketed within the European Union [12]. Within Europe, it is now illegal for companies to manufacture and sell unlicensed herbal medicines without an appropriate license (marketing authorization or traditional herbal registration). The United Kingdom differs slightly from the rest of Europe in that, since April 2012, herbal practitioners have been allowed to prescribe prefabricated herbal products, including processed herbal and TCM decoction pieces, after in-person consultations. According to the requirements of Health Canada and the NHP regulations issued in 2004, herbal products can be manufactured, sold, and applied only after registration and approval. Licensed NHPs with an eight-digit natural product number or homeopathic medicine number on their labels represent products that have been assessed by Health Canada and are considered to be safe, effective, and of high quality under their recommended conditions of use [11].

2.1.2 Differentiation of Concepts of TCM and Pharmacology in China

According to the China Food and Drug Administration (CFDA) law and administration classification, medicinal products in China include TCMs and natural drugs, chemicals, and biological products. TCM drugs are as important as chemicals and biological products. Almost all policies and regulations published by the CFDA are applicable to TCM drugs. Like patented chemical and biological products approved and licensed by the CFDA, the quality, safety, and efficacy of all Chinese patent medicines should be proved and assured under the guidance of Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and GMP, and they should be approved by the CFDA before they are licensed and made available on the market. It is illegal for any company to manufacture and sell unlicensed TCM patent medicines in China.

Differentiation of Concepts of TCM and Those of Natural Medicine

According to the Measures for the Administration of Drug Registration, the following definitions are used: "TCM drugs" refer to medicinal substances and preparations used under the guidance of TCM practice, whereas "natural medicines" (NMs) refer to natural medicinal substances and preparations used under the guidance of modern medicine practice. Both types of product derive from natural plants, animals, and minerals, but they differ in that the research and development, production, and clinical application of NM are guided by modern theories of medicine, whereas the collection, processing, prescription, and clinical application of

TCM are guided by TCM practices and approaches. The criterion to distinguish between TCM and herbal/NM products is whether the products are guided by TCM theory. The registration regulation and control standards of active ingredients also are different. For example, the Di'ao Xinxuekang capsule is considered a TCM product because it was researched and developed under the guidance of TCM theories, whereas artemisinin is a natural product because it was researched and developed under the guidance of Western medicinal theories; however, both are a component extracted from a single herb.

Classification of TCM Drugs

According to the Chinese *Pharmacopoeia* [4], TCM drugs contain Chinese material medica (CMM), prepared slices of Chinese crude drugs (PSCCDs), Chinese patent medicines (CPMs), and simple preparations.

- CMM: the raw medicinal materials for prepared slices of Chinese crude drugs, including materials derived from plants, animals, and minerals, and processed products.
- PSCCDs: CMMs processed according to TCM practices and principals; also called "TCM decoction pieces" or "Yin Pian." These can be directly used by physicians as drugs in prescriptions and as the raw material to produce CPMs [4].
- CPMs and simple preparations: preparations using PSCCDs as the raw material, with certain formulations, specifications, functions, and cautions; these can be used directly to diagnose and treat diseases under the guidance of TCM practices and principles. Most CPMs are compound-ingredient preparations; only a few preparations include only one ingredient.

Brief Introductions to the TCM Supervision and Management System in China

China's healthcare system is unique in that TCM and WM exist simultaneously throughout the country. TCM plays a role that is at least as equally critical as that of WM in the Chinese healthcare medical system. The CFDA has published a series of regulations and provisions to ensure the quality, safety, and efficacy of CMM, PSCCDs, and CPMs. The regulation of CPM has realized supervision of the entire course of research and development, including registration, production, distribution, and clinical application. For example during the registration period, the application documents and research of registration should be prepared carefully, and the research on pharmaceutical, nonclinical, and clinical trials should strictly obey the laws and regulations. CFDA also pays great attention to postmarketing safety surveillance and evaluation [13]; it has implemented a series of regulations—such as Good Agricultural Practice of Herbals, Measures for Certification Management of Good Agricultural Practice, and Criteria for Inspection and

Evaluation of TCM GAP Certification—to guarantee the quality of CMM. PSCCDs, whether used as drugs in prescriptions by physicians or as the raw materials to produce CPMs, are required to be prepared under the guidance of GMP provisions and to meet Chinese Pharmacopoeia and Ministerial Health standards.

2.2 Difference Between Conventional Medicine and T&CM Products

Both TCM and Indian Ayurveda are considered to be part of the TM system. Compared to conventional (Western) medicine, which applies allopathic clinical practice and emphasizes local diagnostic symptoms or the objective index changes such as laboratory and imaging examinations, T&CM, under the guidance of traditional theory-based systems, broadly affect the body's ability to deal with a variety of illnesses. For example, the prominent characteristic and advantage of clinical method in TCM is its holism and it application of treatment based on syndrome differentiation. TCM practice emphasizes a holistic concept of life and attends to the relations between one's body, one's mental state, and the environment—it is not confined to certain diseases or symptoms. It aims to strengthen the individual treatment according to the TCM syndrome diagnosis. The characteristics of TCM appear in traditional theory and clinical practice. The formula principle of drugs in TCM is also different from that of chemical and herbal drugs in WM. Most TCM products are compound preparations containing several herbs; these act as monarch, minister, assistant, and guide, and are considered complementary and more effective when used together. TCM products regulate Qi and blood and harmonize the Yin and Yang by using the characteristic bias of TCM drugs, such as cold, hot, warm, and cool, to keep the body in balance. A few TCM products also contain extract components from a single herb.

In summary, a multicomponent strategy, rather than the strong effects of any single component, is the fundamental basis of herbal medicine effects. It is very difficult to objectively evaluate the efficacy and safety of H&TM products from the perspective of WM because the two disciplines are so different. Another major challenge is scientifically evaluating H&TM products because of the complicated manufacturing process and requirements for their rational use.

3 Global Application and Regulatory Environment for Complementary and Integrated Medicine

It is estimated that 80% of the world's population, or over four billion people, use herbal remedies as their primary care, especially in Asia and Africa [14]. As described above, in China, TCM has been completely integrated into the health care system. TCM and conventional medicine are governed by the same national

legislation on medical institutions, are practiced alongside each other at every level of the healthcare service, and have equally important status, with health insurance covering both. About 440,700 healthcare institutions (with 520,600 patient beds) provide TCM services. About 90% of general hospitals include a TCM department and provide TCM services to patients [15].

H&TM products are being used more and more often not only in developing countries (both as a primary treatment option and in combination with conventional remedies), but also in developed countries as an integrated therapeutic strategy becomes mainstream in European countries, North America, and Australia. For instance, more than 67% of Swiss national voters opted for a new constitutional article on complementary and AM in 2009, and thus Switzerland became the first country in Europe to instate and integrate T&CM into the foundational health insurance scheme and therefore its health system [1]. T&CM is partially integrated into the national health systems of many other countries, such as Asian countries (including China, Korea, and Japan).

According to China's National Bureau of Statistics, the value of industrial output from TCM reached $68 billion (¥418 billion) in 2011, with an annual growth rate of 37.9%. Worldwide, the TCM market is increasing by 10–20% annually [16]. According to data from the American Botanical Council, in the United States alone total estimated herb retail sales through all channels rose from $4.23 billion in 2000 to $6.03 billion in 2013, equaling a 42.6% increase overall and 3.3% annually [17]. Because the use of complementary approaches has increased to the point that Americans no longer consider them an alternative to medical care, the National Institutes of Health complementary and integrative health agency got a new name on December 17, 2014, as part of an omnibus budget measure signed by then President Obama: Congress changed the name of the National Center for Complementary and Alternative Medicine to the National Center for Complementary and Integrative Health so as to more accurately reflect the Center's research commitment to studying promising health approaches already in widespread use by the American public [18]. As an increasing proportion of the population turns to complementary and integrative therapies, whether alone or in combination with conventional medicine, more and more T&CM products are made available on the global market; the need for clinical quality research on their safety and efficacy and scientific regulation clearly need to be reinforced.

4 Methodological Approaches to Pharmacovigilance for Herbal and TM Products

Safety surveillance and postmarketing monitoring of H&TMs started much later than that for conventional medicines and

therefore was built on the existing pharmacovigilance system used for conventional medicines; this included spontaneous reporting, prescription event monitoring (PEM) [19], hospital- intensive monitoring, and a key monitoring scheme (KMS). [13] Academic researchers and pharmaceutical companies in China also attempt to use different databases—such as clinical study results, the Healthcare Information System, and health insurance databases—as sources for identifying safety signals. Pharmacovigilance practices and tools developed in the context of conventional medicine rarely consider the complexities and characteristics of monitoring the safety of H&TMs [20]. Specific challenges with H&TM mean that approaches need to be adapted, for example, for H&TM quality and labeling issues and for the use of botanical nomenclature. As part of ongoing pharmacovigilance programs, safety information should be collected through SRSs and carefully designed postmarketing studies (PMSs) so as to better reflect real-world treatment settings.

4.1 Detecting Signals from SRSs and the Medical Literature

Drug safety signals are commonly monitored and detected through SRSs, and pharmaceutical companies, healthcare professionals, and consumers report suspected adverse reactions to the national center of the regulatory authorities. National pharmacovigilance centers around the world submit those reports to VigiBase, the WHO Global Individual Case Safety Report (ICSR) Database maintained by the WHO Collaborating Centre for Monitoring Drug Safety (Uppsala Monitoring Center [UMC]). Since 1978, the UMC has managed the primary aspects of the expanding worldwide pharmacovigilance network; by the end of April 2017, counting both full and associate members, this network included 154 countries with 95% of the global population, known as the WHO Programme for International Drug Monitoring, and more than 15 million ICSRs in the VigiBase. The UMC necessarily had to address nomenclature issues given that herbal reports are received from countries with different TM systems, and this resulted in the development of an Herbal Anatomical Therapeutic Chemical (HATC) classification system [21] and an ICSR database for herbal products [22, 23]. Quantitative methods are used to identify herb–adverse event pairs that are reported at disproportionate frequencies, which can lead to the detection of safety signals in both national pharmacovigilance center databases and VigiBase [24]. Signal detection activity improves national awareness of pharmacovigilance [25]. Numerous H&TM reports are now included in VigiBase. For example, in United Kingdom, where herbal medicines/natural products are supplied as dietary or herbal supplements, the concerning case reports are submitted to the Medicines & Healthcare products Regulatory Agency [MHRA], which uses a “yellow card”. In countries where TM products are regulated and licensed like conventional medicines,

as in China, safety information concerning TM products has to be reported to an SRS in compliance with local pharmacovigilance regulations. For example, by the end of 2015, the National Centre for Adverse Drug Reaction Monitoring (NCADRM) of the CFDA had received more than 9.3 million reports. In that year alone the Centre received 1,398,000 case reports, of which 393,734 (28.2% of the total case reports) were unexpected and serious adverse drug reactions (ADRs), an increase of 15.3% from 2014. The mean number of case reports per million people was 1044 in 2015 [26]. From 2009 to 2015, the proportion of case reports involving TCM was 13.3%, 13.8%, 15.3%, 17.1%, 17.3%, 17.3%, and 17.3%, respectively, in the China Adverse Drug Reaction Monitoring System database of the NCADRM. By June 2017, 75 issues of the *ADR Information Bulletin* had been published; of the 115 ADR alerts, 21 concerned TCMs (9 injections and 12 oral preparations). Four specific warning issues also were published, including warnings of the risk of Chinese and Western medicinal compounds as mixed preparations, of drugs containing aristolochic acid with the potential risk for renal injury, of drugs containing tripterygium glycosides with potential risk for renal, reproductive system, blood system and liver injury, and of drugs containing *Polygonum multiflorum*, which could cause liver injury. According to safety information, the CFDA implemented risk management through several approaches, including arranging manufacturer communication meetings; modifying medication package inserts; and restricting, suspending, or withdrawing drugs [27]. An analysis of spontaneous reports in the database of the Pharmacovigilance Programme of India during the period July 2011 through December 2013 showed 39 suspected ICSRs were submitted. The majority of the ICSRs were related to polypharmacy, that is, the concomitant use of herbal products and allopathic medicines. The herbal preparations for which unexpected ADRs were reported included senna extract, aloe, mustard oil, digitalis, garlic, menthol, and turmeric [28]. Data retrieved from spontaneous reports of the Thai Food and Drug Administration from 2002 to 2013 showed that of 4208 Thai traditional medicine–ADR pairs examined, 3 had statistically significantly disproportionate reporting odds ratios (RORs), namely *Andrographis paniculata* and anaphylactic shock (ROR 2.32; 95% confidence interval [CI] 1.03–5.21); green traditional medicine and Stevens-Johnson syndrome (ROR 13.04; 95% CI 5.4–31.51), and *Derris scandens* Benth and angioedema (ROR 2.71; 95% CI 1.05–6.95) [29].

Similar to how WM and complementary medicine data are both reported to SRSs, a source of pharmacovigilance for and safety information on herbal medicines is that reported to poison control centers [30–32].ADRs for dietary supplements often are reported directly to poison control centers. For example, a study from the United States found more reporting to poison centers than

traditional spontaneous reporting [33]. However, strengthening the supervision of licensed Chinese health food products and managing against the increasing danger from substandard, spurious, falsified, falsely labeled, counterfeit drugs remain challenges worldwide [34].

In the current international medical literature, the lack of systematic gathering and recording of safety information on H&TM leads to deficient understanding of risks. Even the medical literature describing well-designed nonclinical evidence-based research, safety case reports, and clinical safety research written in Chinese, which provide the primary safety information on TCMs, are also naturally very limited. SRSs therefore play a particularly important role in H&TM pharmacovigilance.

4.2 Collecting More and Detailed Evidence by Active Surveillance of H&TM and the Use of Pharmacoepidemiological Methods to Test Signals

WHO emphasizes that the quality, safety, and efficacy of medicinal plants should be evaluated to ensure rational use of plant-based products through an integrated approach [35]. Traditional medicines such as TCM and Ayurveda, with their unique fundamental principles and systematic approaches, record a diversity of health care practices. Because the SRS that was developed according to the characteristics of chemical drugs is not fully fit for H&TM characteristics, and because underreporting is a well-known problem with SRSs, signals detected from SRSs only indicate potential adverse effects of interest, and the link to a drug or herb cannot yet be considered confirmed; determinations of causality require further evaluation and testing, as does quantification of risk, for example, through incidence estimation. Pharmacoepidemiologic research is necessary to investigate and gain more detailed insights into information about products and their uses in the real world, and to conduct continual active surveillance and evaluate how patient characteristics influence drug utilization and clinical outcomes in large populations and how these change over time.

Some observational, comparative pharmacoepidemiological methods such as case-control and cohort studies are used to investigate the safety of herbal medicines through tests of the signals detected from SRSs [32]. One such signal was identified from reports of possible liver injury associated with the use of Chinese herbs [36]. A pilot case-control study examined and tested a selection of Chinese herbs and found no increased association with liver injury [37].

An ongoing prospective, longitudinal, population-based cohort study in Taiwan shows that Chinese herbal medicines are frequently used by women during pregnancy and the postpartum period; it also showed that those with high education and primiparas used more such herbs [38]. At least one Chinese herbal medicine was used by 33.6% and 87.7% of the interviewed subjects during pregnancy and the postpartum period, respectively. An-Tai-Yin, pearl powder, and Huanglian were the most commonly

used during pregnancy, whereas Shen-Hua-Tang and Suz-Wu-Tang were the most commonly used by postpartum women. Because of the limited safety information on these herbs, it is important for nurses/midwifes to enquire about such habits and to provide adequate education to women during prenatal and postpartum care to prevent potential side effects [38].

Prescription event monitoring (PEM), the New Zealand Intensive Medicines Monitoring Programme, Sentinel site-based analyses, specific registry screenings, and the Chinese KMS are all forms of active surveillance that are potentially appropriate for H&TM monitoring. PEM, discussed in detail in Chap. 9, is routinely used in the United Kingdom to study drugs or vaccines once they are approved and on the market, through monitoring of individual prescriptions. In the United Kingdom a modified version of PEM has been developed on the basis of monitoring prescriptions from herbal practitioners [32] and is considered a useful method for investigating specific safety concerns for frequently used medicinal herbs [20]. Similar work has been done in both Thailand and New Zealand through the Intensive Medicines Monitoring Programme [39, 40].

Research on the methodology of active surveillance has been conducted in China for over 10 years. For example, active surveillance through primary data collection from original medical records was carried out by the National ADR Monitoring Center, Beijing, after an *ADR Information Bulletin* publication on a signal of "puerarin injection and acute haemolytic anaemia" from 2002. They designed a prospective case-control study involving 32 hospitals and clarified the ADR characteristics, risk factors, and incidence of hemolytic anaemia [41–43]. The Guangdong provincial center for ADR monitoring designed a nested case-control study to investigate shengmai injection and shenqi fuzheng injection; it estimated an incidence of allergic reaction of 1.23 and 1.84 for the two injections, respectively, and the ADRs were mild to moderate [44, 45].

After evaluating active monitoring methodology, a KMS was included in the new 2011 ADR Provision in order to promote active monitoring and compensate for limitations in the China ADR Monitoring SRS. This active surveillance for all postmarking products, including TCM, requires manufacturers and researchers to formulate and implement a scientific monitoring program and to collect complete safety information for the listed drug in order to detect the characteristics of safety issues and influential factors in clinical practice among the large population [13]. According to the past 10 years of TCM pharmacovigilance experience, the key monitoring targets are TCM drug injections, mixed preparations that include Chinese and Western compounds, formulae containing known toxic materia medica, and newly formulated TCM drugs [27]. To comply with the new pharmacovigilance regulations of the CFDA, the pharmaceutical industry, in collaboration with academic

researchers, has attempted to implement a KMS. For example, a clinical reevaluation project conducted by the China Academy of Chinese Medical Sciences was launched toward the end of 2011 in cooperation with the pharmaceutical industry and funded by the China Ministry of Science and Technology. The project includes ten injectable TCM drugs. Several methods were applied in the study. Further, a prospective, multicenter, large-sample registration study was designed and developed to find influential factors for safety on the basis of a literature review, a meta-analysis, a retrospective study of the Hospital Information System, and a nested case-control study. The prospective, multicenter investigation uses a noninterventional design and includes over 200 Chinese hospitals in order to collect detailed clinical information on real-world use. The sample size for each TCM injectable was over 30,000 individuals. This program was finished at the time this chapter was written.

Looking to establish a routine active surveillance system with a large amount of continuous, traceable, observational, and linked data, several provincial centers have been focusing on the exploratory development of alarm systems for active monitoring and assessment of adverse drug events on the basis of the linkage of provincial ADR data with information from each hospital region. The Shanghai ADR Monitor Center established the Shanghai Drug Monitoring and Evaluative System (SDMES) designed to locally monitor marketed drugs. It works in partnership with ten hospitals in Shanghai that permit direct access to patient information. These ten hospitals installed software in their HISs to capture required information, and then they periodically send the information to the Shanghai ADR Monitor Center [46]. The China People's Liberation Army ADR Monitoring Center set up the system that actively monitors and assesses ADE warnings for hospitalized patients. This system has already realized "real-time monitoring" and "prevention first" drug risk control modes, which aim to provide new approaches to effectively prevent clinical medicine risk and reduce adverse drug event–related damage in the age of big data. As a practical tool, the system aims to help clinical pharmacists actively and more efficiently monitor key categories of medicine [47]. In 2012 the Guangdong ADR monitoring center developed an ADR service platform to meet rapid reporting requirements intelligence searches, which are done on the basis of HIS data and realize data exchange and linkage between SRSs and the HIS. That center has been carrying out key monitoring of 15 drugs in 34 pilot hospitals in Guangdong Province.

To apply appropriateness of prescription models to identify potential inappropriate TCM prescriptions, research on 14.5 million prescriptions from the Taiwan National Health Insurance Research Database was conducted through the use of data mining techniques. The results showed that for 1920 prescriptions, the system showed 97.1% of positive predictive value and 19.5% of

negative predictive value as compared with those values calculated by experts. Sensitivity analysis indicated that the negative predictive value could improve up to 27.5% when the model's threshold changed to 0.4 which is the most desirable and sensitive threshold for the model. (To apply sensitivity analysis, in their previous study, the threshold the authors used by default was 1 to test and evaluate the model. However, they found that better predictions could be observed by using different thresholds. Therefore, they used the sensitivity analysis with different thresholds such as 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, and 1.8 to identify the most desirable threshold for the model.) The research shows that the appropriateness of prescription model is a useful tool to automatically identify potential inappropriate TCM prescriptions, and it might be a potential TCM clinical decision support system to improve drug safety and quality of care [48].

In order to better support pharmacovigilance of herbal medicine worldwide in 2004 the WHO developed specific herbal safety monitoring guidelines designed to align to the extent appropriate with traditional Pharmacovigilance practice [49]. As experience quickly accumulates, one can anticipate this might be revised again in the near future.

5 Challenges for Safety Monitoring of H&TM Products

Given the characteristics of the H&TM system, from the perspective of a conventional healthcare system, the challenges for understanding and identifying safety issues mainly lie in judging whether prescriptions and applications of treatment are reasonable, whether H&TM products and drugs are qualified and well controlled, and whether the monitoring methodologies are designed according to H&TM characteristics, and in identifying how to determine the dose-effect relationship of some bidirectional regulation drugs. All these issues are important, and coupled with the increasing use of H&TM in both developed and developing countries, they lead to many challenges. The section that follow provide details.

5.1 Challenges in Qualifying Practitioners and in Public Awareness of H&TM

H&TM administration is being increasingly used worldwide, perhaps particularly because TCM is considered by some to have unique advantages in treating chronic and incurable diseases and is more widely accepted by practitioners and patients worldwide. In China, at least one TCM university and educational system exists in each province. About 95% of general hospitals now have TCM departments. TCM pharmacists and physicians are prohibited from practicing medicine until they pass a strict examination to obtain qualification certification and work through a system of professional, systematical, regular continuing education, and training during medical practice. In some countries where H&TM is popular, however, qualification certification of physicians and

public awareness of H&TM safety are lacking and often subjective. Without legislative support, qualification, and strict evaluation systems, the quality of H&TM practitioners is uneven, and some are even unqualified. Even "quack" doctors without any medicinal education or therapeutic capability may practice H&TM, which inevitably leads to misdiagnoses, delayed diagnoses, and failure to use optimal treatment options. The legal rights of truly qualified and competent H&TM practitioners cannot be guaranteed, so medical risks seem inevitable with regard to the rational application of medicines [1]. Furthermore, consumers are always exposed to misleading or unreliable information, and some media communications exaggerate safety issues of H&TM so applications are (inappropriately) abandoned because of concerns of toxicity, whereas some H&TM providers exaggerate the therapeutic effects of H&TM and consider that H&TM originates from natural materials with no toxic and side effects, especially when consumers self-medicate with NHPs and HDSs that are considered H&TM, which highly increases the risks of ingestion under the misperception that "natural" automatically means "safe."

5.2 Challenges in Guaranteeing the Quality and Safety of H&TM with Imperfections in Drug Regulatory Systems Around the Globe

At present, to protect consumers' health by ensuring medicines are safe and of high quality, one needs to consider in any country both products produced locally and those produced overseas. While some countries do regulate H&TM products and continue to develop, update, and implement new regulations, given the now truly international market—with products in such countries often being made elsewhere—the quality of products may still vary when they are not produced domestically. The use of poor-quality, adulterated, or counterfeit products; clinical diagnosis of ADRs; and patient management are complex and interwoven processes with pharmacovigilance practice. First, the challenge of diagnosing and managing the adverse effects of drugs—especially H&TM products—grows with the increasingly widespread existence of substandard, spurious, falsified, falsely labeled, counterfeit drugs [34]. These products can cause both unexpected failure of effects and unexpected adverse drug effects. Second, because H&TM products are derived from natural materials with complex components, the standards of quality and curative evaluation cannot completely align with those of conventional drugs. Third, because of a lack of efficacy and safety evaluation standards appropriate for H&TM products, specific characteristics of these products are not accepted by drug regulators worldwide, and so in some ways the products face more strict and not necessarily helpful quality standard and registration requirements than do foods or chemical drugs. The overall availability of some effective, safe, and reliable products is therefore limited globally. Because health food products need not be licensed before they are put on the market in some countries, getting accurate lists of ingredients is problematic for

these unregulated/unlicensed products, thus making very difficult the ability to follow and ensure the quality of products for safety monitoring. Greater awareness and acknowledgement that many people living in developing nations are dependent on H&TM as a major source of medicines will help. Finally, it is widely accepted that H&TM products are frequently used as the primary source of healthcare in developing countries. The lack of or weak regulation of H&TM products in most developing countries is challenging, and high-profile safety concerns occur in association with the use of H&TM. Unfortunately, pharmacovigilance systems in some developing countries, which are often established but relatively new members of the WHO Programme for International Drug Monitoring, means that experience with pharmacovigilance approaches and specific safety information are difficult to share globally. The majority of ADR reports for herbals in the WHO-UMC database originate from developed countries, so overall the safety information on herbals is limited within the WHO database. The aforementioned policies and regulatory issues make it difficult to guarantee the safety and efficacy of H&TM worldwide.

5.3 Challenges for Establishing Appropriate Pharmacovigilance Approaches for H&TM

Clinical trials do not typically enroll a sufficient number of patients for infrequent safety events to be detected. Moreover, the populations evaluated may not necessarily represent the nature of the populations expected to receive the after the product is marketed. PMSs through spontaneous reporting, registries, and PMS projects are important resources for the long-term detection of safety events [50, 51], and they better reflect real-world treatment. Methods for assessing risks of postmarketing herbals are still at early stages and lack scientific evaluation methods fitting for herbals' characteristics. Pharmacovigilance of H&TM has various challenges, which are described in the following sections.

5.3.1 Common Challenges for SRS and Designed PMS

Monitoring and evaluation methods that do not map well to the characteristics of H&TM is a common problem for both SRSs and pharmacoepidemiological studies designed after a product is marketed.

1. Specific H&TM factors cause great challenges in exploring and developing an appropriate pharmacovigilance approach: (1) H&TM products contain multiple ingredients with complex compositions, and they often are used in combination with WM; basic research and safety monitoring are weak and recorded safety information are often lacking. (2) Each herbal, as an ingredient of H&TM products, also has a complex composition; these components exert pharmacological effects through multicomponent and multitarget mechanisms. It should also be noted that some H&TM products have bidirectional actions. For example, a low dose of *Ligusticum*

chuanxiong Hort. can cause uterine contractions and exciting heart; however, large doses inhibit heart contractions, dilate blood vessels, and decrease blood pressure. Therefore the normal methods to evaluate a dose-effect relationship used with conventional medicines may not apply to H&TM. (3) Compared with chemical drugs, both nonclinical and clinical research of H&TM are weak before marketing, especially in countries where products can be launched on the market without any approval and registration. Even some TCM products previously approved by the CFDA had insufficiently well-designed drug safety and efficacy clinical studies, and in such cases the specified safety information may be extremely insufficient. (4) H&TM is often used in combination with Western drugs, but safety information about interactions with WM and with other H&TM and foods are often lacking in summaries of product characteristics and the other literature.

2. Poor-quality case report information on interactions with other medications/foods are also specific challenges for H&TM safety monitoring: The poor quality of case reports is often blamed on two reasons. First, the suspected adverse drug event reporting form that is used to collect original information from the patient lacks H&TM characteristics, which, while appropriate for chemicals, does not match the characteristics of herbal medicines. It is impossible to collect all complete and accurate original information. H&TM specificity and the risk factors influencing their safety, such as multiple ingredients, different plant origins, and nonuniform drug names, are typically great challenges for TCM pharmacovigilance. Furthermore, individualized treatment according to TM theory rather than knowledge of WM makes the situation even more challenging [13]. Even in countries like China that have much experience with safety monitoring, and where H&TM monitoring is included in the pharmacovigilance system and, TCM and WM share the same SRS reporting form and a KMS approach similar to that used for WM. Items concerning the safety of TCM diagnosis and treatment characteristics, such as the Latin names of ingredients and symptom and syndrome descriptions for TCM, are not included in currently used case report forms. So, it is difficult to evaluate accurately the causality on the basis of such poor-quality case reports. Second, the lack of an appropriate structure in the underlying databases for H&TM data regarding capture of drug names, medical terminologies, and adverse reactions, among others, not only affects the quality of individual case report data but also makes signal detection and analysis across databases difficult.
3. Causality assessments of case reports are difficult for various reasons: (1) Incomplete information within case reports makes it difficult to determine whether the cause of an H&TM

adverse drug event is due to irrational use or poor quality. In addition, in countries where H&TMs are neither regulated nor standardized, precise identification and quantification of ingredients or possible contaminants are even more challenging. (2) Most H&TM summaries of product characteristics are relatively simple and lack safety alert information. Some H&TM drugs are distributed as over-the-counter (OTC) drugs and do require consultation with a qualified health provider. Therefore off-label applications and overdoses are common. (3) Causality assessment methods fit for and validation of H&TM medicines are lacking, and there exist insufficient literature on safety information and few professional experts trained in pharmacovigilance of H&TM. These shortcomings significantly hamper the ability to definitively assign causality to a particular herb when evidence of a serious ADR is observed. In most instances of reported H&TM toxicity, no attempt is made to conduct phytochemical analysis; normally only a presumptive association can be made on the basis of temporal relations or unintentional rechallenges.

4. Although SRSs and postmarketing clinical studies of H&TM have played an important role in promoting rational drug use and regulation in some countries where H&TMs are popular therapeutic approaches, information from passive and active safety monitoring is still leveraged and communicated to the public in insufficient ways. To be specific, in some countries, SRS data are not always available to and accessible by academic researchers and the wider public. At present, most SRS data utilization is limited to analyses of clinical characteristics and population-level statistics; in-depth research and further exploration are lacking. Moreover, given the lack of guidelines for postmarketing pharmacoepidemiological studies, the quality of PMS pharmacoepidemiological clinical studies should be improved to provide more reliable evidence for national drug regulatory authorities.

5.3.2 Challenges for H&TM Spontaneous Reporting Monitoring Systems

Although passive monitoring is an important means of finding rare safety signals, a large quantity of suspected ADR case reports is a common prerequisite for detecting signals. The adverse event reporting system worldwide suffers from severe underreporting, resulting in a scarcity of safety data on herbal products [52]. It is impossible to identify herbal signals of interest, especially for rare ADRs. Underreporting is a primary disadvantage of SRSs, and this is likely to be a much greater problem with H&TMs. In Europe and some Asian countries where some H&TMs are regulated as medicines, manufacturers have pharmacovigilance obligations under European directives and additional national regulations. In China, for example, all TCMs approved by the CFDA must be monitored

Underreporting

and suspected cases of adverse reactions reported to NCADRM according to regulatory requirements. The requirements with respect to time frames and other specific reporting requirements are the same for both orthodox and herbal medicines when serious or unexpected adverse events occur. However, unlicensed H&TM manufacturers or producers do not have to comply with these directives and national regulations. For example, it has been suggested that herbal reporting has not significantly increased in the United Kingdom despite the widening of reporting from solely medical doctors to nurses, pharmacists, and patients [32]. Factors contributing to underreporting of herbal ADRs include physicians and patients having a lack information regarding potential associations between herbs and ADRs, a lack of awareness that H&TM should be reported, and patients themselves can be reluctant to inform their healthcare providers that they are using H&TM therapies. Even when large numbers of case reports of suspected ADRs with TCM drugs, underreporting in SRSs remains a big problem.

Detection of H&TM Signals in SRS Databases Brings with It Specific Challenges

Bottlenecks constrain signal detection even when relatively large numbers of SRS reports are available. To avoid this, the quality of ICSRs needs to be improved and medical terminology and the names of H&TM drug need to be further standardized so that similar case reports can be appropriately clustered effectively. The lack of follow-up and manual coding of substandard data both make any automatic processing of data normalization and data mapping nearly impossible. Gradually establish and perfect underlying databases of SRSs such as WHO Adverse Reactions Terminology, H&TM drug names, and mapping rules, it would be a huge task to code the substandard data in existing case reports, that has significantly affected timely and effective detection of signals. The limited volume of reports means that clinical review of individual case reports at data entry is manageable, and quantitative signal detection has a limited role in spontaneous reports to date.

5.3.3 Challenges for Pharmacoepidemiologic PMSs Designed for H&TM

As mentioned previously, only a few postmarketing studies exist regarding H&TM in countries in which H&TMs are used as complementary and alternative medicines. Most of these studies are descriptive and noninterventional studies. Limitations of sample size and concomitant drugs mean that some of these studies present biased results [20]. The situation is worse in countries that lack regulation for herbal medicines and where H&TM utilization data are not routinely collected, and where, despite sometimes large existing health databases, it is impossible to develop the large-scale databases for automated studies such as longitudinal registry studies.

It is somewhat easier to accumulate safety signals in countries where H&TM is more popular than other medications. For instance, in China, TCM products are categorized as OTC drugs and prescription drugs, and some TCMs are covered by residential

medical insurance and therefore are incorporated into the National Drug Reimbursement List and National Essential Drug List. The CFDA attaches importance to the supervision of TCMs in order to implement the requirements of a KMS that was put forward in the 2011 ADR Reporting And Monitoring Provision [53], and in notices for doing well in the reevaluation of TCM injections [54] and for publication of the seven principles for technical guidelines on TCM injection safety reevaluation concerning production process, quality control clinical study and so on [55]. Some pharmaceutical companies and academic research institutions have been conducting KMS projects and postmarketing studies of TCM injectables through prospective, multicenter, intensive hospital monitoring of all patients included in a specific drug and registry study [56]. The investigators collect the relevant clinical information directly from the healthcare providers and patients by filling in a specially designed case report form, and they are looking to use data from electronic medical records (EMRs). The sample sizes of such studies are often in the range of 10,000–30,000 patients.

Regulations are developing around pharmacoepidemiological studies of H&TM. The European Union regulates such products on the basis of the Traditional Herbals Medicine Products Directive 2004/24/EC, announced in March 2004. The Directive allowed manufacturers 7 years from its passage to gather the necessary information for their products, and on May 1, 2011, the requirement that herbal medicines and their ingredients be registered with evidence of safety went into effect [12]. Regulations and guidelines for a KMS have not launched officially in China, including that for WMs, and the epidemiological methodology of active surveillance and PMSs are still at an exploratory stage. Active surveillance and PMSs of TCM injectables are at the forefront of development because of special attention to their safety and their novel nature. TCM injectables come with the following main challenges: (1) Insufficiencies in study design and research quality need to be improved. Most studies are designed as descriptive, noninterventional, intensive monitoring studies, and the data elements of case report forms for different drugs and outcomes are always the same irrespective of the study question, which itself is often unclear. The lack of comprehensive follow-up for potential risks is also problematic, as is the lack of formal hypothesis testing in study designs. Data collection often misses specific characteristics of TCM products and information on potential confounding factors (comorbidities, drugs used concomitantly, patient differences, off-label uses, and improper operation during the therapy). (2) Because many TCM products, especially oral preparations, are used as therapies for chronic diseases, and therefore require long-term application, important long-term data may be lost to follow-up. (3) Some ethical issues need to be better defined and addressed, such as off-label use, primary collection of biological specimens, and protection of patient privacy when secondary data (already gathered for

another purpose) are used. (4) At present, existing large healthcare databases are insufficient. Even many existing Chinese healthcare databases, such as the HIS, EMRs, disease registries, and the China Health Insurance Research Association (CHIRA) database [57], have been recognized as important resources for conducting PMSs, but most of these databases are isolated islands of information that lack a common system and linkage to other databases. Access issues due to database ownership have challenged researchers seeking to make good use of these resources [58]. It is difficult to conduct pharmacoepidemiologic studies using the currently available large longitudinal healthcare database.

Most approaches for active surveillance of TCM in China currently aim to combine data collected from clinical practice and existing secondary data sourced from the HIS or EMRs. Most approaches for tentative completed TCM active surveillance in China mainly collect primary data for individual patients from healthcare professionals and patients via case report forms. Even though companies have put much funding into such projects, the data still lack continuity because data collection and entry add extra burden on healthcare providers, data must be shared and reused because of the limited duration of monitoring and coverage. Currently, it is impossible to apply a completely routine and real-time monitoring approach for all TCMs in China.

6 Future Considerations

6.1 Pushing Effective Regulation of H&TM and Promoting Professional Qualifications

Better legislation is needed around the world. Chinese medicine practitioners regulated by the Chinese Medicine Board of Australia (CMBA) is a good example of progress needed in this field. The Australian Health Practitioner Regulation Agency supports the functions of the CMBA, and the Australian Health Workforce Ministerial Council appointed for 3 years the members of the inaugural CMBA [59]. In Australia, Chinese medicine was added in the National Registration and Accreditation Scheme and became a nationally regulated profession on July 1, 2012. For the profession this means that new, nationally consistent registration standards apply and that all practitioners must meet them. Practitioners register once, renew yearly, and can practice anywhere in Australia. For the public it means that they are better protected through assurance that only health practitioners who meet the mandatory standards and qualifications to provide safe care are registered [60]. Chinese medicine has gained legitimacy nationwide in Australia. In order to assist Chinese medicine practitioners to safely practice Chinese herbal medicine and to support the efforts of the CMBA to facilitate public access to safe health services, CMBA address a policy gap by providing clear guidance for practitioners to make sure expectations are clear and transparent for practitioners

providing Chinese herbal medicine services. CMBA disseminated new guidelines for safe Chinese herbal medicine practice in November 2015, and these went into effect November 12, 2017 [61]. These measures are worthy of reference for other countries and regions that lack regulation of herbal practitioners and herbal medicinal products.

6.2 Establish and Perfect Global Regulatory Alliance of Legislative Mechanisms and an Approach of Whole-Process Supervision and Management of H&TM Safety, from Research and Development, Planting, Production, Process, Storage, and Transport to Supply, Marketing, and Utilization

1. According to the characteristics of complex compositions, multiple activities, and target actions, we must strengthen basic and clinical research and explore appropriate evaluation methods, enhance product quality standards and evidence-based scientific research, and emphasize research on drug interactions. We must promote international cooperation of preclinical to clinical scientific research on H&TM, improve intergovernmental communication, and establish reasonable quality control standards and an international registration system, with both fitting H&TM characteristics and common internationally recognized systems. A database of H&TM names must be established and standardized, and it must be updated continuously. In order to ensure the quality, safety, efficacy, and consistency of H&TM, scientists have been cooperating and conducting pioneering and beneficial clinical research on herbal and Chinese medicine pharmacology, such as TCM systemic quality research and the holistic quality control model, to ensure the quality of agriculture, collection, and the continuous production process [62]. To help H&TM safety to progress, research has primarily relied on promoting rational clinical use, avoiding drug interactions, ensuring correct botanical identification and labeling, controlling quality for product consistency, and removing adulterants and contaminants. Integrated toxicological approaches and network pharmacology are required to replace or supplement approaches in classical medicine risk assessment [63]. With regard to TCM clinical trials, for example, one randomized, multicenter, double-blind, parallel-group superiority trial combined aspects of modern medicine—clinical symptoms and signs, laboratory parameters, and clinical laboratory dimensions of the Seattle Angina Questionnaire—with the Xueyu Zheng (a type of TCM syndrome) score, which can be considered a patient-centered outcome particularly from a TCM perspective, to compare the effectiveness of Di'ao Xin Xue Kang capsules and compound Danshen tablets in patients with symptomatic chronic stable angina. TCM diagnosis scores are an appropriate, effective, and valuable approach to evaluate the effects of TCM drugs [64].
2. To compensate for the lack of safety evaluations of H&TM, empirical clinical assessment must be carried out through pharmacovigilance, and international collaboration is an extreme

necessity [63]. Further establishing specific form of H&TM suspected individual case reports in SRSs and underlying literature databases of safety and toxicity H&TM information to enrich the WHO Vigibase to better allow the detection of potential safety signals is important. Information technology has improved signal detection capability, as has the sharing of information across countries. Improvements in both the quantity and quality of reports in national reporting systems through the use of harmonized computer systems and databases will contribute to the development of international pharmacovigilance of H&TM, which will in turn lead improvements in international collaboration. Drug administration departments in each country and region should establish a routine mechanism for communicating and tracking information for serious/unexpected adverse events so reports and information related to H&TM safety can be calmly and objectively evaluated [65].

3. Regulate sales and circulation
   The fight against counterfeit H&TM products and misleading or exaggerating advertisements must be a priority. At the same time, increasing awareness of H&TM safety and rational use among healthcare professionals, the public, and stakeholders through the education and the dissemination of information is an effective way to enhance safe use by the public. H&TM safety information and warnings are disseminated through several means, and various methods can be considered for all relevant target audiences; these methods include involving the mass media and consumer associations in creating locally appropriate language, educating health professionals through the delivery of adverse reaction bulletins or through articles and meetings, and providing education about the implications for H&TM providers, academics, researchers, and the pharmaceutical and herbal medicine industries [66].

6.3 Explore and Establish SRSs, Active Surveillance Systems, and Epidemiological PMS Models Adapted to H&TM Characteristics

6.3.1 Strategies for Overcoming Common Challenges of Passive Monitoring, Active Monitoring, and Epidemiological PMSs

1. It is imperative that H&TM safety monitoring and evaluation systems be gradually established according to the characteristics of H&TM. Appropriate forms for collecting information on adverse event cases are desirable in order to differentiate between intrinsic H&TM toxicity and malpractice. A recent Hong Kong study found that of 52 clinical case reports of aconite poisoning, the majority were actually related to poor-quality herbs, poor prescribing practices, or dispensing errors [67]. In Europe, adverse events have mainly resulted from contaminated products and a practitioner's incompetence, rather than any inherent risks in the use of herbal medicines [66]. Thus well-documented clinical records of original case reports are the basis for ensuring data quality and the objective evaluation of causality between drugs and adverse events. The

major drawback of H&TM is the lack of accurate and complete case adverse drug event reports. Poor-quality data management and the specific reporting form applied in SRSs and active surveillance systems need to be rectified, with more attention given to the special needs of the H&TM sector, so as to record all desirable information about the case reports. Moreover, the traditional theory of H&TM during clinical practice. Treatment and diagnosis by TM practitioners generally follows TM theory. A coding system for TM diagnostic classifications could improve evaluations of TM treatments and adverse events, and important symptoms and signs that manifest in TM syndromes should also be included in the records.

2. We should strengthen the safety monitoring of PSCCDs (namely Yinpian), herbal oils, extractives, and OTC H&TMs, and explore the methodology and models used to monitor them. Other than the NCADRM SRS database in China, most ADR monitoring systems around the world mainly focus on monitoring the safety of patented H&TM products and ignore PSCCDs. Especially in China, TCM decoctions with a PSCCD as an ingredient are a traditional and popular processing method. So, surveillance methodology needs to be adapted to include specific PSCCD characteristics. Many H&TMs are OTC products, and primary healthcare and consumer reporting needs to be encouraged in order to strengthen the safety monitoring of OTC H&TMs.
3. The UMC HATC has found some signals of herbal medicines. The UMC has attempted to address nomenclature issues as herbal reports come from countries with different TM systems [23]. The approach to further improve the quality of H&TM case reports and signal detection includes two aspects: first, the UMC HATC should be continuously supplemented and enhanced, and domestic H&TM drug name databases in countries and regions should be established and shared with others to harmonize and link data to the extent possible. Second, the specific TM and standard ADR standard terminology based on TM theory should be established and added to the *Medical Dictionary for Regulatory Activities* and the WHO Adverse Reactions Terminology.
4. A good education and background in H&TM is desirable during assessment of the causality of an H&TM-related adverse event. Causality of H&TM-related adverse events can be assessed in the following ways: establishing H&TM pharmacovigilance expert committees and developing guidelines on H&TM safety monitoring and PMSs; setting up a database of the literature on safety and drug interactions of H&TM; strengthening the use of safety information extracted from SRSs, Periodic Safety Update Reports/Periodic Benefit Risk

Evaluation Reports; and paying more attention to cultivating professional talent in H&TM pharmacovigilance education.

5. Exploration of how to make full use of SRS pharmacovigilance data and further optimize the detection of important H&TM signals need to be areas of focus. Moreover, to develop well-designed epidemiological PMSs concerning important safety signals, textbooks introducing practical experiences and pharmacoepidemiology approaches used in PMSs of conventional drugs are also a necessary and valuable reference to H&TM researchers.

6.3.2 Strategies to Overcome the Challenges of SRSs

Underreporting

The following actions are all important areas of focus necessary to streamline reporting procedures so as to reduce underreporting by SRSs: developing consumer/patient reporting systems, organizing general education and policy education for the public and healthcare professionals on H&TM pharmacovigilance and H&TM adverse event reporting; simplifying the evaluation of causality in case reports, linking SRS with EMRs and other secondary databases so as to automatically capture adverse event data from EMRs, thereby reducing the burden of original data collection on researchers.

Signal Detection

We should establish specific H&TM signal detection platforms so as to standardize the basic database structures, optimize signal-filtering tools, and ensure data are collected for drug interaction studies in accordance with the characteristics of H&TM. For example, in China, the NCADRM uses a large SRS database to facilitate automatic signal detection. The NCADRM has done work to retrospectively standardize historical SRS data, including coding of adverse event terms and drug names per standard dictionaries.

6.3.3 Strategies for Pharmacoepidemiologic Studies

PMSs are not only an effective way to remedy underreporting, they are also an approach to identifying, characterizing, qualifying, and confirming the safety of medicinal products. Mature models used for and experience with conventional medicines/WM should be referred to during H&TM PMSs, and noninterventional and interventional clinical trials or nonclinical safety studies could be adopted. In countries where the quantity of H&TM case reports is limited, establishing registration regulations and developing a prospective and specific active surveillance system should be effective.

Quality control and standardization should be improved in countries where H&TM is popular and reports are relatively numerous. PMS design should leverage previous work and information, such as that from SRS databases and systematic literature reviews, or meta-analyses of existing information. Such studies should follow common international principles or guidelines for

clinical PMSs and choose the appropriate epidemiologic methods according to the study question. Ensuring timely entry of the data collected on forms and timely access to long-term medication tracking data, as well as the follow-up and management of emerging safety signals, are all key design considerations. We should conduct PMSs with automated linkage to large, longitudinal healthcare databases in the near future.

To improve the reliability of PMSs, it is necessary to emphasize process quality control. This includes developing meticulous standard operating procedures for long-term monitoring and emphasizing professional knowledge and training related to pharmacovigilance by researchers and the staff of clinical research organizations. Introducing monitoring boards for specific projects can help, and careful control of confounders and bias is of course critical. Finally, ensuring regulation is appropriate will be important to make full use of the results and conclusions of PMSs; this includes adopting risk control measures and essential drug lists.

7 Prospects and Summary

H&TM plays an important role in the global healthcare system, and this is widely accepted and recognized all over the world. The risk-benefit assessment of H&TM has become a new focal issue in the field of pharmacovigilance research. To ensure the safe use of H&TM, from an international perspective it is necessary to promote the registration of qualified H&TMs and H&TM products, to strengthen safety information sharing and communication, and to implement strong cooperation and global safety supervision. At the technical level, it is important to establish an international safety database with a passive monitoring system, to follow up and investigate serious adverse events, fully use as reference good experiences with pharmacovigilance practice and risk management of conventional drugs, and to integrate and link longitude databases with established common mapping databases so as to realize continuous and real-time, routine active surveillance. We should choose and conduct pharmacoepidemiological studies in order to learn from the study of TCM-induced diseases and the important potential risks of and information missing from postmarketing H&TM products,. At the same, given that most H&TMs have relatively broad indications and insufficient clinical evidence, exploration of commonly accepted and appropriate evaluation methodology for studying H&TM efficacy is also an important issue. Pragmatic randomized controlled trials and large simple trials could be introduced to evaluate H&TM efficacy, focusing on the therapeutic

advantages of a product summarized from long-term clinical experience. Furthermore, the scope of H&TM studies should be broadened to include, for example, cost-effective analysis, drug utilization review, prescription sequence symmetric analysis [68], photochemical analysis, quality follow-up, precise identification and quantification of ingredients, and nonclinical safety studies. Herb-drug, herb-food, and herb-herb interactions should also be evaluated.

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Chapter 4

Pediatric Pharmacovigilance: Current Practice and Future Perspectives

Lise Aagaard

Abstract

The aim of this chapter was to review published information about ADRs reported in children and adolescents with respect to occurrence, seriousness, type, suspected medicines, age and gender of the child, and type of reporter. Secondly to review experiences with the EU pediatric regulation and its impact on the conduction of pediatric clinical trials in Europe. This literature review showed that occurrence of ADRs in pediatric populations differs between countries, study design, time periods, and age groups. Many serious ADRs were reported including fatal cases. Across studies, the ADRs most commonly reported in children were of the types: skin and subcutaneous disorders, general administration and site conditions, as well as nervous- and psychiatric disorders. The located ADRs were mainly reported by physicians for the therapeutic groups: antibiotics, vaccines (ATC group J), and psychotropic medicine (ATC group N). The EU pediatric regulation has resulted in the establishment of more pediatric clinical trials, but information about whether the regulation has led to more drugs licensed for pediatric use is not available.

Key words Pediatrics, Children, Adolescents, Pharmacovigilance, Adverse drug reactions, Harms

1 Introduction

Adverse drug reactions (ADRs) contribute substantially to admissions to medical wards [1–8], but the literature review showed conspicuous differences in the reported prevalence of drug-related hospital admissions. The ADR-% varies between 0.3% and 16.8% with a median of 5.6% and the weighted average is 3.1% [7, 9–11]. The drugs primarily involved in ADR-related hospital admissions were psychotropic drugs, antihypertensive drugs, anticoagulants, anti-arrhythmic, NSAIDs, corticosteroids, and antibiotics [9–13]. There are huge gaps in the evidence on the safety of medicines in children, as only few medicines prescribed for children have been systematically tested in the clinical development trials for this patient group [14]. The widespread use of medicines in children and adolescents, and the increasing use within specific therapeutic groups has led to public concern about the limited

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knowledge about long-term safety aspects, particularly in the younger age groups [15–21]. Consequently in 2007 the EU legislation on pediatric medicine came into force with the purpose to stimulate pharmaceutical companies to conduct more clinical studies in children and adolescents [22]. The occurrence of ADRs in children is common, and although some are serious, empirical studies on this topic are scarce. Traditionally ADR reports were the major source of information about unknown ADRs, but with the introduction of pediatric registries, claims databases as well as electronic medical records, more potential information sources are present [23]. The aim of this chapter was to review published information about ADRs reported in children and adolescents with respect to occurrence, seriousness, type, suspected medicines, age and gender of the child and type of reporter. Secondly to review experiences with the EU pediatric regulation and its impact on pediatric research in Europe.

2 Adverse Drug Reaction: Definition and Classification of Seriousness

In the EU an ADR is defined as "any noxious and unintended response to medicines that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of diseases" [24]. ADRs can be divided into dose related/predictable effects and non-related/unpredictable effects [25, 26]. Severity of reported ADRs was classified according to a commonly accepted international standard, which is applied in both adult and pediatric pharmacovigilance. Here serious ADRs are divided into: resulting in death, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity in the reporter's opinion, a congenital anomaly/birth defect, and other medically important conditions [24].

3 Literature Searches

Systematic literature searches performed in PubMed, Embase, Cochrane Library, IPA, PsychInfo, and CINAHL (whole databases without restriction) studies reporting information about ADRs from medicine use in children and adolescents were conducted. The search strategy used the keywords and/or MESH terms "adolescents," "child," "pediatric," "pediatric," combined with any of the following search terms: adverse drug reaction, adverse event, clinical trials, side effect, adverse drug reaction reporting system, EU pediatric regulation, drug surveillance program, medicine use, pharmaocovigilance, pharmacoepidemiology. The reference lists of relevant articles were hand-searched for additional potential relevant articles. Non-peer reviewed articles were not considered. For

all included articles we analyzed time of publication, characteristics of explored patient groups, study design, occurrence of ADRs, suspected medicines, severity and type of reported ADRs, age and sex of the children reporting the ADRs, and type of reporter.

4 Pediatric Age: Definition

Pediatric age can be defined, and is for this chapter, as less than 18 years of age [27]. The following WHO definitions were applied in this chapter: infants (up to 2 years of age), children (2–10-year-olds), and adolescents (11–17-year-olds) [27].

5 Information About ADRs Available Before and After Marketing

The use of randomized controlled clinical trials (RCTs) in drug development has led to a commonly accepted standard for the pharmaceuticals area, which is central to the approval of new drugs, and historically, only few pediatric patients have been included in the clinical development trials [28–31]. Information about the potentially adverse effects of drugs stems primarily from the ADR reports made during the clinical phase II and III studies [29–32]. RCTs have the power to detect information about the most frequently occurring ADRs, but knowledge of the serious and unexpected ADRs is difficult to capture due to the limited inclusion criteria of patients and the relatively short treatment period [29, 30]. Traditionally, the testing and approval of new pharmaceutical substances and/or new indications for already marketed pharmaceuticals was particularly based on RCTs conducted in adults. Hence, after the accumulated safety experiences and considerations in phase IV, a limited number of the medicines have been additionally tested for pediatric use. It is primarily the small pool of patients that makes it difficult to detect rare ADRs that occur in 1 out of 10,000 patients, as the number of patients included in clinical trials is less than 3000 [26]. Despite the limited power of RCTs to detect serious and unexpected ADRs these trials are still the primary sources of collecting/gathering knowledge about the ADRs reported [29, 30, 33]. Information about ADRs is collected primarily through observation and talking to patients. Observation is conducted on the basis of an observation guide, in which the pharmaceutical company has indicated the expected ADRs based on the tested drug's effect mechanisms, preclinical studies, class effects, and other observational findings. The treating physicians normally report ADRs occurring after time of marketing to the national pharmacovigilance system; however in many countries it is also possible for other persons to submit data to the national ADR database. The lack of pediatric clinical trials has traditionally

resulted in the use of approved medicines off-label/unlicensed (OL/UL) in children and adolescents despite the lack of information about long-term safety issues [34].

6 ADRs Occurrence Monitored in Systematic Reviews and Meta-Analysis of Randomized Controlled Trials

Impicciatori et al. analyzed 17 articles, reporting information about ADRs studied in both randomized controlled trials and observational studies occurring in pediatric in/and outpatients (0–17-year-olds), and published before the year 2000 [35]. The authors estimated that ADR incidence in hospitalized children were 9.53% (95% CI 6.81, 12.26) and 1.46% in outpatients (95% CI 0.7, 3.03). The review did not assess the type of reporter, the distribution of ADRs by age and gender of the children, type of reported ADRs or therapeutic groups associated with ADRs [34]. Aagaard et al. conducted a qualitative review of all published empirical studies reporting pediatric ADRs occurring in hospital settings, by general practitioners or as ADR data submitted to national ADR databases by 2010 [36]. The average ADR incidence was for inpatients 42% (range 1–179%), for inpatients hospitalized due to an ADR 9% (range 1–28%), for outpatients 14% (range 2–68%), and below 1% in national ADR databases [36]. The average prevalence rate for inpatients was 24% (range 1–72%), for patients hospitalized due to ADRs 4% (range 1–9%), for outpatients 4% (range 1–17%), and below 1% in national ADR databases. The ADRs were mainly reported for the therapeutic groups: vaccines, antibiotics, and psychotropic medicine [36].

7 ADRs by Study Design and Therapeutic Group

7.1 Asthma Medications

A review of 12 clinical studies including approximately 3000 children aged 6–11-year-olds reported ADRs from use of salmeterol, formoterol, fluticasone, montelukast, zafirlukast, and the combination product budesonide/formoterol [37]. The most frequently reported ADRs were exacerbation of asthma, respiratory tract infection, cough, fever, and headache. Only few ADRs were rated as being serious, however a number of children were dropped out of the clinical trials due to serious ADRs [37].

7.2 Psychostimulants

A review including 43 studies reporting ADRs associated with medicines for treatment of ADHD in clinical studies covering approximately 7000 children, the majority of 6- to 12-year-old boys, was made [38]. The most frequently reported ADRs were "decreased appetite," "gastrointestinal pain," and "headache." The children/their parents primarily assessed reported ADRs, and very

few ADRs were rated as being serious. A large number of children were dropped out of studies due to serious ADRs [38].

7.3 Antidepressants and Pregnancy

A systematic review and meta-analysis by Grigoriadis et al. examined the risk for persistent pulmonary hypertension of new-borns' associated with antenatal exposure to antidepressants [39]. Exposure to SSRIs in early pregnancy was not found to be significantly associated with persistent pulmonary hypertension of the newborn, and the absolute risk difference for development of persistent pulmonary hypertension of the newborn after exposure to SSRIs in late pregnancy was 2.9–3.5 per 1000 infants [39].

7.4 Lamotrigine

A systematic review of 78 RCTs involving 3783 patients aged ≤18 years who have received at least a single dose of lamotrigine was conducted by Egunsola and colleagues [40]. In total 2222 adverse events (AEs) were reported. Rash was the most commonly reported AE, occurring in 7.3% of the patients. Stevens-Johnson syndrome was rarely reported, with a risk of 0.09 per 100 patients. Discontinuation due to an ADR was recorded in 72 children (1.9% of all treated patients). Fifty-eight percent of treatment discontinuation was attributed to different forms of "rash" and 21% due to "increased seizures" [40].

7.5 Arthemether-Lumefantrine

Egunsola et al. compared the safety of artemether-lumefantrine (AL) with other artemisinin-based combinations in children reported in RCTs [41]. A total of 4726 adverse events (AEs) were recorded in 6000 patients receiving AL [41]. The most commonly reported AEs were "coryza," "vomiting," "anaemia," "diarrhoea," and "abdominal pain." AL-treated children have a higher risk of body weakness (64.9%) than those on artesunate-mefloquine (58.2%) ($p = 0.004$, RR: 1.12 95% CI: 1.04–1.21). The risk of vomiting was significantly lower in patients on AL (8.8%) than artesunate-amodiaquine (10.6%) ($p = 0.002$, RR: 0.76, 95% CI: 0.63–0.90) [41].

7.6 Antidepressants and Risk of Suicidal Behavior/Suicidal Ideation

In a review by Hetrick et al., the efficacy and adverse outcomes, including definitive suicidal behavior and suicidal ideation, of newer generation antidepressants compared with placebo in children and adolescents (aged 6–18 years old) were determined [42]. Nineteen trials of a range of newer antidepressants compared with placebo, containing 3335 participants, were included in the review. The review found an increased risk (58%) of "suicide-related outcome" for those on antidepressants compared with a placebo (17 trials; $N = 3229$; RR 1.58; 95% CI: 1.02–2.45). This equates to an increased risk in a group with a median baseline risk from 25 in 1000 to 40 in 1000 [42].

8 Cohort Studies in Observational Databases

8.1 ADHD Medications

In a cohort of 1841 youths registered in the Italian ADHD register, 68 of these received a prescription of atomoxetine (ATX) and 8 received a prescription of methylphenidate (MPH). Twenty-five children experienced at least one ADR, and a total of 40 ADRs were found [43]. "Weight loss" was the most frequently reported ADR [43]. Arcieri et al. studied the cardiovascular effects from use of ATX and MPH in an open cohort of 1758 children and adolescents with ADHD treated in a community care center in Italy [44]. Measurements of "blood pressure" and "heart rate," and "electrocardiogram" (ECG) assessment were performed at baseline and at regular intervals up to 24 months [44]. Statistically significant increases were observed in cardiovascular measures: in the MPH group after 6 months in heart rate (+2.01, $p = 0.01$); in the ATX group after 6 months in diastolic pressure (+1.60, $p = 0.01$) and in heart rate (+2.93, $p = 0.001$), and after 12 months in heart rate (+3.26, $p = 0.003$). Compared with the baseline, 59 patients had an alteration of ECG during the follow-up period [44].

9 Register Studies

9.1 Methylphenidate and Malformations

Pottegård et al. investigated the risk of major congenital malformations following first-trimester in utero exposure to methylphenidate [45]. Data from 2005 to 2012 were extracted from the Danish National Patient Register, the Danish National Prescription Registry, the Medical Birth Registry, and the Danish Civil Registration System. Exposure was defined as having redeemed one or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester [45]. In total 222 exposed and 2220 unexposed pregnancies were included in the analysis. There was no statistically significant increase in major malformations (point prevalence ratio = 0.8; 95% CI, 0.3–1.8) or "cardiac malformations" (point prevalence ratio = 0.9; 95% CI, 0.2–3.0) [45]. In another study Dideriksen et al. systematically reviewed available data on birth outcome after human in utero exposure to methylphenidate [46]. Systematic literature searches in PubMed and Embase were performed and data from Michigan Medicaid recipients, The Collaborative Perinatal Project, and the Swedish Birth Registry were evaluated. Excluding three case reports, a total of 180 children exposed to methylphenidate in utero during first trimester were identified, among whom, four children with major malformations were observed [46].

9.2 Antidepressants and Malformations

Furu et al. assessed the use of SSRIs and venlafaxine in early pregnancy is associated with an increased risk of birth defects, particularly birth defects [47]. The Nordic populations identified from nationwide health registers at different periods in 1996–2010 were included in the study [47]. The full study cohort included women giving birth to 2.3 million live singletons. Among the 36,772 infants exposed to any SSRI in early pregnancy, 3.7% ($n = 1357$) had a birth defect compared with 3.1% of 2,266,875 unexposed infants, yielding a covariate adjusted odds ratio of 1.13 (95% CI: 1.06–1.20) [46]. The odds ratios for any cardiac birth defect with use of any SSRI or venlafaxine were 1.15 (95% CI: 1.05–1.26). For "atrial and ventricular septal" defects the covariate adjusted odds ratio was 1.17 (1.05–1.31). Exposure to any SSRI or venlafaxine increased the prevalence of "right ventricular outflow tract obstruction defects," with an adjusted odds ratio of 1.48 (1.15–1.89) [47]. Huybrechts et al. studied the association between SSRI use during pregnancy and risk of "persistent pulmonary hypertension" of the new-borns (PPHN) in a nested cohort study enrolling 3,789,330 pregnant women that were enrolled from 2 months after the date of last menstrual period through at least 1 month after delivery [48]. The cohort was restricted to women with a depression diagnosis and logistic regression analysis with propensity score adjustment applied to control for potential confounders, and restricted to SSRI and non-SSRI mono-therapy use during the 90 days before delivery versus no use [48]. Analysis showed that a total of 128,950 women (3.4%) filled at least one prescription for antidepressants late in pregnancy and 2.7% of these, used an SSRI and 26,771 (0.7%) a non-SSRI. Overall, 7630 infants not exposed to antidepressants were diagnosed with PPHN (20.8; 95% CI: 20.4–21.3 per 10,000 births) compared with 322 infants exposed to SSRIs (31.5; 95% CI: 28.3–35.2 per 10,000 births), and 78 infants exposed to non-SSRIs (29.1; 95% CI: 23.3–36.4 per 10,000 births) [48]. Associations between antidepressant use and PPHN were attenuated with increasing levels of confounding adjustment. For SSRIs, odds ratios were 1.51 (95% CI: 1.35–1.69) unadjusted and 1.10 (95% CI: 0.94–1.29) after restricting to women with depression and adjusting for the high-dimensional propensity score [48]. For non-SSRIs, the odds ratios were 1.40 (95% CI, 1.12–1.75) and 1.02 (95% CI, 0.77–1.35), respectively. Upon restriction of the outcome to primary PPHN, the adjusted odds ratio for SSRIs was 1.28 (95% CI, 1.01–1.64) and for non-SSRIs 1.14 (95% CI, 0.74–1.74) [48].

Kieler et al. assessed whether maternal use of SSRIs increased the risk of persistent pulmonary hypertension in the newborns, and whether such an effect might differ between specific SSRIs [49]. A population-based cohort study using data from the national health registers in Denmark, Finland, Iceland, Norway, and Sweden from 1996 to 2007 was conducted, and included more than 1.6 million

infants born after gestational week 33. Around 30,000 women had used SSRIs during pregnancy and 11,014 had been dispensed an SSRI later than gestational week 20 [49]. Exposure to SSRIs in late pregnancy was associated with an increased risk of "persistent pulmonary hypertension" in the newborns: 33 of 11,014 exposed infants (absolute risk 3 per 1000 live born infants compared with the background incidence of 1.2 per 1000); adjusted odds ratio 2.1 (95% confidence interval 1.5–3.0) [49]. The increased risks of "persistent pulmonary hypertension" in the newborns for each of the specific SSRIs (sertraline, citalopram, paroxetine, and fluoxetine) were of similar magnitude. Filling a prescription with SSRIs before gestational week 8 yielded slightly increased risks: adjusted odds ratio 1.4 (95% confidence interval 1.0–2.0) [49]. Li et al. examined whether prenatal antidepressant use increases the risk of "asthma" in the offspring [50]. A cohort study was performed among all live singletons born in Denmark between 1996 and 2007. Mothers who had a diagnosis of "depressive disorder" and/or who used antidepressants 1 year before or during the index pregnancy were identified [50]. Of the 733,685 children identified, 84,683 had a diagnosis of asthma. A total of 21,371 children were exposed to prenatal "maternal depression" and "prenatal maternal depression" was associated with childhood asthma (HR: 1.25, 95% CI: 1.20–1.30) [50]. Overall, 8895 children were exposed to antidepressants in utero. Compared with children born to mothers with prenatal depression and no antidepressant use during pregnancy, the hazard ratio (HR) for asthma after any antidepressant use during pregnancy was 1.00 (95% CI: 0.93–1.08) [50]. HRs after use of SSRIs only, newer antidepressants only, and older antidepressants only were 0.95 (95% CI: 0.88–1.03), 1.11 (95% CI: 0.89–1.39), and 1.26 (95% CI: 1.02–1.55), respectively [50].

10 ADRs Submitted to Spontaneous Reporting Systems

Several studies analyzing ADR data reported to national databases for general pediatric populations as well as selected populations and therapeutic groups have been published. Table 1 displays the characteristics of studies by date of publication, country, data collection period, reported ADRs, ADR reporting rate, serious ADRs, number of fatal cases, type of reporter, and distribution of ADRs by age and gender in general pediatric populations [50–58]. Articles were published from 2000 onward, however data were collected previously. The period under study varied from 5 to 42 years, and the articles included ADR reports submitted to national ADR databases in many countries as well as the international ADR databases VigiBase and EudraVigilance [51–59]. Different types of reporters, e.g., physicians, consumers, other healthcare

Table 1
Characteristics of studies of pediatric adverse drug reactions (ADRs) reported to national and international pharmacovigilance databases, 2000–2014

Studies by year and country	Period	Age (year)	Reported ADRs (*n*)	Serious ADRs (*n*) (%)	Fatal cases (*n*)	ADRs by reporter (%)	ADRs by male (%)	ADRs by age group (year) (%)
Morales-Olivas 2000 [51] ES	1982–1991	≤14	2454	665(27)	4	NA	55	<1:13% 1–4:38% 5–9:25% 10–14:24%
Moore 2002 [52] US	1997–2000	≤2	7111	4338(61)	769	94%: Company 6%: Others	57	<1:31% 1–12:50% 13–23:18%
Kimland 2005 [53] SE	1987–2001	≤15	7887	1025(13)	8	NA	55	0–4:44% 5–9:12% 10–15:17%
Carleton 2007 [54] CA	1998–2002	≤19	1193	726(61)	41	NA	NA	<1:12% 1–3:9% 3–6:1% 6–13:18% 13–19:60%
Aagaard 2010 [55] DK	2000–2009	≤17	4500	1874(42)	28	89%: Physician 7%: OHCP[a] 4%: Consumer	49	<1:27% 1–2:25% 2–10:25% 11–17:23%
Star 2011 [56] WHO	1968–2010	≤17	268,145	NA	NA	55%: Physician 25%: OHCP[a] 4%: Consumer 3%: Pharmacist 13%: Others	39	<1:17% 2–11:46% 12–17:37%
Barzaga 2012 [57] CU	2009–2010	≤17	533	54(10)	1	73%: Physician 15%: Pharmacist 9%: Nurse 3%: Others	47	<1:27% 1–2:17% 2–10:30% 11–17:26%
Aldea 2012 [58] SE	2004–2009	≤17	8196	1590(20)	33	63%: Physician 24%: OHCP[a] 11%: Pharmacist 2%: Others	51	<1:28% 1–2: 17% 2–11:46% 12–17:26%
Aagaard 2014 [59] EU	2007–2011	≤17	670	114(17)	3	100%: Consumer	40	<1:24% 1–9:30% 10–17:45%

[a]OHCP

professionals, and pharmacists reported the ADR data; however, physicians reported the majority of ADR reports. Across studies on average 30% (range 10–61%) of ADRs were serious. Approximately up to one-half of ADRs were reported in children up to 2 years of age [51–59]. Table 2 displays the reported ADRs by type (system organ class) and suspected medicines (ATC level 1). Across studies

Table 2
Spontaneous reported adverse drug reactions (ADRs) distributed by type (system organ class [SOC]), therapeutic group (ATC level 1) and study

Studies by year	ADRs by type (SOC) (% of total)	ADRs by medications (ATC level 1) (% of total)
Morales-Olivas 2000 [51]	32%: Skin 20%: Gastro 10%: Nervous 8%: General 5%: Psychiatric 5%: Cardiovascular	52%: Antibiotics and vaccines 22%: Respiratory tract medicine 10%: Digestive tract drugs 5%: Analgesics 3%: Antiepileptics 3%: NSAID
Moore 2002 [52]	NA	28%: Palivizumab 4%: Cisapride 4%: Indomethacin
Kimland 2005 [53]	45%: Skin 20%: General 8%: Psychiatric 7%: Nervous 5%: Gastro	74%: Antibiotics and vaccines 5%: Respiratory 3%: Anti-epileptics 18%: Others
Carleton 2007 [54]	Psychiatric disorders Nervous system disorders	4%: Isotretionin 4%: Paroxetine 3%: Methylphenidate 3%: Amoxicillin 2%: Valproic acid
Aagaard 2010 [55]	31%: General 18%: Skin 15%: Nervous	65%: Antibiotics and vaccines 17%: Nervous
Star 2011 [56]	35%: Skin 22%: General disorders 18%: Nervous 15%: Gastro	32%: Antiinfectives for systemic use 28%: Nervous system 12%: Dermatologicals 12%: Respiratory system
Barzaga 2012 [57]	29%: Skin 11%: General 9%: Gastro	44%: Antibiotics 22%: Antihistamines 14%: Analgesics (nonopioid) 6%: Bronchodilators
Aldea 2012 [58]	34%: General 15%: Skin 14%: Nervous 8%: Gastro	67%: Antibiotics and vaccines 9%: Nervous 9%: Respiratory
Aagaard 2014 [59]	20%: General 15%: Nervous	30%: Antibiotics and vaccines 23%: Antineoplastic and immunomodulating agents 13%: Sex hormones

the majority of the ADRs were reported for immunization therapies and antibiotics (ATC J), psychotropic medicine (ATC N), and respiratory medicine (ATC R). The majority of reported ADRs were "dizziness," "injection site reactions"), "rash," "headache," "anxiety," "depression," and "aggression") [51–59].

10.1 Psychostimulants

Aagaard et al. conducted a retrospective study of ADRs reported for ADHD medications to the Danish Medicines Agency from 2000 to 2009 [14]. In total 130 ADR reports corresponding to 329 ADRs were located in the ADR database for children aged 0–17-year-olds. One half of ADRs were serious but no fatal cases were reported. Physicians reported more than one-half of all ADRs. Approximately 85% of ADRs were reported in boys, the majority for methylphenidate and atomoxetine. The largest share of reported ADRs were of the type "psychiatric disorders" (21% of total ADRs) followed by "general disorders" (21% of total ADRs) and "nervous system disorders" (16% of total ADRs). More than 90% of ADRs reported for methylphenidate were "dizziness," "dyskinesia," and "headache" [14].

10.2 Systemic Antibacterials

Aagaard et al. 2010 characterized ADRs reported for systemic antibacterials to the Danish Medicines Agency from 1998 to 2007 [60]. In total 66 ADR cases corresponding to 113 ADRs were reported. Two-thirds of ADRs were reported for azithromycin, erythromycin, and dicloxacillin, and almost all were serious. The majority of reported ADRs were of the type skin disorders (23% of total ADRs), general disorders (16% of total ADRs), and gastrointestinal disorders (15% of total ADRs) [60].

10.3 Immunization therapies

Aagaard et al. characterized reported adverse events (AEFIs) following immunization in 0- to 17-year-olds reported between 1998 and 2007 [61]. A total of 1365 reports covering 2600 AEFIs, corresponding to 60% of all adverse events reported for children, were reported [61]. One-third of the AEFIs were classified as serious, and two deaths were reported. Approximately 80% of AEFIs were reported in children aged 0–2 years [61]. Of all reported AEs, 45% were in the category "general disorders,"followed by the categories "skin disorders" (20% of total AEFIs) and "nervous system disorders" (16% of total AEFIs). The most frequently reported serious AEs were "febrile convulsions," "pyrexia," and "injection-site reactions" [61]. Galindo et al. investigated vaccine-related adverse events in Cuban children (<16 years) reported from 1999 to 2008 [62]. A total of 45,237,532 vaccine doses were administered, and 26,159 vaccine-associated adverse events were reported (overall rate: 57.8 per 100,000 doses) [62]. The group aged 0–5 years reported the highest rate of vaccine-associated adverse events (82/100,000 doses) for the DTwP vaccine, and the majority of reported events were "fever" and "injection site reactions" [62].

10.4 Respiratory Medicine

Aagaard et al. studied ADRs reported from use of the following asthma medications licensed for pediatric use submitted to the EudraVigilance database from 2007 to 2011 [63]. A total of 326 spontaneous reports corresponding to 774 ADRs for the included asthma medications were located in the database, and approximately 85% of reported ADRs were serious including six fatal cases. In total, 57% of ADRs were reported for boys. One quarter of all ADRs occurred in children up to 1 year of age [63]. ; Physicians reported the majority of ADRs. Across medicines, the majority of reported ADRs were of the type "psychiatric disorders" (13% of total ADRs), followed by "respiratory disorders" (10% of total ADRs) and "skin disorders" (9% of total ADRs). The largest number of ADRs was reported for budesonide (21% of total ADRs) and salbutamol (20% of total ADRs). For salbutamol, the largest numbers of serious ADRs were "tachycardia," "accidental exposure/incorrect dose administered," and "respiratory failure" [63].

10.5 Psychotropic Medicine

Aagaard et al. studied spontaneous ADR reports for children from birth to 17 years of age submitted in Denmark for psychotropic medicine [64]. Results showed that a total of 429 ADRs were reported for psychotropic medicines and 56% of these were classified as serious. Almost 20% of psychotropic ADRs were reported for children from birth up to 2 years of age and one half of ADRs were reported in adolescents, especially for antidepressants and psychostimulants. Approximately 60% of ADRs were reported for boys, and 40% of all ADRs were from the category "nervous and psychiatric disorders" [64].

10.6 Valproic Acid and Fatalities

Star et al. 2014 reviewed valproic acid reports on children (<17 years) with fatal outcome and secondly to determine reporting over time of hepatotoxicity with fatal outcome retrieved from the WHO ADR database, VigiBase in June 2013 [65]. A total of 268 ADR reports with valproic acid and fatal outcome in children reported from 25 countries since 1977 were located in VigiBase. A total of 156 fatalities (ADRs) were reported with hepatotoxicity, which has been continuously and disproportionally reported over time. There were 31 fatal cases with pancreatitis, and other frequently reported events were "coma/encephalopathy," "seizures," "respiratory disorders," and "coagulopathy" [65].

10.7 Off-Label Prescribing

A retrospective study of 4388 ADRs reported in 0–17-year-olds to the Danish ADR database showed that 17% of the reported ADRs were associated with off-label (OL) and unlicensed (UL) prescribing [66]. More than one half of off-label ADRs were reported in adolescents, and serious ADRs were more likely to be reported for hormonal contraceptives, anti-acne preparations, and allergens [66]. Posthumus et al. demonstrated that for 683 patients aged 0–18 year, 7% of their hospital admissions were

due to ADRs [67]. Of the children admitted to hospital due to ADRs from OL/UL prescribing, 33% of these ADRs were reported for chemotherapy, particularly methotrexate, doxorubicin, and vincristine [67]. Hence, other studies have monitored ADR occurrence from OL/UL prescribing in selected patient cohorts and for specific therapeutic groups, e.g., use of antiretroviral drugs in HIV infected children, prescribing of topical drugs in pediatric outpatients, and sildenafil use in pediatric pulmonary patients [68].

10.8 EU Pediatric Regulation

Conducting clinical trials in the pediatric population has been difficult mainly because of the lack of funding for academic studies, and the lack of interest by pharmaceutical companies [69–71]. The EU pediatric regulation established a EU study programme for medicines with different initiatives and benefits for pharmaceutical companies in order to stimulate to the conduction of pediatric trials (*see* Table 3) [72]. Since 2007, EMA has issued a number of standard pediatric investigation plans (PIPs) for specific types of medications: tetanus-diphtheria-pertussis vaccines, H1N1 pandemic influenza vaccines, allergen extracts for immunotherapy, and medicines for treatment of acute myeloid leukaemia and rhabdomyosarcoma [73]. By July 2015 the EMA has approved several PIPs for substances within several therapeutic areas, i.e., oncology, endocrinology, psychiatry [74], juvenile idiopathic arthritis [68], and melanoma PIPs, but only few pediatric trials have been completed, and results made public [75]. A study of the impact of the EU pediatric regulation on the number and quality of completed pediatric clinical trials is missing. Additionally EMA should define specific areas of interest and special need for pediatric research, e.g., therapeutic areas with a high level of OL/UL medicine use in children, and within orphan diseases [71]. Hence, a comparative study of the impact of national pediatric regulations on the available information about pediatric medicine use, including safety profiles for pediatric use, has not yet been conducted [76].

11 Conclusions and Future Perspectives

This review showed that only few systematic reviews analyzing pediatric ADR occurrence have been conducted. Hence, some pediatric clinical studies, particularly of the type RCTs, were conducted for the therapeutic groups: antidepressants, ADHD medications (ATC group N), and immunization therapies (ATC group J). The study designs applied in the articles were meta-analysis of clinical trials, cohort studies, register studies, and analysis of ADRs submitted to national and international ADR databases. The identified studies showed that ADR prevalence in pediatric populations differed largely between countries, hospitals, study design, time

Table 3
Overview of the principles of the EU pediatric regulation

Task/activity	
Establishment of an Expert Pediatric Committee (PDCO)	• CHMP members ($n = 5$) • Patient/family and healthcare professionals ($n = 6$) • Experts appointed by member states ($n = 22$) • Experts appointed by the European Medicines Agency ($n = 2$)
An agreed pediatric development: the Pediatric Investigation Plan (PIP)	• PIP includes details of the timing and the measures to demonstrate efficacy, safety and quality of the substance in children and adults • PIP are to be approved by the PDCO • PIP is binding upon the pharmaceutical company
Rewards and incentives	*New medicinal products:* • 6-months extension of the patent protection period • Authorization in all member states • Pediatric information available in the product information *Authorised medicinal products with a patent:* • 6-months extension of the patent protection period/1-year extension of market protection • Authorization in all member states • Pediatric information available in the product information *Orphan drugs:* • Two years of market exclusivity added to the existing 10 years. *Off-patent medicinal products:* • 10 years data protection/exclusivity • Brand name can be retained
Scientific advice	• PIP guidelines developed by EU • Free scientific advice before submission of a PIP or during the PIP implementation process
Other initiatives	• EU pediatric research network • Funding of studies for off-patent products • Database of pediatric clinical trials (EudraCT) • Database of Authorised Products in the EU • Medical product information available

periods, and age groups, and therefore it was difficult to extrapolate the findings from the identified studies to other pediatric populations. Many serious ADRs were reported including fatal cases. Across studies, the most commonly reported pediatric ADRs were of the types: "skin and subcutaneous disorders" (rash), "general administration and site conditions" (injection site reactions, dizziness), "gastrointestinal disorders" (nausea, vomiting, stomach pain), as well as "nervous"-and "psychiatric disorders" (anxiety, depression, nervousness). Pediatric ADRs were mainly reported for the therapeutic groups: antibiotics, vaccines, and psychotropic

medicine. The majority of reported ADRs concerned pediatric populations from North America and Europe. ADRs were predominantly reported by physicians, however also consumers and pharmacists contributed with data to the spontaneous reporting systems. Information about ADRs from mothers' use of drugs during pregnancy is limited. The identified studies examined the risk of malformations from use of antidepressants and methylphenidate during pregnancy. Hence medicine use during pregnancy must be studied further, particularly for medications used for chronic diseases, e.g., asthma medications, NSAIDs, and drugs used in treatment of rare diseases.

11.1 Quality of ADR Data in the Included Studies

The ADR material analyzed in this study was collected over many years and varied in quality and extent, because a large number of reports and case handlers have been involved in processing the ADR reports. The definitions of seriousness and the reliability of the assessment of ADRs vary among scientists, but have not been reported in the materials and are therefore not part of this literature review. Additionally, we do not know the causality of the reported ADRs, which should be borne in mind by interpreting the data. Furthermore spontaneous reporting systems suffer from different barriers such as incomplete recognition of suspected ADRs and administrative barriers to reporting, which may result in under reporting of suspected ADRs. ADR data collected through clinical trials are biased by lack of information about causality assessment of the reported events, and selected reporting in the articles.

11.2 Research Implications

In order to increase knowledge about the occurrence of ADRs in the pediatric population, more clinical studies, preferably RCTs, must be conducted, as well as large observation studies in order to detect new signals about possible serious and rare occurring ADRs. Research must focus on products frequently prescribed OL/UL, as well as medicines used for chronic use, e.g., opioids, hormonal contraceptives, dermatological products, chemotherapy treatments, and NSAIDs. From a legal point of view physicians are required to monitor off-label medicine use in the patients. Therefore in the patients' health records a large amount of information about suspected adverse events from OL/UL medicine must be present. Previous studies have documented that text-mining techniques can be used in screening of electronic health records in order to identify ADRs from medicine use [77, 78]. Hence the selection and use of available study designs in pediatric research must be considered further, as rare occurring ADRs cannot be detected in the RCTs. Additionally, the RCTs are primarily designed to test efficacy, and not safety. Use of crossover designs has also limited value in children because of the large amount of time varying confounding as the trials developed. Use of good observational studies could be of additive value in the identification of long-

term safety aspects; hence problems with confounding and definition of baseline values must be handled in these studies. Until more clinical trials have been conducted, and more medicines are licensed for pediatric use, prescribers and other healthcare professionals must rely on spontaneous ADR reports as the only information source for information about rare and unknown ADRs. Therefore, regulators should continue to stimulate healthcare professionals and patients to continue to report ADRs to the national ADR databases and make comprehensive signal detection analysis of data, in order to be able to detect new signals of potentially harmful occurring ADRs earlier than practise is today. Reporting of patient ADR information through the social medias could increase the numbers of ADRs, but only few of these data have been routinely used in the drug surveillance process due to lack of medical confirmation and impreciseness of data. Pharmacogenomics research in children has been rarely conducted, but studies of this type could add more valuable information about dose response effects in the different age groups, infants, children, and adolescents.

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Chapter 5

Detecting Safety Issues in Clinical Trials

Emma Heeley

Abstract

Randomized controlled trials (RCTs) are primarily designed to determine efficacy of the investigational product. Information on serious adverse events is collected and often undergoes a detailed review by the sponsor. Detecting safety issues during a trial has revolved primarily around the Data Safety Monitoring Board (DSMB) who review unblinded summarized data and case reports. Final trial publications typically contain descriptive analyses on the SAEs, sometimes with simple statistics that often presents a problem of multiplicity. As most trials lack the power to test for harm related hypothesis analysis of adverse event data from clinical trials can be formulated as a data-mining exercise rather than a problem for hypothesis testing; that is, seeking to identify or prioritize adverse events that may be affected by the investigational product, rather than starting out with a large number of null hypotheses and analyzing the data to look for formal null rejections. Data mining techniques have been applied to adverse event data from clinical trials that include Bayesian hierarchical models and pattern data mining but they have not yet been widely adopted. There is a large potential benefit from the use of these techniques and meta-analyses of adverse events across trials, but it does require standardization in the coding of events and determining if the adverse event was "on treatment" or "Intention To Treat." Different approaches are discussed including The Safety Planning, Evaluation and Reporting Team (SPERT) 3 tier system for analyzing adverse events and tackling multiplicity.

Key words Clinical trials, Serious adverse events, Drug safety

1 Randomized Clinical Trials

Randomized clinical trials (RCTs) are considered the gold standard for evaluating interventions because of their ability to minimize the chances of obtaining the incorrect answer due to bias. Eligible participants are randomly allocated to one of the treatment groups to avoid selection bias and then participants are followed prospectively. Other potential biases are dependent on the design of the RCT, the most rigorous is a double blind RCT where neither the participant nor the trial staff are aware of the treatment group. However, this type of design is not always feasible and some RCTs are open (open-label if it is a medication) where both the participant and trial staff are aware of the treatment group. Bias can

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be minimized in open trials by using the Prospective Randomized Open Blinded End-point (PROBE) study design [1]. For some outcomes such as blood pressure PROBE designed studies have reported similar results to RCTs, suggesting biases can be successfully minimized [2].

To safeguard against publication bias, whereby only positive RCTs are published and outcome-reporting bias, where the published outcomes differ from the original protocol, the International Committee of Medical Journal Editors (ICMJE) introduced the requirement of trial registration prior to commencement of recruitment as a consideration for publication in 2005 [3]. However, the impact of these changes may take many years to come to fruition with studies in 2014 and 2015 suggesting that there is still a discrepancy between registered trials and what is published, those with positive results often published earlier, but many published trials were not registered or potential reporting bias in the primary outcome (i.e., adding/omitting or downgrading/upgrading the original primary outcome) [4–6].

RCTs are primarily designed to determine the efficacy of a treatment. Typically, the sample size of an RCT is calculated prior to beginning the study and is based on the primary outcome, which tends to be a clinically relevant measure such as seizure counts in epilepsy studies. Generally RCTs are not powered to detect safety outcomes, at best predefined safety concerns such as liver failure are listed as secondary outcomes but the overall sample size is significantly underpowered to determine these. Data on adverse events are collected and often reviewed on a case by case basis looking for signals, as the questions relating to drug safety are not easy to define until potential signals in the data have been identified. There is growing support that the approach to the evaluation of drug safety data from RCTs would be better considered an exercise in data mining rather than hypothesis testing and that a meta-analysis of safety data from multiple trials would be valuable [7].

1.1 Phases of Clinical Trials

During the development of a new intervention clinical studies are conducted in a series of steps, called phases (Fig. 1). Each phase is designed to answer a separate research question and details of each phase is described below.

1.2 Preclinical

Preclinical studies are conducted in vitro and in vivo (laboratory animals), where the aim is to determine if the product is safe enough to be tested on humans and what the maximum recommended starting dose (MRSD) in humans should be. For medicines, studies are conducted to determine the pharmacodynamics (PD) (what the drug does to the body), pharmacokinetics (PK) (what the body does to the drug) and toxicity. Studies of a drug's toxicity include which organs are targeted by that drug, as well as if there are any long-term carcinogenic effects or toxic effects on

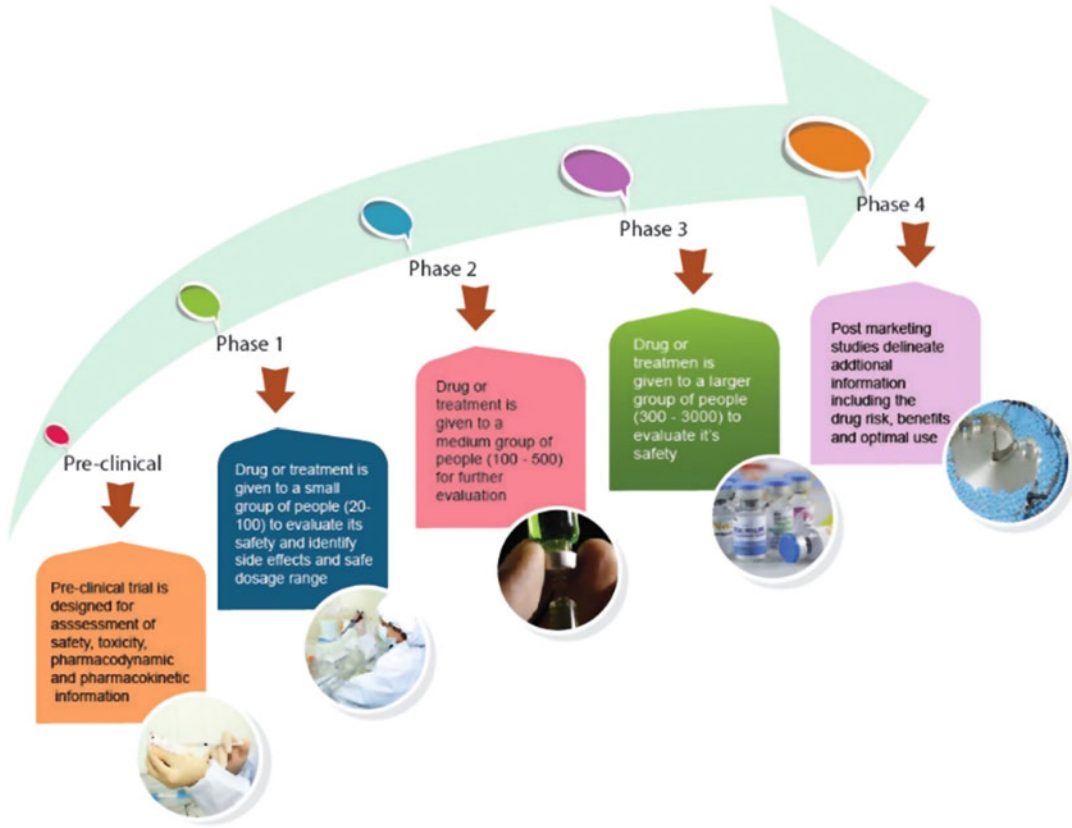

Fig. 1 Clinical trial phases

mammalian reproduction. Data from the preclinical studies are used to determine the No Observable Adverse Effect Levels (NOAEL), which is the highest dose level that does not produce a significant increase in adverse effects in comparison with the control group. The NOAEL is then converted to a human equivalent dose (HED) and divided by a safety factor (of at least 10) to determine the MRSD. The purpose of the safety factor is to increase assurance that the first dose in humans will not cause adverse effects.

1.3 Phase I

Phase I RCTs are the first time a new product is tested in humans. The aim of these RCTs is to evaluate its safety and determine a safe dosage range. Generally, 20–100 healthy volunteers are enrolled in a phase I trial and very closely monitored in a specialized phase I clinical trial unit, studies take several months. In cases of severe or life-threatening illnesses, volunteers with the disease may be used. These RCTs usually start with very low doses, which are gradually increased. On average, about 70% of phase I compounds will be found safe enough to progress to phase II.

1.4 Phase II

Phase II RCTs are designed to primarily evaluate the efficacy of products. The aim is to determine the effective dose, the method of delivery (e.g., oral or intravenous), and the dosing interval, as well as to reconfirm product safety. Typically, phase II studies involve 100–300 patients with the disease/condition and studies take from several months to years. On average only a third of products move to phase III. Some products turn out to be ineffective, while others have safety problems or intolerable side effects.

1.5 Phase III

Phase III RCTs confirm the products efficacy, monitor side effects of longer term use, and compare it to commonly used treatments. These RCTs are the final step before seeking approval from the drug regulatory authorities to market the new product. Phase III RCTs usually last from 2 to 10 years and involve thousands of patients across multiple sites. Approximately 25–33% of products move to phase IV RCTs.

1.6 Phase IV

Phase IV RCTs are conducted after the product has been approved and marketed, and examine the effect of the product in various populations along with side effects associated with long-term use. The reasons to conduct phase IV RCTs vary; they may be to examine the effectiveness of the drug for additional indications or a requirement from the drug regulator as part of the postmarketing surveillance plan.

2 Serious Adverse Events and Adverse Events

Safety data in RCTs can be from many sources, laboratory values, outcomes, and adverse event data. The protocol of the RCT should outline if the investigators report adverse events (AEs) and Serious Adverse Events (SAEs), selected AEs or SAEs only. RCTs typically collect information on all SAEs. The US Food and Drug Administration (FDA) define an AE as any undesirable experience associated with the use of a medical product in a patient. A SAE is defined as any untoward medical occurrence that happens to trial participants that:

- results in death (fatal),
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- is a medically significant/important event or reaction.

SAEs are reported to the trial sponsor typically within 24 h on a standard data collection form, which includes a description of the event, start/stop dates, outcome, severity, and likely causality. The trial sponsors safety team then evaluate the information, collecting further details if required, perform a medical review of the SAE case narratives, and decide whether the information meets the criteria for expedited reporting to the regulatory authorities.

Where the sponsors are a pharmaceutical company they typically have a separate safety database which should be used to conduct ongoing safety evaluations, including periodic review and analyses of their entire safety database, not only for safety reporting purposes, but also to update investigator brochures, protocols, and consent forms with new safety information.

3 Role of Data Safety Monitoring Board

Since the early 1980s independent Data Safety Monitoring Boards (DSMB), also referred to as the Data Monitoring Committee (DMC), have been an essential component to the safety monitoring of RCTs. The DMC is comprised of 3–8 members, typically statisticians, clinicians, and trialists. A DMC's primary purpose is to ensure that continuing a trial according to its protocol is ethical, taking account of both individual and collective ethics. The DMC monitors the data of the trial at regular intervals and alerts the sponsors of the trial if they think the pattern of data—on benefits or hazards, or both—is sufficiently persuasive to warrant either closing recruitment to a trial or changing the protocol, such as terminating recruitment in one or more subgroups of trial participants [8]. The unblinded statistician prepares the DMC report which is specific for each trial but usually contains tables by treatment group of baseline characteristics, outcomes, deaths, and SAEs. SAEs tend to be reported at the preferred term level of the Medical Dictionary for Regulatory Activities (MedDRA).

Stopping rules are often clearly defined based on statistical criteria around the main efficacy or safety outcome such as mortality and typically not around secondary outcomes due to lack of power. Stopping rules are prespecified and outlined in the DMC charter, some trials may have a stopping rule around the number of cases of Serious Adverse Events but others ask the DMC to take in the totality of the evidence to assess safety. The DMC also takes into account the types and frequency of SAEs, the risk versus benefit ratio and external evidence from other trials when considering if they recommend to the sponsor to continue enrolment into the trial. RCTs may be stopped early if an intervention produces "larger than expected benefit or harm," or if "investigators find evidence of no important difference between experimental and control interventions" [3]. An example of a trial that was stopped early for safety

is the ILLUMINATE trial that recruited in 15,067 patients at high risk of CVD between August 2004 and December 2005 [9]. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina. There was emerging evidence of excess deaths on torcetrapib on the monthly safety report 30th November 2006, 82 vs. 51 deaths $P = 0.007$ with a statistical stopping guideline for safety: $P < 0.01$. The DSMB teleconference 1st December 2006 recommend stopping the trial, the sponsor stopped torcetrapib trials on 2nd December 2006.

4 Reporting Safety Data from a Single Trial

The reporting of adverse event data in the trial result publications is often inadequate, missing information on serious adverse events and withdrawals due to adverse events, despite attempts to standardize and mandate reporting [10–12]. An international group of scientists and editors published Consolidated Standards of Reporting Trials (CONSORT) Statements in 1996, 2001 and 2010, that are working toward improving the standard of what is reported in the medical literature [12, 13]. In 2004, the CONSORT group issued guidelines on Better Reporting of Harms in RCTs [14]. The recommendations for statistical methods [14] were to *Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)*. The recommendations included:

- Using only descriptive statistics to report harms is perfectly appropriate in most RCTs because most trials lack power to test harms-related hypotheses and indeed have no explicit prespecified harms-related hypotheses. If investigators combine data for different adverse events into one outcome measure, they should describe each combination, cite the dictionary that lists the definitions of the adverse events, and state whether they decided the grouping of events post hoc or a priori.
- Incidence rates, period prevalence rates, and point prevalence rates may provide complementary information about the occurrence of an adverse event. Kaplan–Meier curves showing cumulative incidence of important adverse events can be helpful. Simple summaries with person-time denominators (for example, median months after treatment) can be misleading if the event occurs only after extended treatment and long follow-up, and most participants had short follow-up and therefore no events.

- For continuous variables (such as reported for most laboratory tests), means and SDs or medians and interquartile ranges may provide an aggregate picture, but they may not convey information on extreme values that correspond to severe toxicity.

Despite these guidelines for improving the standards of safety reporting in journal articles, there are still inconsistencies and discrepancies between what adverse events are reported in sponsors database or clinical trial registry and what is reported in the journal article [10, 15, 16].

A notable example of obscured safety reporting is from the VIOXX™ Gastrointestinal Outcomes Research (VIGOR) trial [17–19]. The original publication in 2000 did not include three additional myocardial infarctions that occurred in the rofecoxib (vioxx) group and none missing from the naproxen (control) group. The lack of reporting of these three myocardial infarctions was attributed to an irregular analysis approach that was not described in the publication whereby the study reported SAEs that occurred at different time windows after the end of the trial for cardiovascular and gastrointestinal events (gastrointestinal events were counted for 1 month longer than the cardiovascular events). The data irregularity was detected when a comparison was made with the SAE reports that were submitted to the FDA. The publication concealed the cardiovascular risk even further by presenting the hazard of myocardial infarction as if naproxen was the intervention group (relative risk 0.2, 0.1–0.7) and without reporting the absolute number of cardiovascular events, even though all other results were presented appropriately with rofecoxib as the intervention group [20]. Vioxx was voluntarily removed from the market by Merck on 30th September 2004 following the data safety monitoring board overseeing a long-term study of Vioxx recommended that the RCT in patients at risk of developing recurrent colon polyps be halted because of an increased risk of serious cardiovascular events, including heart attacks and strokes, among study patients taking Vioxx compared to patients receiving placebo. Merck has paid $6billion in compensation to over 35,000 people or relatives who had cardiovascular events while taking the drug [18, 19]. During investigations into the Vioxx saga [20] it also became apparent that the Merck was not very transparent in releasing its research findings and several early large clinical trials of Vioxx were not published in the academic literature for years after Merck made them available to the FDA, preventing independent investigators from accurately determining its cardiovascular risk using meta-analysis.

To increase transparency and ensure that trial results and safety data are reported, the 2007 US Food and Drug Administration Amendments Act (FDAAA 801) required that, after September 2008, results from clinical trials conducted in the United States

be made publicly available at ClinicalTrials.gov within 1 year of the completion of the trial [21, 22]. The European Union followed suit, making it mandatory to post a summary of the clinical trial results in European Clinical Trials Database (EudraCT) within 6–-12 months of trial completion for all registered trials that are completed after 21 July 2014. However, this will be dependent on sponsors providing reliable, accurate, and complete data [23].

The FDA also introduced a new regulation that was effective from 28 March 2011, with a change in requirements of what AE/SAEs needs to be reported to the FDA and ethics committees [24]. It is expected that this new approach will reduce reporting-data noise that may mask true signals of significant adverse events, and what is reported is more relevant to patient safety. The new regulation also went onto state that the sponsor must analyze in the aggregate events that are not interpretable as single cases and report them only if there is an observed imbalance between the drug-treatment group and a control group suggesting that the event is caused by the drug, thereby increasing the importance of signal detection in RCTs.

5 Analyzing Safety Data in a Single Clinical Trial

Analysis of safety data from a single RCT is more difficult than efficacy analyses, the analyses are underpowered, with no predefined hypothesis and the issue of potential adjustment for multiplicity. Signal detection from RCTs is better conducted on drug safety databases containing safety data from multiple trials. However, these safety databases can be difficult to analyze due to the heterogeneity of the studies included and they are not always available externally to independent organizations which can lead to assessing safety of a product by the analysis of data from a single clinical trial. The considerations for analyses are outlined below.

5.1 Defining the Study Population

When analyzing the safety data from an RCT, the first stage is to define which of the trial participants are included in the safety analysis. Efficacy analyses in RCTs typically use the intention to treat (ITT) population, whereby participants are analyzed by the treatment group they were randomized to and not necessarily the treatment they actually received. ITT analysis includes all patients including those who prematurely stop taking the investigational product. The CONSORT group recommend using the ITT approach for safety data analysis in general to reduce potential bias [14]. However, the CIOMS VI working group [25] suggested that ITT analyses are not always the most appropriate for analyzing safety data, as the results may have a tendency to underestimate the true differences between the groups. CIOMS VI suggested that other analysis populations, such as only those subjects who received

a prespecified minimum number of doses of the study drug, might be more appropriate for analysis of safety data. When selecting an "on-treatment" or treatment emergent population considerations should also be made around events with a long latency and whether to include (or collect) events that occur after the discontinuation of drug therapy, often a window of 30 days after discontinuation of drug therapy is used. This window should be prespecified and described when presenting the safety data unlike in the example from the VIGOR trial where cardiovascular and gastrointestinal events had different time windows and were not detailed in the publication. It is important to prespecify the chosen study population as multiple analyses by different study populations could be perceived as a method to present the results that best support the authors' views as unbiasedness and power are not always in the same direction [26].

5.2 Coding of SAEs

Events should be coded using a structured standardized medical terminology such as Medical Dictionary for Regulatory Activities (MedDRA) to assist with analyses and combining data from multiple trials. MedDRA was developed in 1994 by pharmaceutical companies and regulatory agencies to overcome the difficulty of multiple dictionaries being used to categorize adverse events, such as WHO's Adverse Reaction Terminology (WHO-ART), the Thesaurus of Adverse Reaction Terms (COSTART), or the International Classification of Diseases (ICD 9 and ICD 10), and frequently these were customized for a specific trial. Dictionaries such as MedDRA provide a hierarchical structure whereby events can be coded at the lowest level term, e.g., feeling queasy, but grouped for analysis at a higher level to provide sufficient numbers of events to be compared, *see* Fig. 2 for MedDRA hierarchy. Use of different terminologies in RCTs makes comparison between trials challenging. Although there are mapping tables that are available to convert many terminologies into MedDRA, careful consideration needs to be made when analyzing results especially where no apparent events were reported, where there was no suitable code in the coding dictionary, an expensive and time-consuming option can be to recode all the SAEs from the verbatim text.

An advantage of MedDRA is that it has Standardized Medical Queries (SMQs), which is a grouping of terms from one or more System Organ Classes (SOCs) related to defined medical condition or area of interest, e.g., acute renal failure. The list of SMQs is not exhaustive but they could be considered useful groupings for analysis of safety data from clinical trials where the number of events is small. Although signal detection in post marketing databases has looked at appropriate data mining techniques to optimize the structure of MedDRA, this is not common practice for clinical trials where they often solely report at PT level [27].

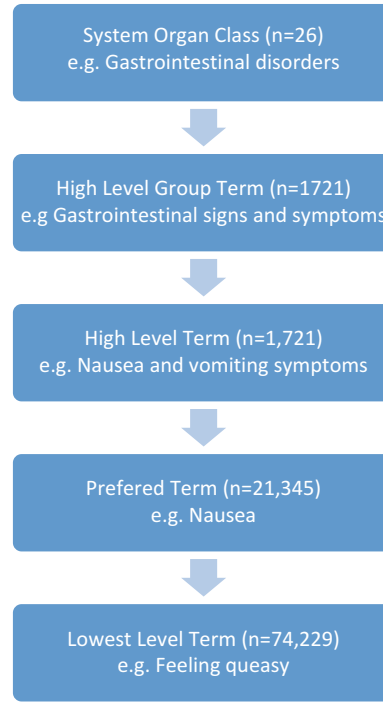

Fig. 2 Hierarchy structure of MedDRA

MedDRA as well as having widespread use in RCT coding, is also a standard in spontaneous report coding facilitating comparison and contextualization across the two data sources once a product is marketed. There are challenges with retrospective analyses of trials where the SAEs were coded into a different terminology, options are to recode into MedDRA or to use mapping dictionaries when available but be aware that possible mislabeling of events could occur.

Mislabeling of adverse events can skew the interpretation of a drug's harms. One example of this is from when the antidepressant paroxetine was tested in adolescents in an infamous trial that initially declared that the drug was "generally well tolerated" [28]. The paroxetine group, however, had an overrepresentation of "emotional lability." After scrutiny by the FDA and independent experts, it turned out that this term was only used when patients had "suicidal tendencies." Other cases of suicidal tendencies had been coded as aggression or "exacerbation of depression" [29].

The Clinical Data Interchange Standards Consortium (CDISC) has been created with a mission to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare. CDISC standards are vendor-neutral, platform-independent, and freely available via the CDISC website (www.cdisc.org).

5.3 Determining the Events to Be Analyzed

RCTs collect different safety data, it is important to determine which events have been reported and will be analyzed, it may be SAEs, AEs, and SAEs, or Serious Unexpected Serious Adverse Reaction (SUSARs). The investigators or safety team may have reported if they suspect the event was related to the investigational product. Typically SAEs that are outcome events are adjudicated by an independent person reviewing the blinded medical records to ascertain if the event met the outcome definition for the trial, these adjudicated events are considered more robust. The comparator treatment might be placebo, usual care, or another medication. It is important to bear in mind that trial participants may have more than one event and may have repeated events.

5.4 Descriptive Analysis

The crude and exposure-adjusted incidence rates are frequently used to evaluate AE data in clinical trials. For a valid estimate, both methods require some statistical assumptions that are often not valid in safety datasets of clinical trials. Both methods fail to provide the time or exposure duration trajectories of AE profiles over study periods, especially for all events and in particular for two or more events that occur to the same subject. These trajectories of AE profiles are important to understand the cumulative history of all possible AEs over study periods. It is possible that some AEs are correlated, and one type of AE or several AEs jointly might lead to another type of delayed AE in the future. For example, abnormalities in some indicators of heart functioning might lead to heart attack in the near future.

If there are comparisons made between the groups there are difficulties interpreting P values. For example, in a typical large-scale RCT there may be 500 individual AE terms. If P values were calculated for each pairwise comparison, then by chance alone one would expect; 25 events (5%) to have $P \leq 0.05$ and 5 events (1%) to have $P \leq 0.01$. Consideration should be made around using SMQs which group related terms, increasing the number of events and power while also reducing the number of individual terms to be compared, not all terms are included in SMQs but those that are can be removed from the individual analyses. Graphical presentation of safety data can also help with interpreting and identifying potential signals [30]. The AEs are ordered by relative risk so that events with the largest increases in risk for the active group are at the top of the display (*see* Fig. 3).

Analysis of adverse event data from clinical trials can be fruitfully formulated as a data-mining exercise rather than a problem for hypothesis testing; that is, seeking to identify or prioritize adverse events that may be affected by the treatment, rather than starting out with a large number of null hypotheses and analyzing the data to look for formal null rejections.

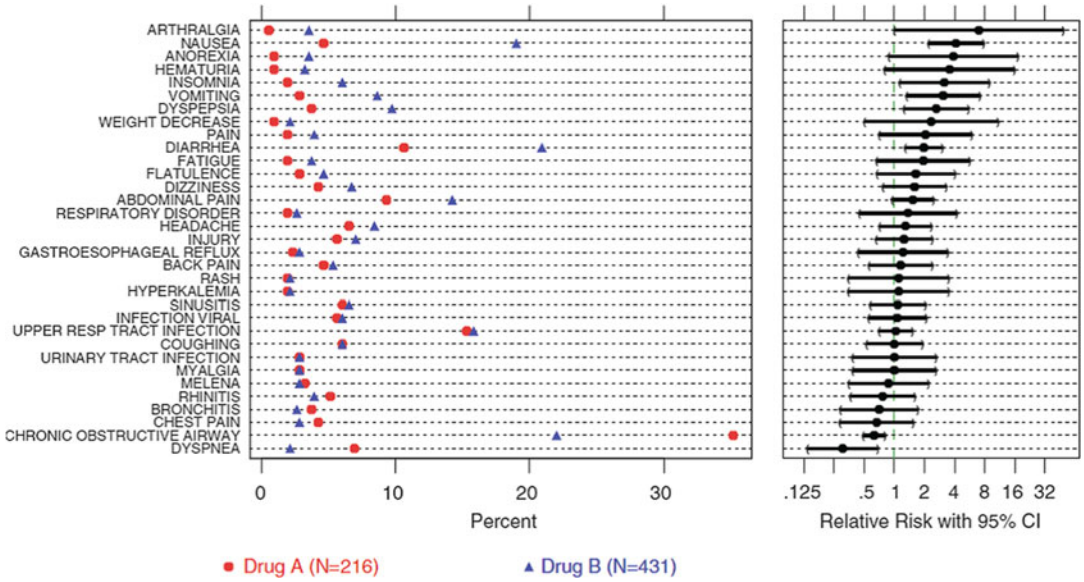

Fig. 3 Most frequent on-therapy adverse events by relative risk [30]

5.5 Bayesian Data Mining

In 2004, Berry and Berry proposed a novel Bayesian hierarchical modeling approach in analyzing binary outcomes in adverse event data in clinical trials to deal with the multiplicity problem [31]. However, this has not been adopted in clinical trials, despite more recent modifications that include graphical representation to display flagged signals to guide the clinical review and the proposal that it is appropriate for individual RCTs [7, 32]. Berry and Berry stated that there are at least four considerations in determining whether to flag an adverse event as a signal. The first two are considerations that are common in the frequentist approach to multiplicity: (1) the actual significance levels; (2) the total number of types of AEs. The last two can be considered in Bayesian modeling (3) the rates of AEs not being flagged including their similarity with those being flagged; and (4) the biological relationships among various AEs. Given that most AEs are now coded in the hierarchical MedDRA structure and AEs in the same SOC are more likely to be similar, Berry and Berry proposed a borrowing power rather than just considering coded terms as independent of one another. For example, if differences in several cardiac vascular events were observed, then each would be more likely to be causal than if differences came from medically unrelated areas (say, if they arose from skin, neurological, thrombosis, and cancer). Bayesian hierarchical modeling allows a scientific, explicit, and more formal way to take this into consideration.

5.6 Pattern Data Mining

Pattern data mining in adverse events was performed on 11,362 adverse event reports extracted from 4317 clinical trials on

clinicaltrials.gov [33]. They identified two types of patterns; co-occurrence of symptoms e.g., (Dizziness, Headache) => (Pain) shows the common co-occurrence of symptoms for a patient in pain. The second, sequential event, e.g., (Cardiac Failure, Convulsion) => (Death) indicates that cardiac failure and convulsion events might lead to the death of a patient. The result patterns are ranked by the Lift score (also called interest), which is a measure of the strength of an association pattern, and very similar to the measures of disproportionality routinely used in signal detection of spontaneous reports. Lift scores larger than 1 indicate positive association between X and Y. The higher the lift score, the stronger the association of the pattern, the authors used a cutoff of 4 for strong association. This study generated many signals that would need further evaluation. There is a need for additional studies into pattern data mining in adverse events from clinical trials to fully assess the utility of this approach.

6 Program Safety Analysis Plan

The Safety Planning, Evaluation and Reporting Team (SPERT) was formed in 2006 by the Pharmaceutical Research and Manufacturers of America. SPERT recommended that sponsors develop a PSAP as a tool to plan early for the program-level safety data analysis [34]. The PSAP is a living document (amended as needed in response to the emerging safety profile) that eventually will form the basis for the statistical analysis plan for the Summary of Clinical Safety. The PSAP may also specify methods for signal detection among common adverse events including multiplicity adjustments for multiple testing. For example, the ICH E9 Guideline (ICH, 1998) states that for safety data "statistical adjustments for multiplicity to quantify the type I error are appropriate, but the type II error is usually of more concern," whereas the CPMP Points to Consider on Multiplicity (CPMP, 2002) takes an opposing position, stating that "an adjustment for multiplicity is counterproductive for considerations of safety." The report of the CIOMS Working Group VI (CIOMS, 2005) contains a great deal of discussion about multiplicity and power, but ultimately does not take a position for or against multiplicity adjustment, advising only that "Since we will always be concerned about the lack of power in looking for adverse effects, if adjustment for multiple comparisons is made, then it should use a more sensitive method than Bonferroni." There was a consensus in the SPERT discussion that multiplicity should be addressed in analyzing adverse events that were not prespecified.

7 SPERT: 3 Tier System for Analyzing AEs and Tackling Multiplicity

7.1 Tier 1: Prespecified Detailed Analysis and Hypothesis

These are suspected "signals" that are prespecified and undergo a detailed evaluation including a comprehensive statistical analysis such as time to event plots and rate ratios, including confidence intervals and *p* values.

7.2 Tier 2: Signal Detection Among Common Events

Common events are described as those not prespecified and in tier 1, but are common based on a predefinition. SPERT propose that the "Rule of 4" is a reasonable way to discriminate between events in Tier 2 and those in Tier 3 for RCTs with 400 or fewer participants per group, if there are four or more patients with the MedDRA preferred term in any treatment group, that preferred term will be included in Tier 2. Four was chosen because unless the split between two treatment groups is at least 4 and 0, the *p*-value will not be less than 0.05 (for most reasonable sample sizes), and confidence intervals will be very wide. Larger trials could use a larger cutoff but this should all be prespecified. These events should be reported with risk differences, risk ratios, or odds ratios including confidence intervals and/or *p*-values adjusted for multiplicity where the method is prespecified.

7.3 Tier 3: Descriptive Analysis of Infrequent AEs

All events that are not in Tier 1 or 2 are included in Tier 3. These are reported with descriptive statistics (*n*, %, and possibly rates per persontime) but without *p*-values or confidence intervals. Clinical judgement of these events is important as some may be serious. Tiers 2 and 3 are where signal detection can occur.

8 Meta-Analysis of Safety Data from RCTs

Meta-analyses of safety data from multiple trials has the potential to increase the power for detecting drug safety signals. Meta-analysis should ideally be preceded by a systematic review and search of clinical trial registries to ensure all relevant trials are included, rigorous observational studies or if examining a company safety database spontaneous adverse drug reaction reports (ADR) can potentially be included. The power of the meta-analysis depends on the number of events, not the number of trials. Considerations need to be made around the heterogeneity of the RCTs, events that are reported, doses used and an assessment on the risk of bias and quality of the evidence needs to be made. Combining RCTs and post marketing data can also be used to investigate safety signals as was conducted for sildenafil by combining 67 RCTs and post marketing ADR reports [35]. Recently, there have been efforts to conduct network meta-analysis where indirect comparisons are inferred based on other pair-wise direct comparisons.

9 Limitations with Safety Signals Generated from Clinical Trials

One of the main challenges with analyzing safety data is much of it is performed at a single trial level, which in themselves are already underpowered for safety outcomes. RCTs often recruit low-risk population and as such may be further underpowered to identify safety signals and also the findings may not be generalizable to the whole population. Safety data is subject to many interpretative difficulties, including ascertainment biases and inflated false positive rates due to the multiplicity of comparisons and imprecision of estimates inherent in analysis of small numbers.

10 Future Perspectives

There is a growing trend to conduct phase IV trials in the "real-world" using administrative data to collect outcome events, this potentially reduces trial participant burden, reduces costs and time taken to conduct the trial. Techniques for data mining for side effects in the administrative data used in RCTs need to be further explored. Other measures to optimize trial conduct that are currently being explored include developing a sufficiently large placebo controls database that would provide expected distribution of expected side effects in the representative populations both during the planning and conduct of the trial which would supplement, not eliminate, the placebo arm of future clinical trials.[36].

The sharing of individual patient safety data would facilitate meta-analyses of safety data and increase the power to analyze rare adverse events. Adoption of Bayesian hierarchical models as part of routine analyses of safety databases and transparent reporting of the results will require a paradigm shift. Fundamentally communication with the public needs to be improved on global scale so they have a clearer understanding of the risks of new medicines, lack of evidence for harm does not mean the drug is safe.

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Chapter 6

Developments and Future Directions of Prescription-Based Observational Cohort Pharmacovigilance

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Abstract

Lessons learnt from recent examples of drug safety hazards include the acknowledgment of discordance in learning about safety of new medicines during development as compared to during use within routine clinical practice, post marketing. Changes in pharmacovigilance regulations and legislation have given greater weight to the importance of post-marketing observational research and understanding more regarding natural variation in patients and their responses to treatment. In this chapter the origin and evolution of prescription-based event monitoring is described, with examples of real-life studies presented to offer some insight into the contributions and challenges of these post marketing systems in relation to monitoring the safety and use of new medicines.

Key words Prescription-based event monitoring, Post authorization safety studies, Observational research, Drug utilization

1 The Origins of Prescription-Based Observational Cohort Monitoring Schemes

Thalidomide was the biggest turning point for drug safety worldwide. Thalidomide was developed as an anticonvulsant drug in the 1950s, but marketed as a tranquilizer. During testing scientists observed that the drug was not lethal at overdose—unlike barbiturates that were commonly used at that time. Animal tests did not include monitoring for congenital effects during use in pregnancy. Since the drug has also anti-emetic properties, it became popular with pregnant women. Introduced originally in West Germany in 1956, thalidomide was marketed in 1958 in the United Kingdom as Distaval®. By 1960, doctors became concerned about possible side effects. No link was made until November 1961, when investigations at obstetric units in West Germany showed a large rise in the number of children born with limb deformities. By the time thalidomide was withdrawn, over 10,000 babies had been born deformed [1]. This appalling human toll led to the establishment of drug regulatory bodies in a concerted effort to ensure adequate testing of drugs before marketing and pharmacovigilance systems

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to identify drug safety hazards earlier. The lesson learnt was that no drug which is pharmacologically effective is without hazard.

1.1 The United Kingdom

In the UK, the initial effort to improve safety monitoring was based on the formation of the advisory body the Committee on Safety of Drugs (subsequently the Committee on Safety of Medicines—CSM and now the Commission on Human Medicines—CHM) [2]. One of the responsibilities of this committee was to collect and disseminate information relating to adverse effects of drugs. In May 1964 the Yellow Card Scheme was launched within the United Kingdom. This represented the start of organized systems of voluntary spontaneous ADR reporting in Europe. The identification of previously unsuspected hazards depended not only on the ability of doctors to distinguish events that were probably or possibly drug-induced from those that occur spontaneously or as a complication of natural disease, but also on their willingness to transmit their suspicions to the safety committee. Importantly, these activities recognized that unexpected hazards could occur with old drugs as well as newly licensed drugs. However, in the following years, it became clear that the post-marketing surveillance system was in need of augmentation. In 1976, practolol (a selective beta-blocker) was withdrawn following development of oculomucocutaneous syndrome in hundreds of people [3]. That this was a side effect of the drug went unrecognized for 2 years, probably because early symptoms resembled conjunctivitis. This incident demonstrated forcibly that the Yellow Card system could fail to prevent a large-scale incident—principally because doctors did not, for a variety of reasons, use it. It was estimated at that time that the proportion of ADRs actually reported was thought to be less than 10% of serious reactions and less than 1% of significant reactions; one explanation being difficulty in distinguishing adverse drug reactions from events that occur spontaneously. It was acknowledged that the spontaneous reporting scheme was best placed to detect dramatic and very rare adverse events (e.g., 1 in 1,000,000 patients exposed) which contrasted with the ability of clinical trials to detect common adverse events (e.g., 1 in 100 patients exposed). However there were calls for a system to bridge the gap between these extremes, detecting ADRs that occurred uncommonly (e.g., 1 in 1000 patients exposed).

Several systems were proposed in the UK with limited success or were considered too expensive, including "registered release" of new drugs by Professors Dollery and Rawlins in 1977, where pharmaceutical manufacturers should provide evidence of use of the drug with freedom from toxicity in a restricted group of patients (5000–10,000 for a commonly used drug) [4]; "recorded release" by Professor Inman in 1977, which required prescribers to complete a special FP10 prescription form that would be sent for registration to a central agency and follow-up would include completion of a questionnaire by the prescriber to identify adverse events [5]; and "monitored release" by Lawson and Henry also in 1977 in which the

dispensing pharmacist would transcribe information onto a registration form that would be submitted to a central agency and follow-up would be directly undertaken with prescribing physician [6]. A scheme described as the "Retrospective Assessment of Drug Safety (RADS)" was suggested by the CSM and approved by the General Medical Services Committee. This too would monitor all patients taking a new drug through the use of special prescriptions, with the intent to generate safety signals, but the proposal was hindered because of economic difficulties [7]. In 1980 a pilot study was proposed by the Post marketing Drug Surveillance Research Unit at the University of Southampton, run by Professor Bill Inman. This pilot study was for a scheme called Prescription-Event Monitoring to be conducted in the South of England Wessex region, the principal objective of which was to provide an improved method for early detection of potential drug hazards, not only for new products but established medicines in accordance with essential criteria (Box 1). The pilot study was approved by the General Medical Services Committee in December 1980 [8].

Box 1 Essential Criteria for Prescription-Event Monitoring (PEM) as an Improved Method for Early Detection of Potential Drug Hazards [7]:

(I) PEM should measure the relative incidence of adverse events in populations of patients treated with various drugs. To achieve this it will be necessary to obtain both the numerator (the adverse event) and the denominator (the number of patients treated).

(II) Events rather than adverse drug reactions should be recorded, irrespective of whether or not they are related to treatment. This had several advantages, perhaps the greatest of which is that no medical opinion about the probability of a causal relationship between drug and event needs to be given.

(III) PEM is conducted retrospectively and should be clearly distinguished from post-marketing (Phase IV) clinical trials in which doctors and patients are recruited in advance. In PEM there should be no pre-selection of patients, and the study should not in any way interfere with normal prescribing or record keeping.

(IV) PEM should provide for long-term follow-up. It should be appreciated that, at the present time, it is very unlikely that a doubling or event greater increase in the incidence of cancer or other serious diseases caused by a drug would be detected.

(V) PEM would in no way affect freedom to prescribe.

(VI) Because doctors would not be reporting opinions about the cause of adverse events occurring during treatment, the medico-legal risk of participation in PEM should be considerably less than that associated with other currently available methods of drug monitoring.

(VII) Collaboration in PEM would be voluntary.

(VIII) The methods of recording information should be simple and not time-consuming.

(IX) PEM should be inexpensive.

In 1982, benoxaprofen (an NSAID) was withdrawn following reports of fatal hepatotoxicity and renal failure received by the CSM [9]. In June 1983, a CSM Working Party made recommendations to address primarily the under-reporting of ADRS and endorsed the PEM observational cohort monitoring system to provide a complementary system to actively and systematically monitor new drugs destined for widespread, long-term use in primary care. The underlying purpose is to extend the safety database of a new drug to at least 10,000 exposed individuals [10]. In 1986, the Post marketing Drug Surveillance Research Unit was reconstituted as a charitable trust and its title was altered to the Drug Safety Research Unit (DSRU). The Drug Safety Research Trust is a registered independent charity (No. 327206), which now operates in association with the University of Portsmouth.

The prescription-based observational cohort monitoring system remains one of the original principal activities of the DSRU. Data collection begins immediately post-marketing and aims to provide information on safety and use of a new medicine in the first cohorts to which it is prescribed. Patient identification relies on data from dispensed National Health Service (NHS) prescriptions provided securely to the DSRU by the Business Services Authority of the NHS (BSA)[1] whose responsibilities include the remuneration of pharmacists for NHS dispensing services. For each new user patient identified, a questionnaire is sent (in chronological order of prescription issue date) to the prescribing primary-care general practitioner (GP). In the early years this questionnaire was known as a "Green Form". In accordance with the Inman criteria (Box 1), the Green Form was simple and designed for expedited completion, especially since there was no remuneration given, and in particular GPs were requested to provide information on adverse events observed for the given patient, irrespective of whether there was suspicion of drug causality (Box 1). Patients were subsequently included in the cohort for analysis upon receipt of a completed Green Form by the DSRU; this process continued until the target sample size was achieved.

This prescription-based cohort event monitoring scheme was at inception and remains the only national scheme in England available to all primary care general practitioners (GPs), in addition to the Yellow Card Scheme, used to monitor the safety of recently marketed medicines, under the conditions of general practice. The UK PEM studies are conducted in accordance with national and international guidelines [11–14]. A summary of the study design and data collection process for PEM is presented in Table 1. Information of two other systems in Japan and New Zealand is also presented in Table 1. A synopsis of these two schemes is provided

[1] Formally known as the Prescription Pricing Division (PPD).

Table 1

Characteristics of standard non-interventional observational cohort prescription-based event monitoring systems in England, Japan, and New Zealand

Study Characteristics	PEM	IMMP	J-PEM
Country	England	New Zealand	Japan
Selection of Medicines	According to defined criteria- independent of regulator	According to defined criteria- with regulatory consultation	Not published
Internal comparator	No	Yes	
Setting	Primary care	Primary and Secondary care	
Route of establishing cohort	Dispensed Prescriptions via national prescription remuneration scheme	Dispensed Prescriptions within pharmacy networks	
Special conditions	New User	New user with longitudinal prescribing history	New user
Start of observation	Market launch		
Period of follow-up	Censored at 6-12 months	As long as prescribing continues	Censored at 6 months
Health care professional surveyed	Medical Clinician (General Practitioner)	Medical Clinician and Pharmacist	
Survey frequency	Single	Multiple	
Desired sample size	10,000		Study specific
Primary Outcome and exposure data source	Drug utilisation, event [a] and selected risk factor data from secondary use of prescriber held patient medical records	Drug utilisation, event [b] and selected risk factor data from secondary use of prescriber held patient medical records, pharmacy dispensing records	
Additional data sources	None	Record linkage – spontaneous reports and national morbidity and mortality databases	None
Signal generation	Assessment of event listings risk and rate differences between time period at interim and final analysis; every questionnaire evaluated by scientific research fellow; events of interest evaluated by at least one clinical research fellow.	Assessment of event listings throughout study; every event report evaluated by at least one clinical assessor	
Ethics and consent	Consent not required; ethics waiver[c]	Patient opt out system; ethics waiver[d]	Consent required

Similarities highlighted in gray

[a]Event definition in UK original PEM: any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter into the patient's notes

[b]Event definition in IMMP: any new clinical experience since the patient started the medicine, including all new clinical events (common and minor ones), worsening of a pre-existing condition, abnormally changed laboratory values, unexpected failure of therapeutic effect, any possible interactions, accidents, pregnancies and all deaths

[c]Formal waiver under Section 251 of NHS Act 2006

[d]Formal waiver national Ethics Committee 2004

below. The principle difference between PEM and these two schemes is that the UK method is reliant on the unique structure of the NHS which not only has a central processing system for NHS prescriptions but also requires the general population to be registered with GPs. This in turn permits creation of longitudinal medical records that hold all healthcare consultations and interventions that occurred during the life of each patient. In addition to providing valuable drug utilization information the method provides estimates of incidence rates for events reported in the exposed cohort, and also provides the opportunity for further clinical evaluation of selected events of interest using bespoke follow-up questionnaires. Further information on analytical approached is provided later in this chapter.

1.2 Observational Cohort Prescription-Based Monitoring in New Zealand

In New Zealand (NZ), the practolol incident was also the stimulus for supplementing the spontaneous reporting activities with an early post-marketing program. The additional program was called the Intensive Adverse Reaction Reporting Scheme which started in 1977 [15, 16]. The early version of the intensive monitoring system followed a similar framework to the "monitored release" system proposed by Lawson and Henry [6] in which cohorts of new users were proactively established through pharmacies, and adverse events (including but not exclusive to ADRs) captured through more intensive reporting by pharmacists, at various time points after start of treatment. This was because unlike in the UK, there was (and is) no centralized scheme for reimbursement to pharmacists for dispensation. The scheme was extended shortly after to improve response rate by the capture information direct from prescribers for the drugs under surveillance once the product has been marketed for 6 months (called "event-recording surveys"). Drugs monitored in this way on a national scale from almost every pharmacy in New Zealand included labetolol, perhexiline, and sodium valproate [17]. Furthermore, where appropriate, concurrent monitoring of two or more medicines was possible which provided opportunities for a suitable comparator. The use of prescriber-completed questionnaires in PEM arose from this concept, so the method was effectively the first PEM program worldwide. In 1983, the NZ scheme was renamed the Intensive Medicines Monitoring Programme (IMMP). Located in the University of Otago in Dunedin, NZ, this scheme operated within the NZ Pharmacovigilance Centre (NZ PhvC) alongside the Centre for Adverse Reactions Monitoring (CARM) [18]. A brief synopsis of the IMMP cohort event monitoring approach is also shown in Table 1.

Up to 2008, selection of medicines for monitoring by the IMMP was prioritized according to specific conditions including expectations of widespread use, safety issues have been identified pre-marketing or with other drugs within the same class, the risk of interest is uncommon so any impact from therapy would change risk: benefit balance. Following changes to the drug approval

process in NZ in 2008, the number of studies declined, since the plans for post-marketing studies of newly marketed studies did not require an IMMP study to be conducted in NZ. Although Medsafe funding of IMMP ceased in June 2012, the program continued to function on residual research funding sources until they expired December 2013. The system remains intact at the NZPhvC in case funding is identified in the future.

1.3 Observational Cohort Prescription-Based Monitoring in Japan

In the early 1990s in Japan, it was apparent that there were difficulties in conducting pharmacoepidemiological studies because systems for systematically obtaining longitudinal medical records were not available, despite advances in the development of hospital information systems [19]. Insurance was required for health service provision; however, these schemes were not systematically linked to hospital systems. Furthermore, boundaries of care provided between specialists and general practitioners overlapped. It was therefore postulated that the PEM methodology could be extended into Japan (J-PEM). Between 1996 and 1998 a pilot study was conducted in which pharmacists would be used as the source for systematically identifying patients and prescribers following first dispensation of the new medication. As for the IMMP, there was no centralized process for prescription reimbursement. An additional aspect was the identification of a candidate patient newly prescribed a control medication. This offered the potential to explore the impact and magnitude of bias arising from confounding by indication on hypothesis generation [20]. An early limitation proved to be sample size, low participation rates of pharmacists, and low response rate of prescribers. A second pilot study was initiated in 1998 to monitor the safety of the first angiotensin II receptor antagonist (losartan), with concurrent control candidate drugs prescribed for similar indications [21]. A difference in nature and type of event reported by pharmacists was noted whereby some minor events were exclusively reported from pharmacists. This could in turn introduce a higher rate of non-ADR events (false signals). Nevertheless based on the finding of the two pilot studies, a permanent system of J-PEM was proposed. Unfortunately, due to funding issues associated with discordance between needs of PV planning and goals of pharmacoepidemiological research, the scheme was not formally adopted (Personal communication K Kubota September 2015). A brief synopsis of the J-PEM cohort event monitoring approach is also shown in Table 1.

These three examples recognize the importance of prescription-based cohort event monitoring in providing useful insights into patterns of utilization and the adoption of a new drug in clinical practice as well as providing active pharmacovigilance. In the remainder of this chapter, examples of real-life studies will be presented specifically in relation to recent developments in the UK prescription-based cohort event monitoring systems, now known as Modified Prescription-Event Monitoring (M-PEM) [22], and Specialist Cohort Event Monitoring (SCEM) [23].

2 Risk Management and Modified Prescription-Event Monitoring: Responding to Change

The importance of observational studies as a whole has increased dramatically since pharmacovigilance legislation was revised globally to extend the assessment of benefit versus risk from preclinical to cover the full life-cycle. In the EU, the new Pharmacovigilance Legislation came into force, July 2012 [24]. Accordingly every new medicinal product must have comprehensive Risk Management Plan (RMP) in place as part of its approval and to retain its approved status [25].

In 1998, the first modification to PEM was introduced whereby the "Green Form" questionnaire was updated to identify subsets of patients with important cardiovascular risk factors for an anti-impotence drug (Viagra) [26, 27]. This modification to the questionnaire design was in response to the need for additional information requirements in support of risk management of medicines [28]. In parallel with pharmacoepidemiological developments in general [29, 30], a number of further enhancements have since been made to the method to facilitate more targeted safety surveillance of risks identified within the RMP[2] enhance data quality and provide increased scope for more robust data analysis in terms of signal generation and hypothesis strengthening. PEM methodology in the UK relies on the identification of a single inception cohort assembled on the basis of a common exposure (the medication under surveillance). Each study is national in scale and attempt to sample for all GPs in England (*see* Fig. 1 for distribution of participating GPs in England). It is possible that the cohort may be subject to selection bias, arising from phenomena such as "channeling[3]" or "switching[4]," which may affect the generalizability of study results. Furthermore, selection bias may be introduced through non-response, which becomes important if the characteristics of the study cohort are systematically different to non-responders.[5] Another limitation of PEM was paucity of information on baseline characteristics for the whole cohort such as prior medical history, concurrent morbidities, as well as treatment patterns.

[2] Identified risks (known from clinical trials), potential risks (effects not observed in trials but expected e.g. class effects) and missing risks (identified and potential effects that may occur in populations not studied).

[3] Preferential prescribing to subsets of patients defined by a specific characteristic, such as having a condition resistant to previous therapy or pre-existing risk factor that may be a precaution for use or contraindication to certain treatments [31].

[4] Past experience with an alternative drug that modifies the risk of adverse events associated with current use of the study drug [32].

[5] For example, there may be a "depletion of susceptibles" if GPs selectively respond for those patients who tolerate and continue to use the drug. The reverse is also possible whereby GPs may be more likely to respond if patients have experienced adverse events with a new medicine [33].

Fig. 1 Distribution of participating GP practices in England (2013)

The Modified Prescription-Event Monitoring design subsequently evolved in attempt to overcome some of these limitations through innovation in design (bespoke targeted outcome surveillance and data collection), application of new analytical methods, and remuneration to prescribers. M-PEM retains the advantages of the original method (in monitoring general safety and identification of unexpected risks) but with enhancements that permit specific questions to be addressed in accordance with the needs of a RMP [22].

2.1 Modified Prescription-Event Monitoring: Design

Specific details of the M-PEM study methodology is provided elsewhere [34]. In brief, for both PEM and M-PEM studies, primary care dispensed prescription data sources and medical records-based data sources are used to provide data for eligible patients in accordance with the Inman criteria (Box 1). Exposure (index/exit) data are derived from dispensed prescriptions issued by general practitioners (GPs) (Fig. 2). The general design is retrospective since exposure status and outcomes have already occurred prior to the survey being conducted.

A post-authorization safety study (PASS) is defined as: any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures. A PASS

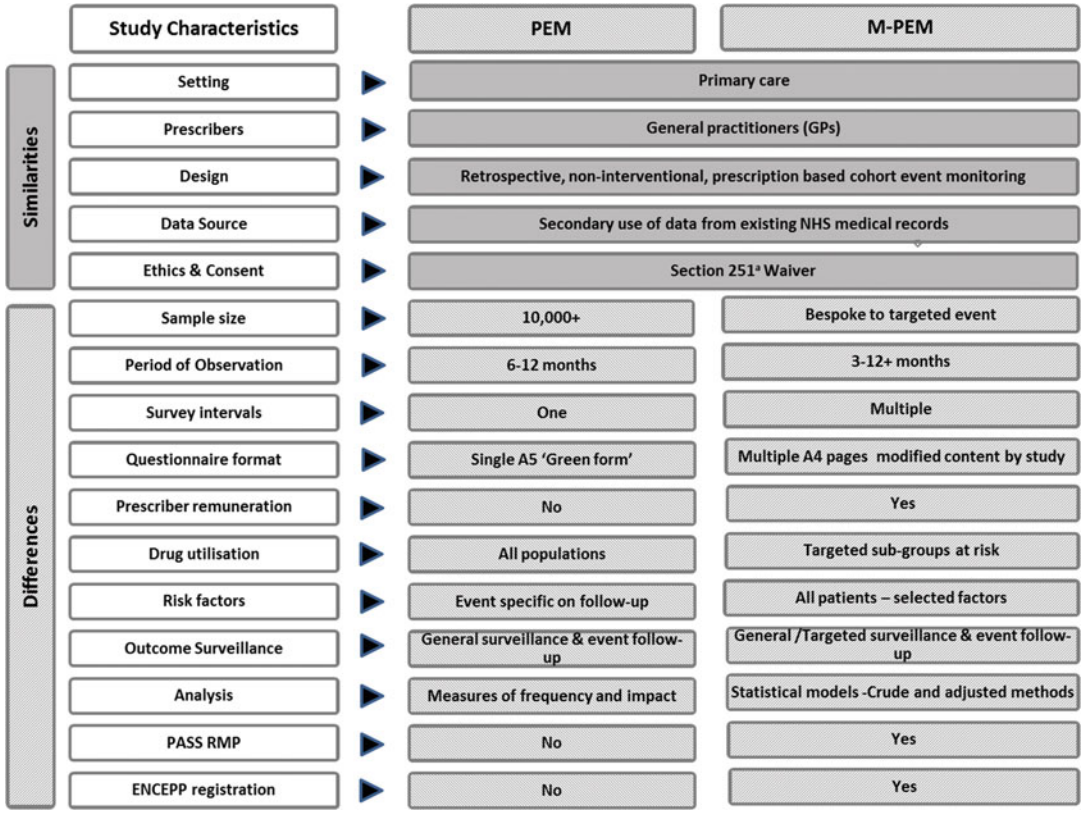

Fig. 2 Characteristics of PEM and M-PEM studies. Section 251 Waiver: under Section 251 of the National Health Service Act 2006, the DSRU has received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009); *ENCEPP* European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance, *NHS* National Health Service, *PASS* Post Authorization Safety Study, *RMP* risk management plan

may be initiated, managed, or financed by a Marketing Authorization Holder (MAH) either voluntarily or following an obligation imposed by a competent authority. PEM and M-PEM studies fulfil cumulatively the definition of a non-interventional PASS in that:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorization;
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study;
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Other types of non-interventional studies also include those that are prospective (where subjects are recruited before outcomes

of interest are developed) with de novo-primary data collection, provided the conditions set out above are met [35]. However non-interventional studies with primary data collection may be subject to adverse reaction reporting requirements [36]. Since prescription-based cohort event monitoring relies on prescribers abstracting information from NHS medical records, data collection is regarded as "secondary use." This means that the legal requirements applicable to expedited reporting of suspected ADRs do not apply (personal communication MHRA January 2015).

Both PEM and M-PEM designs begin data collection immediately after market-launch until sufficient numbers have been identified. There are no specific exclusion criteria. However, one key difference between the two approaches relates to the per-protocol sample size. For the M-PEM, the study is powered to achieve sufficient numbers to provide a reliable estimate of the primary objective—that being the key risk of concern in accordance with the RMP needs which generally requires fewer numbers than the general surveillance studies. For example, in looking at the sample size of completed studies on psychotropic medicines, the median cohort size of 19 standard PEM studies was 11,735 (IQR 9847, 12,713), while that of 6 M-PEM studies was 3586 (IQR 940, 10,371). The explanation is related to the difference in principle study objective: standard PEM studies were intended for general surveillance with a target sample size of at least 10,000 patients to allow for the detection of rare events occurring with a frequency of at least 1 in 2000 patients (assuming the background rate is zero) with 85% power [37, 38].

In terms of duration of observation, for both PEM and M-PEM approaches, a minimum of 3 months lag is required to allow information to be shared between patient and prescriber after the date of each patient's first prescription. Thereafter relevant outcome data (indication, events, and reasons for stopping) can then be collected from study questionnaires sent to each physician at some predefined period.

For PEM the minimum 6-month period of observation was standard. In M-PEM, this duration of follow-up is driven by the expected pattern of risk for events identified within the study primary objectives. Where both short and long terms are of interest, the M-PEM approach permits data collection in multiple waves, e.g., 3 months and 12 months. This permits stratification of data collection to focus on collecting more detailed information on nature of early acute onset risks of interest, treatment details at initiation, selected risk factors-prior medical history/concomitant medicines, and selected prescriber or patient behaviors close to index date. Subsequent waves can collect more detailed information on long-term event, repeated occurrence of acute onset events, changes in morbidity and posology over time. In recognition of the additional work-effort, remuneration is offered to the GP practices for each completed M-PEM questionnaire returned. For both

PEM and M-PEM, events of interest (for example identified risks) may be followed up for purposes of further evaluation. For each patient, trained coding staff prepared a computerized, longitudinal, chronological record of demographic, exposure and outcome data (including additional follow-up).

A wide range of drugs from various therapeutic classes have been studied using either approach (Table 2), the majority of which are those intended for widespread, long-term use. Of the 121 PEM studies completed, the average evaluable cohort size is 10,460 (range 436–19,485), with a response rate of 49.1%. Of the 13 M-PEM studies completed, the average cohort size is 8250 (range 63–14,616) with a response rate of 45.3%.

Table 2
Therapeutic classes of completed studies

Therapeutic class	Average cohort size
M-PEM studies	*N = 8506*
Antiglaucoma Preparations and Miotics	N = 3528
Anti-inflammatory and Anti-rheumatic Products, non-Steroids	N = 285
Antipsychotics	N = 13,276
Beta Blocking Agents	N = 1666
Drugs used in addictive disorders	N = 12,135
Opioids	N = 310
Other Cardiac Preparations	N = 4624
Other Drugs for Obstructive Airway Diseases, Inhalants	N = 11,005
Psychostimulants (agents used for ADHD and Nootropics)	N = 3586
PEM studies	*N = 10,460*
Adrenergics for systemic Use	N = 9761
Agents acting on the renin-angiotensin system	N = 9565
Angiotensin II Antagonists	N = 13,934
Antiadrenergic agents, peripherally acting	N = 11,638
Antidementia	N = 1762
Antidepressants	N = 13,024
Antiepileptics	N = 11,147
Antihistamines for systemic use	N = 10,939
Anti-inflammatory and Anti-rheumatic Products, non-Steroids	N = 10,050

(continued)

Table 2
(continued)

Therapeutic class	Average cohort size
Antimigraine preparations	$N = 14{,}928$
Antimycotics for systemic use	$N = 14{,}330$
Antiobesity Preparations (excl. diet products)	$N = 14{,}179$
Antipsychotics	$N = 4767$
Anxiolytics	$N = 11{,}113$
Beta Blocking Agents	$N = 1531$
Blood Glucose Lowering Drugs, excluding Insulins	$N = 10{,}543$
Cardiac Stimulants excluding cardiac glycosides	$N = 5373$
Direct acting antivirals	$N = 12{,}675$
Drugs affecting Bone Structure and Mineralization	$N = 11{,}038$
Drugs for peptic ulcer and Gastro-oesophageal reflux Disease	$N = 12{,}532$
Drugs used in addictive disorders	$N = 11{,}735$
Drugs used in Benign Prostatic Hypertrophy	$N = 14{,}772$
Hypnotics and Sedatives	$N = 12{,}501$
Lipid Modifying Agents, Plain	$N = 11{,}242$
Macrolides, Lincosamides and streptogramins	$N = 11{,}275$
Opioids	$N = 10{,}532$
Other Agents acting on the renin-angiotensin system	$N = 6285$
Other Dermatological Preparations	$N = 11{,}445$
Other Drugs for Obstructive Airway Diseases, Inhalants	$N = 12{,}294$
Other Sex Hormones and Modulators of the Genital System	$N = 13{,}815$
Other Systemic Drugs for Obstructive Airway Diseases	$N = 11{,}792$
Propulsives	$N = 13{,}234$
Quinolone antibacterials	$N = 9103$
Selective calcium channel blockers	$N = 8151$
Urologicals—erectile dysfunction	$N = 10{,}786$
Urologicals—incontinence	$N = 13{,}151$
Vasodilators used in Cardiac Diseases	$N = 13{,}620$
Other Beta-lactam antibacterials	$N = 11{,}250$

2.2 Specialist Cohort-Event Monitoring: Addressing an Unmet Need in Pharmacovigilance

In 2008, an additional adaptation was introduced that addressed an existing need for safety surveillance of new medicines initiated in the hospital (secondary care setting) [23]. In the UK secondary care data, particularly around prescribing are not well captured in the electronic medical record databases, such as the Clinical Practice research datalink (CPRD) or The Health Improvement Network (THIN). This application of cohort-event monitoring was developed in the recognition that safety studies conducted exclusively in the primary care setting may be at risk of biased conclusions about the prevalence of the types of patients prescribed new medications, and also the frequency of adverse events because of the potential exclusion of patients who are managed predominantly within the secondary care setting. These patients, who may be initiated under the care of a specialist health care professional, may have different characteristics and health experiences to those treated by physicians in the primary care setting for similar indications. Since the adoption of a new medicine into clinical practice in the UK is often initially facilitated by hospital specialists, there is a need for data capture across both the primary and secondary care setting to ensure all relevant exposed populations are characterized and monitored. The SCEM methodology enables cohorts of patients prescribed a new medicine in the secondary care setting to be assembled and monitored.

The principle differences between M-PEM and SCEM methodology relates to the route of identification of patients (through networks of specialists), requirements for consent and ethics approval. In brief, networks of specialists are established facilitated by the UK National Institute of Health Research (NIHR) Clinical Research Network (CRN) [39]. Similar to M-PEM studies, each SCEM study is powered to examine the principle safety issue of concern; and all specialist consultations, exposure data, and outcome data (indication, events, and reasons for stopping) that have been recorded in the patient's medical records are derived from questionnaires sent to the responsible physician for each patient at some predefined period after the date of each patient's first prescription. As for M-PEM studies, a minimum of 3 months' observation is required to allow information to be shared between patient and prescriber (Fig. 3).

2.3 M-PEM and SCEM: Analytical Methods

At inception, PEM was regarded as a surveillance method used to bridge the gap in generating safety signals of uncommon or rare outcomes that could be missed in clinical trials because of size, or missed in spontaneous reporting systems because of underreporting and background noise. Collectively PEM, M-PEM, and SCEM permit the examination of the characteristics of prescriber and new drug user populations and contribute to the accumulation of safety data, through the conduct of both quantitative and qualitative data analyses.

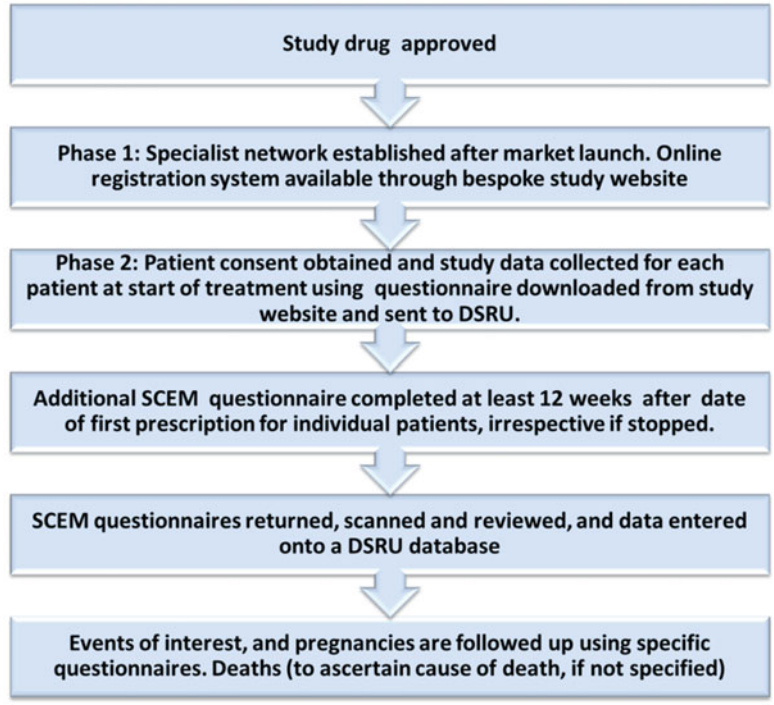

Fig. 3 Specialist Cohort-Event Monitoring (SCEM) generic study process (Data confidentiality maintained throughout)

2.3.1 Qualitative Research

Drug utilization research is an essential part of pharmacoepidemiology as it describes the extent, nature, and determinants of drug exposure at the patient level. The enhancements within M-PEM and SCEM offer much more detail in terms of qualitative analysis of drug utilization factors, prescribing decisions and use in vulnerable populations for whom off-label[6] prescribing has occurred (Tables 3 and 4). Quantitative analyses also underpin the main approach to signal generation. Crude event risks, rates (Incidence densities for a fixed period (t)—ID_t—usually expressed in units of first event reports per 1000 patient-months) are calculated to give estimates of real-world frequency. Calculations of ID differences between periods of observation are effective methods by which disproportionality in risk or ID may be observed suggestive of signals of treatment effects. Enhancements offered by M-PEM have the potential to investigate safety signals in more detail due to the additional data (demographic characteristics, relevant comorbidities, and other potential confounding factors) that are available. Analyses that can be conducted over and above the standard PEM quantitative methods include application of survival

[6] "Off-label" refers to the use of a drug "in situations where a medicinal product is intentionally used for a medicinal purpose not in accordance with the authorized product information." [40].

Table 3
Summary of analytical methods and examples of applications in M-PEM studies

Analytical objective	M-PEM study drug [UK launch date]	Background	Analytical method—examples
Drug utilization			
Describe patient characteristics	Fentanyl buccal tablets (Effentora ™) [2009]	Licensed for management of breakthrough pain in patients with cancer already receiving and tolerant to opioid therapy. Exploratory study objective included evaluation of inappropriate use and characterization of drug misuse	Prescribing indicators were developed based on the SPC Sections 4.3 and 4.4. Unweighted simple risk scores were constructed separately for aberrant behaviours and dependence. The relationship between scores explored using univariate analysis and simple logistic regression. A receiver operating characteristic (ROC) analysis examined model performance [47].
Explore prescribing decisions	Ivabradine (Precoralan ™) [2006]	Licensed for treatment of chronic stable angina pectoris in patients with normal sinus rhythm, who has contraindication or intolerance for beta-blockers. Study objectives included examining contraindications, warnings for use and their impact on incidence of 2 adverse events: visual phosphenes and bradycardia.	An algorithm based prescribing framework was developed to assist with the assessment of available information to reflect prescriber's concordance according to the contraindications and warnings for use in the Summary of Product Characteristics. Univariate analysis explored association between prescriber concordance and event risk [48].
Explore off-label use	Rivaroxaban (Xarelto ™) [2008]	Licensed for prevention of VTE in adults undergoing elective hip or knee replacements. In 2011, 2012 and 2015, the licence was extended.[a] Secondary objectives including informing on important risks (off-label use in non-orthopaedic medical conditions requiring anticoagulation)	Data on reported indication, prior and baseline relevant morbidities and medication use was used to define patient subgroups of special interest including off-label use arising from contraindications and those for which precautions for use were summarised. Off-label indicator scores were created through simple aggregation of counts. Study ongoing [55].
Describe treatment patterns	Quetiapine extended-release (Seroquel XL ™) [2008]	Licensed for treatment of Schizophrenia, manic episodes associated with bipolar disorder or as add-on therapy for major depressive disorder. Study objectives included exploration of posology	Several methods explored time to maintenance dose and time to treatment cessation with the first 12 months after starting treatment [49].

Safety evaluation			
Measures of disease frequency	Modafinil (Provigil ™) [1998]	Indicated for treatment of narcolepsy; license extended 2004 to include chronic pathological sleep conditions but restricted 2006 to patients with shift work sleep disorder, narcolepsy and obstructive sleep apnoea. Study objectives included evaluating use in special populations	In post 2004 cohort, risk of treatment cessation stratified by (a) past medical history (hypertension, arrhythmia, coronary heart disease, psychiatric illness and skin reactions) and (b) licensed indication (narcolepsy, sleep apnoea) and (c) off-label indications (lassitude and multiple sclerosis) [50].
	Varenicline (Champix ™) [2006]	Indicated for the treatment of smoking cessation in adults (18+ years). In 2008 a regulatory warning was issued regarding an association with neuropsychiatric symptoms. Study objectives included estimating incidence and examine pattern of neuropsychiatric events in new users.	Pattern of events were examined by plotting smoothed hazard function estimates to describe how baseline risk of event changes over time. The Weibull parametric time to event model was fitted to explore whether the hazard significantly increased or decreased over time [51].
Measures of association	Rimonabant (Acomplia ™) [2006]	Indicated as an adjunct to diet and exercise for the treatment of obese and overweight patients with associated risk factors, Rimonabant was withdrawn because risk minimization effort s could not address psychiatric adverse effects. Study objectives included comparing risk of major and minor depressive episodes in new users before and after start of treatment.	Information on recent (6 month) medical history of psychiatric illness prior to starting treatment was collected. A matched pair analysis was performed; the Mantel-Haenszel risk ratio between the two time period and 95% CI were calculated. Assumption that decision to treat was not associated with depression [52].
	Quetiapine extended-release (Seroquel XL ™) [2008]	Two supplementary studies were conducted on behalf of MAH to meet a post-approval commitment for an extension to the M-PEM study to explore if identified risks within the Risk-Management Plan (EPS; somnolence and/or sedation) were dose dependent.	A matched case control study nested within the M-PEM study. Incidence density sampling matched controls with cases. Risk factor data included current/prior antipsychotic use and current/prior medical conditions. Multivariable fractional polynomial logistic models were used to explore functional form of exposure as continuous variables in relation to outcome. Multiple conditional logistic regression models estimated crude Odds Ratios (OR) and age and sex adjusted ORs (+95%

(continued)

Table 3
(continued)

Analytical objective	M-PEM study drug [UK launch date]	Background	Analytical method—examples
			CI) to explore dose response relationship between quetiapine use (above a regulatory defined threshold of interest (600 mg) compared to lower doses) and the selected identified risks [53].
	Asenapine (Sycrest ™) [2009]	Indicated in EU for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. The primary objective is to describe the incidence of selected identified risks which are not well-characterized (i.e., somnolence and sedation, weight gain, oral hypoaesthesia, swelling of the tongue and throat, and allergic reactions).	To estimate the relative incidence of newly diagnosed oral adverse events during the early high risk period after starting treatment compared to low risk time periods with asenapine using self-controlled case series methodology [54].

[a]2011: prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults'; 2012: for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults'; 2015: co-administration with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers

Table 4
Examples of enhanced analytical methods and applications in SCEM studies

SCEM study drug [UK launch date]	Background to SCEM	Examples of analytical objectives and approach
Rivaroxaban (Xarelto ™) [2008]	SCEM study was initiated 2012 as part of a broader Post-Authorization Commitment requested by CHMP to further investigate the safety of rivaroxaban (XARELTO®) in clinical practice. It aims to monitor short-term (first 3 months) safety and drug utilization of rivaroxaban prescribed for medical conditions requiring anticoagulation by specialists in the secondary care setting in England and Wales. A concurrent contextual new user cohort prescribed standard care therapy was also being recruited [55].	*Analytical objective:* To characterise differences in prevalence of prognostic factors and clinical risk factors in new users of rivaroxaban and contextual cohort. *Analytical approach*: A multilevel model for discrete response data explored the effect of trust, prescriber and patient characteristics on treatment choice, with calculation of odds ratios and 95% confidence intervals.
Quetiapine extended-release (Seroquel XL™) [2008]	The Observational Assessment of Safety in Seroquel (OASIS) study was a SCEM study that aimed to extend the post-authorization safety knowledge of quetiapine extended release (Seroquel XL™) in the mental health secondary care setting, as prescribed by psychiatrists in new user adult (≥18 years) patients with Schizophrenia or Bipolar Disorder compared to quetiapine immediate release (IR). The primary aim was to examine short-term (12-week) safety, with a focus on safety during titration and at doses above a regulatory defined threshold of interest (600 mg) [56].	*Analytical objective:* To examine posology and titration *Analytical approach:* The relationship of dose with time was explored by two methods: calculating group-level bi-weekly mean model dose from univariate person-period data assuming data are independent; calculating exploratory empirical and fitted within-person OLS dose trajectories accounting for repeated measures within patient.

methods (parametric and nonparametric, and calculation of measures of disease frequency and/or association within and between special populations of interest, as defined a priori within the RMP (Table 3). The feasibility of the application of adjusted regression models as an additional tool for general surveillance purposes to support the identification of multiple safety signals within M-PEM studies is also currently underway [41].

Augmentation to SCEM study questionnaires has also provided superior information than that available in M-PEM on posology, identified and potential risks, selected risk factors-prior medical history/concomitant medicines, and selected prescriber or patient behaviours. Accordingly superior analytical methods have been applied (Table 4) to explore important issues such as the effect of time and repeated measures. Multi-level hierarchical models are being applied to inform on decisions to prescribe and better understand drivers of adoption of new medicines in the UK NHS, as are geographical special mapping tools to explore generalizability.

2.3.2 Quantitative Research

In terms of qualitative research all approaches include medical assessment of safety signals and/or outcomes of interest at the individual patient-level. Both approaches permit additional information to be collected from the prescriber and a semi-quantitative case series constructed. Several safety signals have been explored in this way, for example the association between use of vigabatrin and visual field defects [42]. To gain a better understanding of outcomes of interest, frameworks used in clinical practice or applied to clinical trials are being applied to improve their identification and classification. One example is the application of the Columbia-Classification Algorithm for Suicide Assessment (C-CASA) [43] in combination with the Columbia Suicide Severity rating Scale (C-SSRS) [44] to assist in the identification and classification of suicidal events [45]. Another example is the application of the International Society on Thrombosis and Haemostasis (ISTH) criteria in the identification and classification of hemorrhage. A third example is the application of the Ready Reckoner algorithm tool used in psychiatry to monitor antipsychotic dosing [46]. By systematically applying such criteria, not only will it be possible but more meaningful inference can be made in estimating incidence and rates obtained in observational settings.

3 M-PEM and SCEM: Issues in Interpretation

Like all observational studies, data should be interpreted with due consideration to bias and confounding. PEM and M-PEM approaches do not monitor an "unexposed cohort" concurrently, therefore assessment of selection bias in terms of how different a

PEM or M-PEM cohort is compared to all other patients with the same indication receiving other health-care in general practice in England cannot be undertaken. There is no selection criteria, therefore ascertainment bias is likely to be minimal; all patients for whom treatment is initiated in general practice are identified in the months following launch until the desired sample size is achieved. Also the method has no influence on the prescribing decision making process. This combination makes it likely (but not certain) that the eligible cohort is representative of all patients who have started a new drug under similar circumstances during the same time frame. Event incidence estimates represent an unknown combination of those events occurring in the general population and those attributable to use of the drug. Although subject to bias, these estimates are likely to be more precise because of the large sample size used.

Non-response bias is another form of selection bias which occurs during the conduct of a study. It is not known whether the prescribers who do not participate (and their patients), differ from those prescribers (and their patients) who do participate. Thus it is unknown whether findings from such studies are representative of the likely experiences of patients for whom no data was collected. Non-response by prescribers has also been described elsewhere [57–59], including spontaneous reporting schemes. Inman described "Seven Deadly Sins" (ignorance, diffidence, fear, lethargy, guilt, ambition, and complacency) which might cause low participation in reporting suspected adverse drug reactions [60]. However, prescriber characteristics should not be considered in isolation of the changing face of research overall. In the UK, research and academic medical practice were until recently considered to be non-core activities [61]. The introduction of the National Institute for Health Research (NIHR) in 2006 and the UK Department of Health's endorsement of a national health research strategy [62] have served to raise awareness of the importance of research and public health. The DSRU is taking this very seriously, and is developing activities to increase awareness of pharmacovigilance in the UK and improve response to both M-PEM and SCEM. The emphasis is on improving communications (e.g., personalized follow-up letters in response to participation and regular newsletters) as well as on providing education (e.g., continuing professional development packages and postgraduate teaching). With expanding development of mobile phone technology, the DSRU is looking to the future with the possibility of the use of mobile apps for improving prescriber participation. Pilot studies have also been conducted to test the feasibility of use of mobile technology for direct from patient reporting [63].

Confounding by indication and channelling of new drugs introduces selection bias through preferential prescribing to subsets of patients. The validity of then comparing safety outcomes of these

new drugs to existing treatments is determined by the extent to which the observed difference in risk of an event between the comparison groups can be attributed to the drug rather than other factors. For the SCEM studies the introduction of an internal comparator improves the ability to make inferences in external validity and generalizability of results. Such inference is also dependent on good quality data and sufficient sample size to enable robust statistical modeling. The enhancements that M-PEM and SCEM offer in terms of incorporating additional information on relevant data variables also minimize the possibility of residual confounding on estimates of risk due to misspecification of statistical models constructed. Missing information can also lead to residual confounding, and the reasons for missingness are often beyond the control of the investigator. External validation procedures from providers of exposure and outcome data are not made available to the DSRU. Therefore robust methods to deal with missing data through imputation and sensitivity analysis have also been incorporated within each statistical analysis plan that is created alongside each study protocol.

Misclassification is a form of information bias which occurs during data collection. It occurs when individuals are wrongly classified with regard to exposure or outcome. Such error may be differential or non-differential depending on whether the misclassification between two groups is random. Differential misclassification is a consequence of defect in study design and cannot be controlled for or effect minimized. Non-differential misclassification may reduce confidence in study findings but can be minimized using good scientific practice. In prescription-based event monitoring, exposure misclassification is important because inappropriately calculated exposure windows can result in a biased estimate of effect, particularly if unnecessarily long because relative differences get diluted as the time window widens, and a potential signal may be lost. Exposure is calculated from the date of issue of dispensed prescriptions, which means that exposure data used are more accurate than exposure data based on written prescriptions alone. In this regard, the misclassification of exposure is likely to be non-differential, being the same across the new drug cohorts, and the effect estimate (ID rate difference/ratio) biased toward the null. In PEM, assumptions are also made regarding compliance because it cannot be measured. Although variable compliance is likely [64], particularly with treatments for persistent conditions [65], for drugs indicated for chronic conditions, the assumption is made that the patient took the medication up to the end of treatment (or stop date) unless indicated otherwise. Intermittent use is more difficult to quantify. It is important to consider the effect of such transient exposures when separating acute effects from chronic effects, which may also be related to the disease being treated (confounding by indication). Ideally such patients should be

examined separately; firstly, their baseline risk is very likely to differ from those patients with chronic conditions; secondly, their potential risk window may be overestimated if recorded exposure data do not reflect intermittent use, thus diluting estimates of effect.

The possibility of outcome misclassification has been acknowledged as a limitation of the early PEM studies. Only selected outcomes were followed up for further evaluation. Incidence rates were calculated based purely on the number of events reported. Both M-PEM and SCEM offer opportunities to address the possibility of misclassification through more sensitive data capture, validation of relevant outcomes via clinical adjudication, and use of industry and regulatory approved medical terminology dictionaries for coding purposes.

Good clinical data management is a high priority for all prescription-based cohort event -monitoring studies. Data quality is assured through a number of methods based on error-prevention, data monitoring, data cleaning, and documentation. Data cleaning is undertaken to screen for errors, missing values, and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardized logical checks. Various initiatives have been proposed to highlight and minimize the principle cause of error, human error. These include automation of certain elements of coding with critical review of current coding conventions (e.g., coding of recurrent events, conflicting or missing data); improved flexibility of data interrogation software to facilitate regular review and audit; training and channelling of expertise to improve coding efficiency; testing of study documentation and drug-specific data management portfolios.

4 Prescription-Based Cohort Event Monitoring: Future Directions and New Horizons

Electronic Healthcare Records (EHR) and health insurance administrative databases have been used extensively in the past 40 years to identify, refine, and evaluate potential safety signals of marketed medicinal products [66]. These systems take advance of record linkage to provide rapid access to thousands of patients and thus reduce the time and expense required to explore relationships between drug exposure and outcomes. EHR has been embraced by regulators, marketing authorizations, and researchers alike in providing real-work data. There are many EHR already available that support health research, but despite the application of sophisticated analytical methods to extract and analyses data there remains uncertainty in their fitness for purpose for studying medicines safety, particularly in terms of representativeness, missingness, and data architecture. Nevertheless, the potential remains to exploit the use of such large databases for the systematic intensive monitoring of new medicines. This could be through prospectively applying the

principle of prescription-based cohort event monitoring to new user patients in real time. The global expansion of such databases also offers the potential for collaborative multinational studies to examine rare outcomes and the DSRU is currently engaged in such a model which will evaluate identified and potential risk associated with use of an antidiabetic agent through a multinational database study undertaken concurrently with a M-PEM study.

The application of SCEM at an international level is also being evaluated, given the need for multicenter studies, particularly for products for which marketing approval is being sought through the centralized procedure. Important considerations that need to be addressed in such proposals include variation in health care systems and medical information recording systems within and between EU countries. The DSRU is exploring the extension of SCEM through the development of online web-portals to support prescriber engagement and data collection at an international level.

Both M-PEM, SCEM, and EHR systems can establish new user cohorts to permit the investigation of selected risks outlined within a RMP based on specific exposure and outcome definitions. However, despite the wider use of EHR being used to conduct PASS, the M-PEM and SCEM approaches remain important tools for drug safety surveillance. This is because of methodological advantages such as the option of providing general safety surveillance through routine collection of data on multiple events, the possibility to conduct complementary studies across the primary and secondary care interface for the same product, and to gather information on factors that affect the implementation and adoption of a new medicinal product within clinical practice.

Similarly, there are other longitudinal records systems in the UK for which the research potential for prescription-based cohort event -monitoring has not yet been realized, such as pharmacy medicines management systems—both in hospital and primary care setting. The advent of electronic prescribing and pharmacist access to NHS patient Summary Care Records offers another valuable opportunity for a prescription-based intensive monitoring system. A pilot study conducted in the Netherlands explored the feasibility of the approach of using pharmacist networks for safety surveillance [67].

Direct from patient reported adverse events (PAER) have been shown to positively contribute to the ongoing benefit: risk assessment of medicines. Cohort event-monitoring has been applied to monitor the introduction of vaccines, utilizing electronic media to gather PAER, and has shown that some events are reported more frequently and earlier after starting treatment than by medical clinicians [63]. Thus PAER from web-based sources have the potential to be exploited as alternative sources of data that may, if extracted and analyzed appropriately, provide complementary data to that obtained from routine or additional PV activities [68].

The future also holds a desire for improved visualization for intuitive communication of results for PV needs. New innovations

include the use of visual analytical tools that display and interact with large datasets that can be achieved through cohort event-monitoring. The UK Visual Analytics Consortium (UKVAC), which partners academics from universities in Middlesex, Bangor, Imperial, Oxford, and University College London, is working on such proposals. Other research institutes in the UK such as Warwick Institute for Science of Cities are using Big Data systems to inform on real-world data-flows in health service (for targeting health support) and patient-based simulations for modeling growth of adoption of health technologies or hazards for risk management. Such "Fast data" analytics has the potential to accelerate time to insight for signal detection purposes.

Methods for measuring effectiveness of risk minimization activities for marketed medicines are receiving a great deal of attention by the Pharmaceutical industry, since systems do not exist. For all medicines the delicate balance that exists between efficacy and safety is affected by many factors including the prescriber, the patient, the disease, as well as other environmental effects. Recent examples of drug safety hazards may be suggestive of a failure of risk minimization activities, but they also represent the difficulties in understanding the natural variation that exists in general practice. Appropriately designed cohort event-monitoring studies could offer new opportunities to systematically monitor the effectiveness of risk minimization activities.

5 Observational Cohort Monitoring in Developing Countries

In the early 1980s, in close collaboration with the World Health organization (WHO), the Council for International Organizations of Medical Sciences (CIOMS) launched a programme on Drug development and used Medical Social and Economic Implications. In 1990s, the WHO Collaborating Centre for Drug Monitoring at Uppsala, Sweden, drew attention to problems in drug-safety monitoring within developing countries [69]. Developing countries had not kept pace with the successful establishment of various post-marketing techniques in Western countries. Reasons cited then, and which appear to remain in the present day, include: a lack of recognition of ADRs by patients, prolific use of indigenous medicines with sometimes obscure ingredients making identification of causative ingredient difficult, fluidity of accessing healthcare from different providers plus limited availability of patient medical records which make seeking further information on drug reactions a challenge; and in some cases misguided notions by prescribers that drug reactions were evidence of clinical therapeutic in adequacy.

An extension to observational cohort pharmacovigilance has been the application of cohort event-monitoring for surveillance of

medicines used in infectious diseases in developing countries, particularly to examine use and safety in those populations not included in the pre-marketing development clinical trials. It follows the same principles of active surveillance of patients prescribed a drug over an appropriate time frame following start of treatment and active follow-up to gain information on adverse events. However instead of collecting data directly from health care professionals who have access to patient healthcare records, the surveillance system has been adapted to source event data directly from patients prospectively—either through direct patient contact, or a patient reporting system [70]. The same local requirements for ethics approval apply that are relevant for any public health surveillance activity in each country, with informed consent. Examples of applications include the surveillance of the management and treatment malaria in sub-Saharan Africa [71, 72], treatment with antiretroviral drugs [73], and also antituberculosis treatment and also following vaccination campaigns [74].

6 Conclusion

Cohort event-monitoring systems provide a method to quantify risks on a drug-specific basis. They use an observational cohort design to systematically monitor the safety of medicines following introduction into clinical practice. They are a hypothesis generating form of pharmacovigilance and also a method which provides opportunities for quantitative analyses and comparative studies to further examine and refine drug safety signals. The method is still evolving in its data collection techniques and use of statistical methods available to minimize the risk of bias. However this chapter has demonstrated the usefulness of PEM, M-PEM, and SCEM methodology in revealing insight into important characteristics of new users of medicines in the UK and elsewhere, including vulnerable populations, and prescribing patterns as well as providing further information on important safety issues.

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Chapter 7

Electronic Health Record, Transactional Insurance Claims, and Distributed Databases in Pharmacovigilance

Kevin Haynes

Abstract

This chapter outlines available resources for pharmacovigilance and drug safety surveillance. The discussion focuses on the utility of electronic health record databases, traditional insurance claims databases, and distributed data networks. Strengths, weaknesses, considerations, and examples are presented. Finally, the chapter covers the concepts and challenges of data linkage across resources and offers several future perspectives on data availability in the field of pharmacovigilance.

Key words Electronic health records, Administrative claims database, Distributed data networks

1 Introduction

Databases represent a core component of the informatics toolbox for pharmacovigilance, pharmacoepidemiology, and comparative effectiveness research. These secondary data resources provide a foundation for a systematic approach to monitor marketed medical products. The heterogeneity of these information systems is apparent within individual systems, across healthcare delivery, and internationally. The key to utilizing databases for pharmacovigilance and observational research is to understand the initial intent for the data collection. The intent of data collection varies across healthcare settings; from the electronic documentation of a clinical encounter, to the electronic submission of an administrative claim, to process documentation of an encounter for reimbursement. Pharmacovigilance researchers must remain vigilant to the dynamic nature of health care systems and the changes that affect the quantity, quality, and utility of data in healthcare data resources available for research. This chapter aims to provide an awareness of the current methodological progress in the utilization of secondary data sources to address active safety surveillance in pharmacovigilance. This chapter will introduce the concepts of various databases used in research

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and provide a framework for evaluating the utility of a resource to address the clinical and quantitative aspects of pharmacovigilance.

The approach of this chapter will not be able to provide an exhaustive list of all available resources as these resources are dynamic and may become outdated over time. The approach will be able to provide a foundation of available resources and provide an in-depth review of the types of questions researchers should ask when approaching the utilization of a particular resource to address a pharmacovigilance activity. The chapter will discuss electronic medical record (EMR) and electronic health record (EHR) databases found routinely at the point of care in healthcare delivery. Next, the chapter will discuss administrative claims databases and the role of documenting and reporting clinical encounters for either direct reimbursement or documentation for quality care metrics to provide value for the services rendered to individuals or groups of patients. Finally, the chapter will introduce the concepts of distributed research networks. All three sections will provide examples within individual healthcare systems, across healthcare delivery, and internationally.

As a motivating example (Fig. 1) throughout the chapter, consider a patient who obtains care at clinic **A** and obtains a prescription for drug **R** at pharmacy **X** that is paid by health plan **E**. The patient then has an adverse event at hospital **B** and is administered drug **S** while an inpatient that is also paid by health plan **E**. The patient later goes on to have additional complications covered by a different health plan, **F**. A few questions to consider over the next several sections:

Are the EMR systems of clinic **A** and hospital **B** integrated;

Does the EMR system at hospital **A** know if a patient filled drug **R**;

What data does health plan **E** have on the encounter at clinic **A**, pharmacy **X**, and hospital **B**;

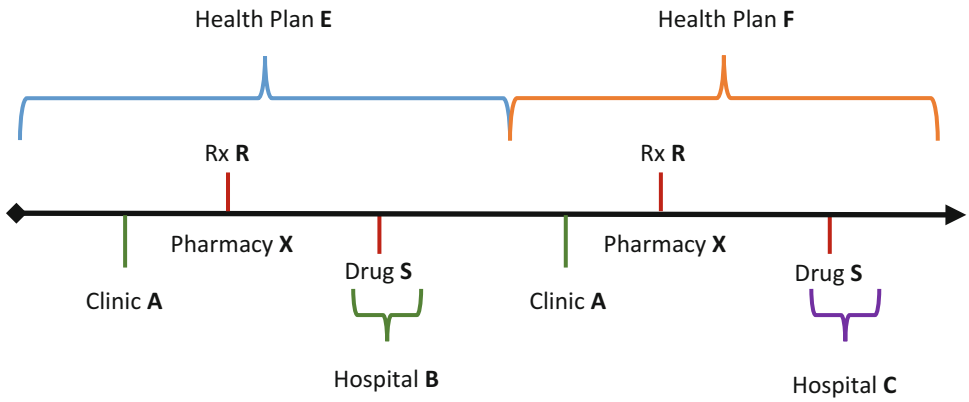

Fig. 1 Example Patient interactions with the health system

Can data from health plans **E** and **F** be linked to provide longitudinal follow-up;

Can all data systems be integrated to provide for longitudinal patient follow-up?

The answers to these questions will aid individual pharmacovigilance researchers in choosing the appropriate resource(s) to address drug safety questions.

2 Electronic Medical Records (EMR) and Electronic Health Records (EHR)

The terms EMR and EHR are often used interchangeably. However, the EMR can be thought of as the digitalized version of the paper chart that existed at a clinician's office practice or at the patient's bedside in an inpatient setting. The EHR is more than simply an EMR; often, the EHR is a collection of EMR systems that typically integrate laboratory, inpatient, outpatient, and speciality care settings. The EHR represents a clinical informatics tool that can facilitate communication and transmission of EMR data both within and across organizations. For example, EHR systems in the United States (US) can integrate inpatient clinical care with outpatient clinics within the same provider network. Additionally, these systems integrate with laboratory data systems and can facilitate e-prescribing that, in some cases, can obtain information back from pharmacy systems regarding prescription dispensing at outpatient pharmacies.

The use of EMRs and EHRs has increased rapidly over the past decade (Fig. 2). However, many interoperability challenges remain for systems to communicate within health systems and across health systems. In our example presented above, Clinic **A** and Hospital **B** may be within the same health system. However, just being present in the same health system does not guarantee that the local systems are interoperable with the entire health data network. Additionally, the health systems may be separate but may allow for the exchange of information on individual patients with consent of treating clinicians across a health information exchange (HIE) [1, 2]. Finally, the prescriptions written at Clinic **A** or the discharge medications written at Hospital **B** may be electronically transmitted to Pharmacy **X**. This is just one hypothetical scenario to keep in mind with the use of EHR data for pharmacovigilance research.

2.1 Strengths

EHR systems record information by providers at the point of health care delivery. Thus the information contained is rich with clinical detail that includes office and bedside records of diagnostic tests results, vital signs, and social histories, including tobacco and alcohol consumption. Additionally, data quantifying the disease burden

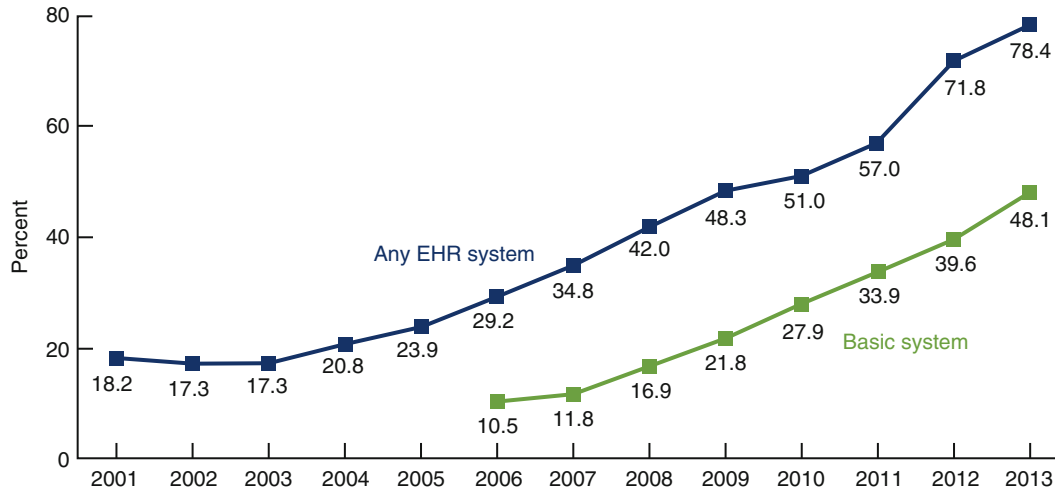

Fig. 2 Percentage of office-based physicians with EHR systems: United States, 2001–2013 [3]. NOTES: EHR is electronic health record. "Any EHR system" is a medical or health record system that is either all or partially electronic (excluding systems solely for billing). Data for 2001–2007 are from in-person National Ambulatory Medical Care Survey (NAMCS) interviews. Data for 2008–2010 are from combined files (in-person NAMCS and mail survey). Estimates for 2011–2013 data are based on the mail survey only. Estimates for a basic system prior to 2006 could not be computed because some items were not collected in the survey. Data include nonfederal, office-based physicians and exclude radiologists, anesthesiologists, and pathologists. SOURCE: CDC/NCHS, National Ambulatory Medical Care Survey and National Ambulatory Medical Care Survey, Electronic Health Records Survey

through severity assessment are more likely available. Finally, medications or injectable product administrations that occur within a clinical encounter or hospitalization are well recorded. The data sources represent information close to the point-of-care and provide an opportunity to obtain data from the provider(s) who treated the patient.

2.2 Weaknesses

Due to the flexibility and customization of EMR/EHR systems, providers can modify systems to build "workflows" and electronic templates for order entry. These can change over time and lead to inconsistent data recording. For example, an office visit may require recording a diagnostic code as a reason for the visit prior to the patient arriving at the office. Office staff may enter in reasonable assumptions or may resort to a "work-around" with the input of incorrect diagnostic codes. When these codes persist in the EMR/EHR systems as workup codes and in some cases incorrect diagnoses they may be falsely inferred as a clinical diagnosis by researchers.

EHR systems may not be able to truly determine patient adherence to prescribed medication regimens since the only system record is a written prescription. Some integration through e-prescribing is starting to provide bidirectional communication

from pharmacy systems back to EHR systems, thus providing the documentation that a patient has picked up the medication from the pharmacy.

Studies in EHR systems may require direct patient contact to provide for longitudinal follow-up as these systems do not capture all of the care a patient or research subject may experience over a defined period of time. This may necessitate primary data collection in all or a subset of the population and may warrant specific subgroup analysis in defined populations where follow-up of clinical exposure, covariate, or outcomes of interest may be incomplete. Additionally, the challenges in linking the EHR system to administrative sources (introduced below) present a current weakness in the longitudinal capture of clinical events outside the EHR system. Datasets that offer the ability to uniquely identify and contact patients offer an opportunity for further data collection to overcome these weaknesses.

2.3 Considerations

In choosing an EMR/EHR to use in pharmacovigilance research, determine if the resource is appropriate to address the clinical question. Determine if the ability to obtain medical records to validate data is possible. Many systems are anonymized without an ability to link data to additional available electronic resources or return to source records for validation. When assessing if the data resource can be linked to external resources, determine the degree of overlap between the resources. For example, many of these resources contain millions of patient records, but the availability to link to other data resources reduces the available records for research when resources are linked to obtain complete data [4, 5]. Researchers should also be familiar with the provision of healthcare within the country or population under consideration to assess the completeness of an available resource and the ability to link to additional resources.

Given the challenges in obtaining longitudinal data, it may be necessary to conduct primary data collection to obtain events outside of the health system or available database. This may be of particular importance to studies that require a long duration of follow-up or in situations where care for a particular condition may be sought from multiple providers in outpatient clinics and specialty clinic settings. The concept of prospective registry design is beyond the scope of this chapter (*see* Chap. 8), but through proper consenting procedures, the establishment of a patient registry with longitudinal access to multiple health systems may improve the data collection to capture exposures and outcomes across care settings.

2.4 Examples

In the United Kingdom (UK), general practice (GP) research databases such as The Health Improvement Network (THIN) or Clinical Practice Research Datalink (CPRD) CPRD are available and

contain all electronic data from the GP office and can be linked to additional external resources. These resources contain over ten million patients, although with notable overlap between the two resources [6, 7]. Due to the nature of the UK healthcare system, virtually all of the care for a patient is presented to the GP for electronic capture, offering the opportunity to obtain a complete capture of clinical detail. Data linkage to the Hospital Episode Statistics (HES) database provides clinical details on inpatient encounters; however, this is not available in all regions or at all GP practices, thus limiting the available population size [8, 9]. The ability of identifiable datasets to conduct data linkage is probably best highlighted by the Medicines Monitoring Unit (MEMO) of the University of Dundee road traffic accident study that linked data from the electronic medical records in Scotland with regional traffic data to assess exposure to prescription drug use [10].

In the US, integrated health care delivery systems, such as Kaiser Permanente, Group Health, Geisinger Health System, and others, have integrated EHRs with data from clinics and hospitals. These systems also integrate with administrative claims data, providing a complete medical encounter history [11]. These data resources each conservatively contain over one million patients with variability based on the size of the health system. Other systems include data directly from vendors of EHR/EMR systems. However, these systems are often deidentified preventing the linkage to additional longitudinal resources but often each contain records on well over ten million patients.

The Veteran's Affairs (VA) system in the US has a detailed clinical repository of inpatient and outpatient medical encounters on over 8.7 million veterans [12]. However, the data resource is limited in the depth of care obtained outside of the VA system. Data linkage with Medicare data has improved the longitudinal ability to follow the population [13].

Outside of the US and UK, the uptake of electronic medical records depends on the motivating factors related to the national health system. Researchers conducting pharmacovigilance work in other countries should determine the factors that motivate electronic data collection of clinical encounters.

3 Transactional Insurance Claims Databases

Health insurance companies and government agencies tasked with the reimbursement of medical care must maintain data systems to document the claims. In the US, Medicare sets the medical billing process standards that are subsequently adopted by commercial insurers. In other countries, governments or private payers set standards for recording accurate data to provide appropriate remuneration for services rendered. These policies discourage fraud

through audits and rejected claims, providing a motivation for providers to submit accurate claims that adhere to adopted billing and coding standards. Administrative data is extensively utilized in pharmacovigilance research and active surveillance activities.

The utility of these administrative resources is dependent upon the coding requirements affecting reimbursement. As changes are made to the process of reimbursement such as the move from fee-for-service to pay-for-performance, there will undoubtedly be changes to the quality and quantity of available automated administrative information.

3.1 Strengths

These systems represent very large data sources integrated across medical and pharmacy billing systems and have enrolment data that allow for the complete capture of clinical encounters over a defined period of time. Health care delivery systems generate bills that are submitted to a health plan, this process generates a claim for reimbursement purposes. These systems allow for longitudinal follow-up across multiple health systems over defined person-time based on enrolment criteria permitting an accurate estimate of a denominator for incidence and prevalence estimations. Administrative systems are often composed of enriched data environments through direct linkage to additional clinical information.

In our example presented above, health plans **E** and **F** represent administrative payers with an ability to capture the care of the patient as they traverse various health systems containing outpatient clinics, inpatient hospitalizations, and pharmacy encounters.

3.2 Weaknesses

Elements of transactional administrative claims not likely to affect the amount reimbursed are less likely to be reviewed for accuracy and subjected to less audit or rejection scrutiny. Additionally, the depth of the clinical details is routinely not part of the administrative claims. Some datasets have the ability to link to laboratory result systems for a subset of the membership. But, the capture of detailed vital records, social history, and family history is not routinely available. However, through patient or provider survey, these data elements can be obtained on specific cohorts of interest. The challenges in linking the administrative sources to EHR systems present a current weakness in the depth of clinical data capture of encounter details in EHR systems. As presented above, datasets that offer the ability to uniquely identify and contact patients offer an opportunity for further data collection to overcome these weaknesses.

While an increasing number of the US population is insured in either commercial or government sources of insurance, the ability to link enrolment segments across administrative organizations while technically feasible is not routinely performed. Similar problems occur elsewhere, although linkage is better in some countries, e.g., Scandinavia. Patients may change insurance

companies for a variety of reasons based on cost, plan availability, or employment changes, which includes retirement resulting in Medicare eligibility. This churn in insurance coverage may prevent studies that require long follow-up to assess latent outcomes to medical product exposures. However, with advances in health information exchanges the generation of a longitudinal administrative patient record may become available.

Claims data, as for other data sources, e.g., accessible EMR data, may lag from 1–6 months based on the type of service billed and this has implications for surveillance activities [14]. In our example presented above, the clinical data for the encounter at clinic **A** is entered at the time of the patient visit. The administrative processing of the encounter and available data in health plan **E** administrative records may lag while the documentation of the prescription for drug **R** at pharmacy **X** may only lag less than a week due to real-time adjudication of events. Technological advances and changes in payment reimbursement practice may improve the content and availability of the data for active surveillance.

3.3 Considerations

As with EMR/EHR data sources, researchers should determine if the administrative claims resource is appropriate to address the clinical question. Determine if the data source is able to obtain medical records to validate data. Many systems are anonymized without any method to return to source records to provide for further data linkage either back with source data or additional data linkage to other electronic resources or direct patient engagement. Again, these data linkages will likely reduce the size of the population available with complete data. Researchers should also be familiar with the provision of healthcare within the country or population under consideration.

3.4 Examples

There are several examples of administrative sources of longitudinal clinical data. In the US, most patients have private commercial insurance or are covered under the Center for Medicare and Medicaid Services (CMS) Medicaid and Medicare plans. Medicaid is jointly funded by federal and state governments and administered individually by the states to provide medical assistance to individuals and families with low income. Medicare is a federally administered insurance program for the elderly or persons with qualified disabilities administered as either a fee-for-service or medicare advantage plan that is privately contracted with commercial insurance companies. These resources are fully identifiable and offer the opportunity to conduct data linkage to additional resources. Additionally, there are aggregated sources of administrative data of adjudicated or pre-adjudicated claims that are often deidentified data sources for research. Finally, there are integrated delivery systems, such as Kaiser Permanente, that offer both health

insurance as well as clinical care and therefore offer a combined administrative and EHR data environment.

Other countries utilize a health insurance model for the payment of health care services. Pharmacovigilance researchers should understand the purpose of the data collection; data is collected to document care for reimbursement purposes either from a single payer or in a system of public and private insurance payers and, therefore, has limitations in the depth of available clinical detail.

4 Distributed Research Networks

Distributed databases to assess drug safety have become a new tool in the evaluation of pharmacovigilance. The concept is predicated on a common data model (CDM) where multiple data systems are harmonized so that the same programmatic code can run across multiple data systems simultaneously. Data can remain with the data partners who collected the data allowing for identifiable datasets for the purposes of obtaining medical records or linking to additional data resources [15]. Alternatively, datasets can be centrally stored, often anonymized prohibiting the ability to obtain medical records or link to additional data resources.

4.1 Strengths

The key strength of distributed database research is the use of a common data model to facilitate rapid queries across large data resources. For networks that utilize a federated data model, data partners retain access to their individual level data which provides the governance structure favorable to protecting patient privacy and the proprietary nature of the data resources.

4.2 Weaknesses

Data transformations of source data into CDMs may alter the initial meaning of the information collected. Validation is often warranted to confirm that information contained in the CDM accurately reflects underlying clinical conditions. CDMs, which require extensive transformation, may require more validation, while networks, which retain original source codes, may be easier to accommodate diverse coding algorithms for disease identification. A challenge in distributed research involves the ability to track patients across data partners both at a single point in time and over time.

4.3 Considerations

The strengths and weaknesses noted above for EMR/EHR and administrative claims systems are relevant to the distributed databases. Data completeness remains the most important consideration in evaluating the ability of a data resource to longitudinally follow patients for complete capture of relevant pharmacovigilance clinical outcomes.

4.4 Examples

The Observational Health Data Sciences and Informatics (OHDSI) collaborative provides a CDM platform that can be readily applied to administrative and electronic medical record data for rapid analytics. The CDM facilitates the execution of code across multiple resources transformed into the Observational Medical Outcomes Partnership (OMOP) CDM [16, 17]. For a review of available active surveillance systems worldwide, see review by Haung et al. [18].

4.4.1 North America

The Sentinel Initiative, and the recently completed pilot program Mini-Sentinel, was created in response to a Congressional mandate in the Food and Drug Administration (FDA) Amendments Act of 2007. The FDA Sentinel Initiative is designed to monitor the safety of regulated medical products by utilizing existing electronic healthcare data from multiple sources, including large datasets of administrative claims submitted by healthcare providers to insurance companies [19]. This highly collaborative model between academic and private organizations has developed the capacity to rapidly respond to the FDA to perform active surveillance of marketed medical products, including drugs, biologics, and medical devices [20]. The system serves as a model for the use of largely administrative data to address drug safety questions, while preserving privacy by minimizing the transfer of protected health information and proprietary data. Data partners serve as full partners in the implementation of the safety surveillance, and retain full autonomy in the control of their data, including the choice to decline participation in specific activities. The initiative is fully transparent, with public access to the specifics of the creation of the common data model (CDM) and active safety surveillance system tools. While the Initiative includes nearly half of the US population, with approximately 150 million lives, the clinical depth of the data is limited. The majority of the data partners contribute administrative claims data electronically with access to medical records for validation studies. Among the Health Care Systems Research Network HCSRN, formally the health maintenance organizations research network (HMORN), data partners who have a long history of providing integrated data for research, there is diversity and varying levels of access to deep clinical encounter level data (e.g., sites that own their hospitals) [11]. The ability to integrate administrative claims data from large health plans with clinical data from EHR systems will advance the ability of Sentinel to respond to medical product safety surveillance.

The Canadian Institutes of Health Research formed the Canadian Network for Observational Drug Effect Studies (CNODES) as a network to link data across Canadian provincial databases [21]. The CNODES network coordinates drug safety and effectiveness research across multiple databases, including the CPRD in the UK.

4.4.2 Europe

The European Union Adverse Drug Reporting (EU-ADR) Project collects anonymous healthcare data from eight established European databases located in four countries (Denmark, Italy, the Netherlands, and the United Kingdom). Additionally, The Innovative Medicines Initiative (IMI) has formed the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) and was tasked with monitoring of the benefit-risk ratio of medicines in Europe across multiple databases. The consortium developed multiple working groups to advance the methods and data structure necessary for routine pharmacovigilance [22] and published extensive results on conducting hypothesis testing studies across multiple databases (as discussed in more detail in Chap. 11).

4.4.3 Asia

The Asian Pharmacoepidemiology Network (AsPEN) is a multinational voluntary research network formed to provide a mechanism to support identification of emerging drug safety issues across Asia. The network utilizes a CDM approach to execute queries [23, 24].

5 Current Challenges to Utilizing Databases for Pharmacovigilance

As more patient data becomes electronic and available for safety surveillance activities the challenges of linking disparate datasets at single points of time (hospital, clinic, and claims-based systems) as well as longitudinally (across claims-based systems and healthcare systems) will increase. These challenges will require data governance to allow for the use of various data linkage across disparate organizations capturing unique health information on individual patients. As resources are linked, the population available for research is reduced. This is evident in both fragmented health care delivery systems, as well as nationalized systems, as individuals seek care across a spectrum of health systems and care settings.

As EHR and administrative claims data are routinely used to address pharmacovigiliance surveillance activities and drug safety research, multi-stakeholder engagement will become necessary across health systems, payers, and patients. A systematic literature review and a focus group evaluated the views of health care professionals to routine data linkage and highlighted the costs, governance, and interference with the prescriber–patient relationship as key barriers to routine data linkage [25, 26].

6 Future Perspectives

The future of pharmacovigilance systems will continue to blend administrative claims-based data environments with electronic health record systems. Increasingly, these surveillance systems will

come to engage the patient in both the reporting of medical product events and patient reported outcomes. The ability to take data in distributed research networks and link across data both within a data network and across a data network will become increasingly important to the ability to provide active drug safety surveillance. As we move toward a learning healthcare system that places increased demands on clinicians to electronically document the care provided, as patients begin to capture health data through wearable technology, and as payment models introduce new complexities, the demands on both the data governance and technical capacity to link data sources will become increasingly challenging. However, data linkage will increase the value of the data to address pharmacovigilance research. Collaboration with large regional or national health plans will be essential for broad access to longitudinal data.

In the US, the ability to link patients across health plans and, ultimately, into Medicare will be pivotal in providing true longitudinal patient follow-up and the ability to study long-term outcomes. If an investigator wanted to study the effects of pediatric exposures on the onset of adult outcomes, the data networks available today are insufficient to address the discovery of these potential associations. Longitudinal data transformation will require additional governance challenges to protect the proprietary business interests of the entities that initially collected the information. The decision by the CMS will allow innovators and entrepreneurs access to Medicare claims, which opens the door to the potential of further integration. Researchers will be granted access to the CMS Virtual Research Data Center (VRDC), which contains granular privacy-protected CMS data files. A major innovation will be to use the VRDC to extend the follow-up of commercial health plans to generate a longitudinal patient record.

The preservation of patient privacy will be paramount to building trust among patients for these pharmacovigilance activities as data is integrated across data partners. These collaborations will need to involve researchers, patients, and health system leadership to establish data governance across data resources, this governance will have to establish clear data use agreements for bidirectional data exchange of the minimum data necessary to respond to a drug safety inquiry. Activities will need to clearly demonstrate benefit to public health through either active surveillance or through the generation of comparative effectiveness of therapeutic modalities. Ethical and regulatory oversight will continue to evolve as data queries will require access to multiple resources. Within health systems, observational clinical research is often performed within a single "covered entity" and can thus seek a waiver of informed consent according to the Health Insurance Portability and Accountability Act (HIPAA). Such protocols stress in the Institutional Review Board (IRB) process that the research poses no more

than minimal risk, and the only risk is loss of confidentiality. In situations requiring data linkage with external resources to the specific covered entity, provisions such as anonymous linkage will need to be employed to maintain patient privacy [27, 28]. There are other examples of linking EMR data with claims data from health insurers while maintaining patient privacy through a trusted third party [5]. Additionally, proposed changes to the Common Rule will likely impact the conduct of public health surveillance and observational clinical research in secondary data. Regardless of the strategies employed, major governance and technical innovations are essential to alleviate the burden and costs associated with conducting linkage for the conduct of public health surveillance and clinical research.

The era of "big data" will shift from the pharmacovigilance discussion of how many patients or members are in the database, to how linked the data is to capture the full picture of the patient's interactions with the healthcare system(s), and over what period of time the patient is followed. Undoubtedly, healthcare will continue to need "big data" but arguably in the form of "deeper data" to address clinical research questions and patient care. The question is how broad and deep are the data on an individual, both in terms of longitudinal follow-up and depth of detail on clinical encounters, with health systems. These are exciting times for availability of pharmacovigilance data systems.

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Chapter 8

Patient Registries for Safetyness

Marcus Schmitt-Egenolf

Abstract

We are experiencing a revolution in the distribution of knowledge in the twenty-first century. Knowledge is no more centrifugally dispensed, means centrally produced and distributed in the periphery—today knowledge is produced everywhere and can be accessed instantaneously everywhere. Technological and methodological progress allows us now to evaluate the real world directly, by collecting information in unselected populations not accessible via randomized clinical trials. The term safetyness is suggested to mark that we have to appreciate that the world of randomized clinical trials and the real world are different in nature. In this context this chapter investigates patient registries, as a powerful tool for the future of health technology assessment in general and pharmacovigilance in particular.

Key words Pharmacovigilance, Effectiveness, Safetyness, Register, Registry, Real world, Outcome analyses, Randomized controlled trial RCT

1 Introduction

1.1 The Allegory of the Cave

In the Republic [1], we find a scene where prisoners have lived chained to the wall of a cave all of their lives, facing a blank wall. They watch shadows projected on the wall from things passing in front of a fire behind them, and their life consists of giving names to these shadows. These shadows are as close as the unfortunate prisoners get to view real life.

1.2 Development of Pharmacovigilance

The first generation of pharmacovigilance was based primarily on spontaneous reporting of adverse events (AEs). However, the needs of today can no longer be satisfied with this type of passive pharmacovigilance alone, which is blind to the population of interest and only analyses AE as shadows on the wall. Some key developments of pharmacovigilance could be condensed as seen in Table 1.

Andrew Bate (ed.), *Evidence-Based Pharmacovigilance: Clinical and Quantitative Aspects*, Methods in Pharmacology and Toxicology, https://doi.org/10.1007/978-1-4939-8818-1_8,

Table 1
Milestones of pharmacovigilance

1961	1.0	The Lancet letter of McBride on Thaldomide—the birthdate of pharmacovigilance [2]
1968	1.1	Establishment of WHO's VigiBase database
1996	1.2	Introduction of risk benefit analyses
1997	1.3	The Erice Declaration on effective communication [3]
1998	1.4	Development of advanced computer based disproportionality analysis [4]
2008	2.0	The FDA's Sentinel Initiative [5]

With the start of the Sentinel Initiative, allowing linking and analyzing healthcare safety data (e.g., patient registries) from multiple sources in near-real time a new concept for pharmacovigilance has become officially recognized

2 Spontaneous Reporting of Adverse Events

Spontaneous reports are case reports of adverse events that health professionals voluntarily submit to either drug regulatory agencies or drug manufacturers. Traditionally, regulatory agencies and drug companies have used spontaneous reporting to signal adverse events in the post-marketing settings.

2.1 Lack of Numerator and Denominator

Insofar as spontaneous reporting is voluntary, ascertainment of all relevant cases is incomplete. Assuming that reported information is well documented, spontaneous reports at best give a sense of the quality of the adverse event that patients are exposed to during a particular drug treatment, but in the end the number of unreported cases is not possible to assess—we do not have a numerator. Furthermore, as spontaneous reports include no information about the extent of drug exposure in the treated population, we do not have a denominator either. However, to calculate an incidence rate: "How often does this event occur," one needs both the number of affected individuals (the numerator) as well as the person-time at risk (the denominator).

2.2 Unexpected Side Effects

In classical pharmacovigilance in Europe, prescribers are urged to report only those adverse events where there is a chance that the drug is related to the event. Such a system may reduce our ability to detect new, previously unexpected adverse events. In the USA, the FDA encourages the reporting of any adverse event after drug exposure, even if the relationship to drug use is nothing more than temporal association. However, in both settings health professionals are less likely to suspect and report adverse events that are also common comorbidities. Prescribing cox-2 inhibitors, physicians surely were alert as far as the "classical" side-effect profiles of NSAIDs were concerned, but were not necessarily capable of relating a stroke or heart attack to these drugs.

2.3 Delayed Side Effects

Spontaneous reporting may also fail to give a signal because of several years delay between starting the drug and the eventual development of, e.g., a malignancy. If a patient at the time of the malignancy diagnosis no longer receives the drug in question, the chance for the detection of the "culprit" drug is even lower.

2.4 Conclusion

Despite the named shortcomings, today's organized global system for collecting signals from both healthcare professionals and increasingly consumers is a fantastic component of a surveillance system that has proven its value—still almost all label changes in systematic studies are due to spontaneous reporting. Quantitative analysis of spontaneous reports provides an effective filtering system for triaging the vast numbers of submitted reports. However, alternative data sources are needed, as spontaneous reporting cannot as a sole system satisfy the higher demands on pharmacovigilance in the future.

3 Randomized Clinical Trials (RCTs)

RCTs are an important and necessary step between the preclinical evaluation of pharmaceuticals and procedures and their use in real life. The randomization guarantees a high internal validity (*see* Chap. 5 for a detailed treatment of RCTs).

3.1 Low External Validity

However, there are some major problems attached to the current application of RCTs, which are centered on the low external validity of RCTs. As RCTs do not represent real life, there is an active design process required, which can lead to selecting those parameters that will produce a favorable outcome for the sponsors drug. This has led to a discussion about the ethical integrity of RCTs [6–9].

RCTs create an artificial situation that can be quite remote from real life. This starts with the selection of the study subjects, who may well differ from the majority of patients seen in clinical practice with respect to concomitant diseases, lifestyle and medications (Fig. 1), as well as in compliance and sex/age/socioeconomic distribution [10]. Furthermore, special risks and opportunities in patient subpopulations may remain undetected. For example, it is known that patients with moderate to severe psoriasis are at increased risk of developing a variety of concomitant diseases, such as cardiovascular morbidity and metabolic syndrome. However, in RCTs those patients are regularly excluded. Potential AEs in this population, including interactions between the investigated psoriasis drug and medications for comorbidities, will therefore *by design* escape detection in RCTs [11, 12].

As RCTs regularly only have a short duration, they can hardly address long-term efficacy and long-term side effects (e.g.,

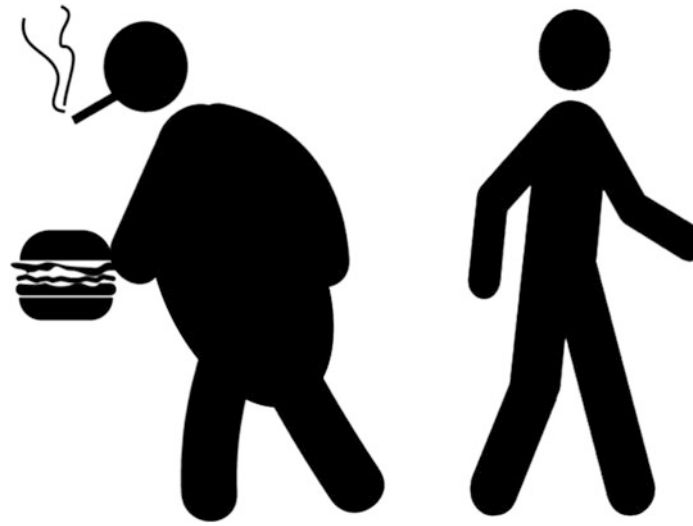

Fig. 1 Real world patients (registries) versus healthy subjects with one isolated disease (RCTs). On the left an average real life patient with his typical life-style and age-inflicted comorbidities that are often associated with the disease under investigation. On the right a typical RCT patient, a healthy (beside the isolated existence of the disease under investigation) young male, not representing the real life patient population

malignancies). Furthermore, in real life physicians individualize treatments in terms of dosing and treatment combinations, including off-label use. All this together leads to a high internal, but low external validity. That means that the findings of an RCT are true within the borders of this particular RCT, but cannot be generalized to the different and complex real life situation. The famous expression from the peace negotiations at the end of the Vietnam War:

> "That may be so, but it is also irrelevant"

comes to mind.[1]

3.2 RCTs: An Important Stepping Stone

RCTs are both important and necessary. Nobody would suggest leaving out RCTs and moving a drug from preclinical testing to real life directly. The problem lies in the interpretation of RCTs. *RCTs create an island of simplicity in an otherwise complex world* (Fig. 2). We have to use this island as a stepping-stone between preclinical and real life, but it is prone to disaster to just rest on it. A particular hazard is that RCTs can produce entrenched thinking—a reaction that occurs when we are blocked from using new ways of thought by the perspective we have acquired through past

[1] Colonel Summers, U.S. Delegation: "You know you never defeated us on the battlefield", Colonel Tu, North Vietnamese Delegation: "That may be so, but it is also irrelevant" [13].

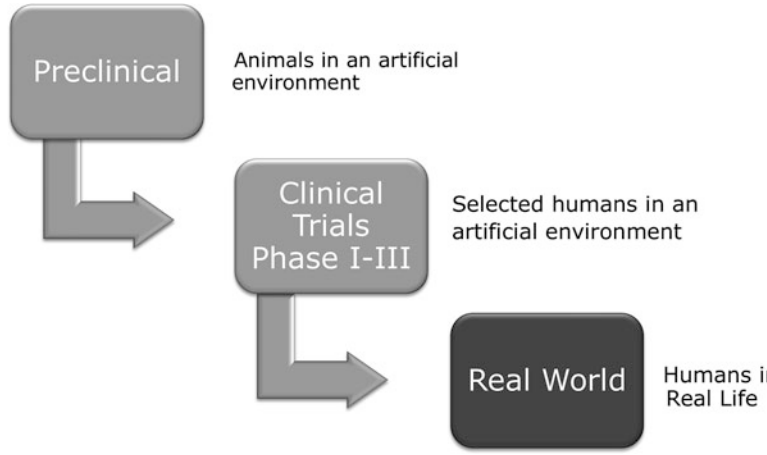

Fig. 2 RCTs do not provide a representative model for real life. RCTs and real life studies both investigate humans. However, RCTs include non-representative patient populations. Therefore, the use of RCTs leads to results with high internal, but low external validity. For this reason it is essential that a new drug is extensively monitored post marketing (*see* Sect. 5.8.1)

experience. A prescriber in today's health care system with information overload may not be able to react to the complexity of a clinical situation, and falls back to the simplified picture retrieved from a RCT.

4 Safetyness

The terms "effectiveness" and "efficacy" have been set apart to describe the benefit of a drug in a RCT setting (efficacy) compared to what we see in "real world" (effectiveness). The lack of a corresponding nomenclature for harm has caused confusion, on both the practical and the scholarly level. We therefore suggest here introducing a new term into pharmacovigilance, safetyness, which describes the real life situation in contrast to the term safety, which describes the artificial situations in a RCT (*see* Table 2). The term safetyness brings the desired clarity. For example, if we shall analyze risk/benefit ratios it is self-evident that we can either talk about a RCT derived risk/benefit ratios based upon efficacy and safety or about real world risk/benefit ratios based upon effectiveness and safetyness. Approaches to extrapolate between safety and safetyness are problematic. Toxicity in RCTs normally (but not always) can translate to lack of safety in real world use, but lack of toxicity in clinical trials gives only limited confidence that a drug will be nontoxic in widespread real world use. One problem in the

Table 2
Introducing the term Safetyness

	RCTs	Real world
Benefit	Efficacy	Effectiveness
Harm	Safety	Safetyness

The term safetyness allows for the evaluation of risk and benefit in the separate worlds of RCTs and real life. Real world experiences can only be made in real life. This insight is the rationale behind the establishment of patient registries and adaptive licensing

introduction phase of a new pharmaceutical is that there is a tendency to compare the safety of the new competitor with the safetyness of the established product, as in this phase the diverse real life patient population has not yet been exposed over a sufficient time to manifest eventual AE.

5 Patient Registries

5.1 Definition and History

A patient registry is a database of identifiable persons containing a defined set of health- and demographic data. More specifically, the U.S. Agency for Healthcare Research and Quality defines a patient registry for evaluating outcomes as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)" [14]. Registries are regularly aimed at the monitoring of a specific disease or treatment in a real life extended population. Consequently there design fits pharmacovigilance well. A registry can be employed for pharmacovigilance either retrospectively, or prospectively, the latter being similar to primary data collection observational studies. In contrast, Electronic medical records (EMRs) and Insurance Claims databases have as their primary purpose the individual patients healthcare and billing, respectively, and are therefore usually by design inferior to the use of registries in pharmacovigilance.

Today's patient registers have evolved historically; only three milestones in this amazing journey can be mentioned briefly here, to remind us that we are standing on the shoulders of giants.

1858—Florence Nightingale (1820–1910) nurse, statistician, and reformer pioneered modern nursing while treating and registering the wounded in the British army in the Crimean-war (Fig. 3). She produced the famous rose-diagram of the "Causes of Mortality in the Army in the East" (Fig. 4), documenting that the main reason of death was avoidable sickness (blue) and not battle wounds (red), and that the former could be controlled by, e.g., nutrition,

Fig. 3 Colored mezzotint: Florence Nightingale, by J. Butterworth. *Credit: Wellcome L0019661, Wellcome Collection. CC BY.*

ventilation, and shelter [15]. The logotype for the central national quality register administration in Sweden, facilitating today about 100 registers in all areas of medicine, is inspired by Florence Nightingale's rose-diagram.

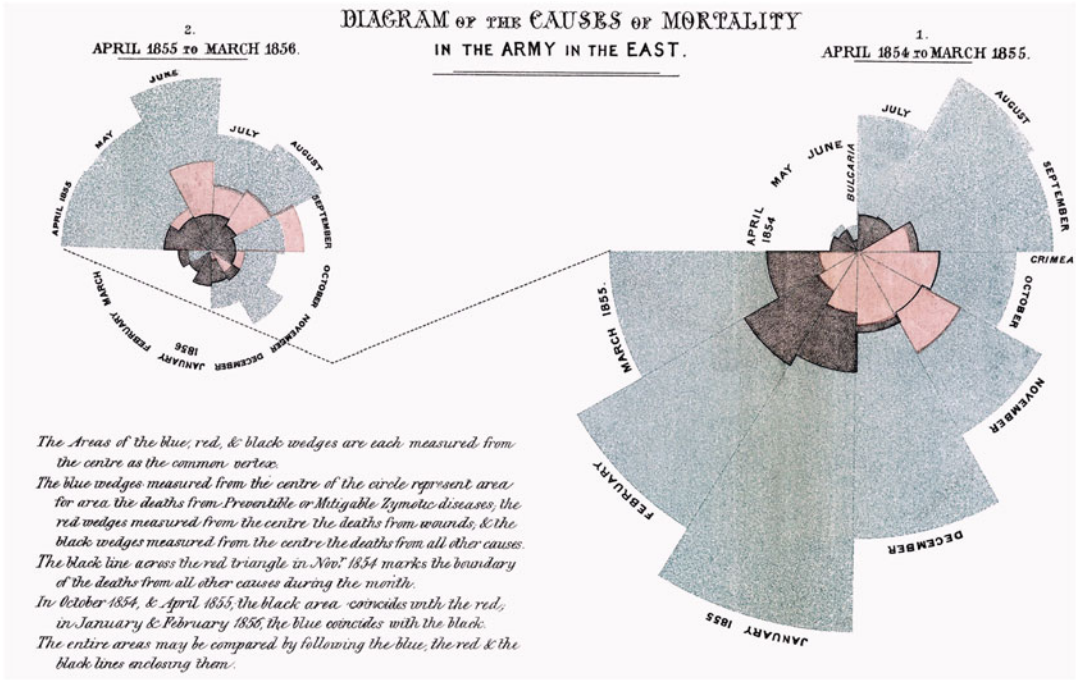

Fig. 4 Causes of Mortality in the Army in the East. Florence Nightingale's famous "rose-diagram" [15]

1918—E. A. Codman (1869–1940) is the inventor of outcome management in patient care. He published annually the outcome of the patients in his private hospital, including negative outcomes based on his personal mistakes: "In other words, I had made an error of skill of the most gross character and even failed to recognize it" He kept track of his patients via end result cards showing demographic data along with the diagnosis, the treatment, and of course the outcome. Each patient was followed up for at least 1 year to observe long-term outcomes [16].

1975—Göran Bauer (1923–1994) founded the first national quality register in Sweden, dedicated to knee-prostheses. An at this time modern computer system, the UNIVAC 1100/80, was employed to process and store the data [17].

5.2 The Cultural Connotation of Registries in Sweden

If a foreigner comes to Sweden she might get the impression that the ten digit unique person identifier covering the entire population and its near ubiquitous use, is the secret behind the success of Swedish registries. However, the truth is not that simple. It is important to understand that there is a special social contract in Sweden. Sweden has never been occupied by an imperialistic force such as the Roman Empire, nor was it born through liberation from a colonial power. Consequently, unlike most other countries, where freedom may be defined as the absence of the state in daily life, Swedes feel comfortable with the apparent active direct

involvement of the state in most details of their life, in a way that does not seem to generalize to other countries, not even in this extent to other Nordic countries. The public perception is that the state exists for everybody's benefit and guarantees rather than threatens personal freedom. This intimate relationship between the individual and the state in Sweden is referred to as "statsindividualismen" [18] or states-individualism. Although this relationship has been criticized, it definitely facilitates the development or registries. It is self-evident in Sweden that the state collects sensitive information from its citizens. The accomplishment of government run registries that helped to reduce early infant death in Sweden is a matter of national pride. It is consequently difficult for a Swede to understand in the context of EC legislation the argument from other European Nations who want to limit the states access to personal information, in order to "protect" the individual. Although privacy concerns are taken seriously in Sweden, they are differently balanced by the understanding that everybody profits from the greater good of good registries. How can the state improve services and benefit society if the state is ignorant about the well-being of the citizens, wonder Swedish politicians and citizens alike.

Although Scandinavian and Swedish cultural values facilitate the successful development and use of registries, particularly through robust data collection and linkage, important registries can be found in, e.g., the UK and the US, a few of them are mentioned in Table 3.

5.3 Practical Use of Patient Registries

Depending on the purpose of the registry and practical circumstances, a patient registry can be built on a diagnose, e.g., diabetes, or medical procedures, e.g., hip replacement. In contrast to the electronic medical record (EMR) (*see* Chap. 7), which is a digital version of the traditional paper-based medical record for an individual, the unit under primary investigation in a patient registry is not the single patient but a large number of patients. However, in Sweden there is a convergence between EMR and patient registries as doctors have realized that a register can be used as an optimal tool in following up even individual patients. This convergence is promising, as it would solve the problem of double data entry in both the EMR and a register. However there are still legal hurdles to such a practice, in part based on the fact that patient registries are, in contrast to EMRs, normally voluntary. This could lead to the situation where a patient in a registry could be better monitored than a patient who "opted out."

A patient registry allows calculating the incidence rate of an AE (the number of new cases in a given time period divided by the total person-time at risk during that time period) as it provides both the number of people affected by a given AE as well as the person-time at risk [20]. Thus registries enable us to generate and test

Table 3
Examples of major registries

Name	Sposor	Start	Content	Population size	Reference
Hungarian Congenital Abnormality Registry (HCAR)	Ministry of Health, Hungary	1962 due to [2]	Congenital abnormalities	5000 yearly	[19]
Surveillance, Epidemiology, and End Results (SEER)	National Cancer Institute, US	1973	Cancer cases	9 million	http://seer.cancer.gov
The Clinical Practice Research Datalink	Department of Health, UK	1987	Medical treatment information	20 million	https://www.cprd.com
The Kaiser Permanente National Total Joint Replacement Registry (TJRR)	Kaiser Permanente, US	2001	Total knee and hip replacement	140,000 joint replacements	https://national-implantregistries.kaiserpermanente.org
The CORRONA Data Collection Program	The Consortium of Rheumatology Researchers of North America	2001	Autoimmune diseases in particular RA	40,000 RA patients	http://www.corrona.org
The BSRBR Rheumatoid Arthritis Register	The British Society for Rheumatology	2001	Rheumatology patients receiving anti-TNFα therapy	20,000	http://www.rheumatology.org.uk

hypotheses about suspected adverse events. With a registry, we have moreover the chance to see if a side effect only manifests in specific constellations, such as in combination with a specific phenotype or concomitant medication/disease. *See* Chap. 11 for a discussion of Pharmacoepidemiology methods for testing hypotheses of outcomes due to medicinal products.

The main objectives of a patient registry are:

- To comparatively assess safetyness and effectiveness of different treatments.
- To identify which specific patient subgroups have the best risk/benefit ratio for a given drug/procedure.
- To create benchmark data for quality assurance of the medical service.
- To monitor equality.

5.4 Population-Based Health Registries, Drug Registries, and Linkage

Health registries covering an entire population containing, e.g., all cancer diagnoses were already widely established in the Nordic Countries when the first patient registries focusing on a given disease or medical procedure started from 1975. Based on the established unique person identification numbers in the Nordic countries linkage between these registries is possible. In the last decades, national databases on drug exposure data were established in all Nordic countries. These can also be linked to both health and patient registries. There are now an increasing number of registries around the world.

5.5 Pitfalls

Like all observational studies and data sources, registries are more vulnerable to bias and confounding than RCTs. However, the combined approach of RCTs and registries complements the deficiencies of the other. Naturally, we want to provide every individual patient with the best possible individualized therapy. The choice of drug for a patient depends on the *indication*—e.g., the clinical pattern of the disease and *contraindication*—e.g., pre-existing comorbidity. Consequently different drugs will be channeled to different subpopulations of patients. If this is not considered carefully, a direct comparison of the performance of two drugs may be misleading. A patient registry regularly asks several questions concerning the phenotype of the disease, alongside questions concerning concomitant diseases and medication. Therefore, a potential confounding by indication/contraindication bias can be handled when the analysis is carefully done. As participation in many registries is optional, there is a risk that patient groups with a higher risk profile can over proportionally "Opt-out" leading to bias.

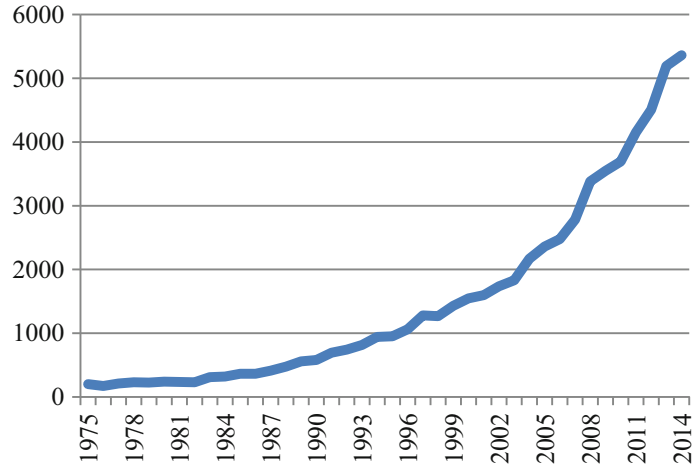

Fig. 5 Shows the increasing number of PubMed records containing the MeSH Term "registries"

5.6 Registry-Based Research

Registry-based research has dramatically accelerated in recent years (Fig. 5). Some examples can illustrate the breadth of the impact of patient registries on the medical development: Data from Swedeheart could demonstrate that drug-eluting coronary stents were associated with an increased rate of death, as compared with bare-metal stents [21]. Riks-Stroke could uncover disturbing sex differences in the medical treatment of stroke patients [22], and The Swedish Rheumatoid Arthritis Registry, could show that treatment of rheumatoid arthritis patients with TNF-antagonists leads to an increased risk of hospitalization with infection [23], but not to a higher lymphoma risk [24]. The psoriasis registry PsoReg could reveal evidence for discrimination of older patients in the access to drugs with high acquisition costs [25]. The Swedish Hip Arthroplasty Register was one of the first registries in Sweden. Discussions of registry data among orthopedic surgeons resulted in a restrictive attitude to operation techniques involving uncemented components and in a standardization and limitation of the number of prostheses that are routinely used. The effect of this has been to halve the number of cases of mechanical loosening in connection with hip replacement surgery in Sweden during a 10-year period. This has led to great savings both in terms of human suffering and expense. In this context, it is not surprising that the revision-free survival of total hip arthroplasties in Sweden is higher than in all other countries compared so far, e.g., as in the United States [26]. The British Society for Rheumatology Biologics Register (BSRBR) could study under now 15 years the safetyness of biologics in several aspects [27].

5.7 Pharmacovigilance Example Using a Registry: Misinterpretation of the Association of Sildenafil (Viagra) with Melanoma

Recently, an association between sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor used in the treatment of erectile dysfunction, and melanoma, was described [28]. Although no data were presented that indicated causality, this association appeared to be interesting as PDE5 is part of a signaling pathway in melanoma. A deeper analysis including an analysis of dose response was subsequently performed based on the Swedish Melanoma Register and Prescribed Drug Register [29]. Although this study corroborated the association (odds ratio: 1.21; 95% CI, 1.08–1.36) it "excluded" causality: (1) there was no dose-response gradient—more filled prescriptions of sildenafil were not associated with higher risk; (2) the association was with early-stage melanoma only; and (3) sildenafil use was also associated with basal cell cancer, a skin cancer form not connected to the PDE5 pathway. The authors of this study concluded that the observed association is based on confounding, as high socioeconomic status is strongly associated with both PDE5-I use and skin cancer risk; individuals who can afford it like to travel during winter months on vacation to warmer climes and may get sunburnt which predisposes to melanoma. This case study shows that associations must be scrutinized before a clinical assessment can be made. Patient registries, aligned with other health registries, can discriminate between confounding and causation.

5.8 The Future of Registries

We are just seeing the beginning of a revolution of medical science approaches by widespread use of real world data retrieved by registries.

5.8.1 Adaptive Licensing

As the life cycle of drugs becomes more and more accelerated, traditional drug licensing approaches with a binary decision become outdated. *Adaptive (or progressive) licensing* [30] means drug candidates can be initially approved for use in a restricted patient group, and later on progressively expanded to broader patient populations as additional effectiveness and safetyness data is analyzed. Data are gathered on an on-going basis, e.g., with the help of patient registries. The main advantage is that this allows licensing to align more closely with patient needs for timely access to new medicines. Also the need for pharmacovigilance of biosimilars requires the implementation of registries.

5.8.2 Alternate Pricing Strategies Based on Patient Outcome

The current model of pricing pharmaceuticals by milligram is an outdated model in particular for pharmaceuticals with high acquisition costs. Patient registries can deliver the data required for alternate pricing strategies based on patient outcome. Such a system offers a win-win solution for both payer and producer: The price is relevant as it reflects the real world performance. The costs do not come as a surprise but can be estimated in advance within a certain performance-based corridor. Consideration of international

pricing is not relevant as an easy internationally comparable milligram price is not part of the deal, allowing for price-discrimination between nations of differing wealth. This solves the current problem that poor nations do not have access to certain high-priced pharmaceuticals at all. The current delay to access, where a part of the potential patient-population has to wait until the patent has expired, can be avoided too.

5.9 Confluence of Cohort Event Monitoring (CEM) and Registries

Whereas registries have developed foremost in economical richer countries, CEM is more often used in economical less rich regions such as in the HIV and Malaria product roll out in part of Africa. However, as the technical costs for registries have decreased, and the information technology infrastructure such as mobile phones has increased drastically in Africa, in the future CEM programs may transform toward registries.

5.10 International Collaboration of Patient Registries

International collaboration across patient registries is an ideal tool to collect a critical amount of data in the shortest possible time. Although there are several hurdles [31], it is worth the effort as size clearly matters for early robust signal detection, and for ensuring power for hypothesis testing studies as often as possible. Several, e.g., European nations do not have the critical size on their own, but can by means of international collaboration solve this problem.

5.11 Current Challenges

5.11.1 Double Data Entry

Presently, the patient information is often put into two non-communicating systems in parallel, the EMR and a patient registry. This is causing frustration and is a major obstacle for good registry coverage. It is important to solve the underlying legal and administrative hurdles toward a singular data input. Several pilot projects have proven that this is possible.

5.11.2 Redundancy

In Sweden about 100 different clinical patient registries exist. There is a large redundancy between them, as more generic health questions, e.g., BMI, smoking, and EQ-5D, are asked in many registries. This can in practice mean that one patient has to answer the same question in several registries. The efficiency gain of information coordination between registries has to be carefully balanced against the perception of privacy loss by the patient.

5.11.3 Patient Reported Outcome Measurements (PROMs) and Patient Reported Experience Measurements (PREMs)

Patient empowerment has in the last few years put focus on patient reported outcome measurements as an important endpoint. However, the collection of PROMs in itself does not guarantee that the care-giver is using this endpoint accordingly in her clinical decision making [32]. Patient reported experience measurements are an important tool to continuously improve the patient experience and satisfaction. Several registries have opened up for the possibility to direct data input from patients. For reasons of efficiency in the

case of PROMS and reasons of privacy in the case of PREMs, the data input from the patient should take place in a committed system for patients only.

5.11.4 Cultural Heritage of Registries and RCTs

RCTs are traditionally the instrument of the pharmaceutical industry and perceived as such. Registries, in contrast, are as both the historical examples and more recent ones such as www.patientslikeme.com show, a more "bottom up" grassroots movement. The exploding interest of the pharmaceutical industry in registries might lead in the longer run to a shift in the public perception of registries.

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Chapter 9

Patient Reported Outcomes in Pharmacovigilance

Linda Härmark

Abstract

Patients are becoming an increasingly important source of information about the safety of drugs. By using patients as a source, the information comes first hand from those who have experienced the adverse drug reactions. These experiences are richer in context and information of the impact of an ADR as compared to information from healthcare professionals. New technologies (i.e., Internet) have made the collection of patient reported information (PRI) easier and also more affordable.

This chapter will mainly focus on how PRI is collected and used in safety surveillance of marketed products, their value and the possibilities new technologies create for capturing the data. An overview will be given of different methods for collecting PRI, including patient reporting to spontaneous reporting systems, intensive monitoring and social media data mining.

Key words Patient reported outcomes, Patient reporting, Intensive monitoring, Social media

1 Introduction

In the past, the relation between a healthcare professional (HCP) and a patient was characterized by a sort of paternalism. The HCP knew best, and made decisions on behalf of their patients without involving them. The concept of patient empowerment, defined by the WHO as "*a process in which patients understand their role, are given the knowledge and skills by their health-care provider to perform a task in an environment that recognizes community and cultural differences and encourages patient participation*" [1] has gradually gained more and more recognition in health care. An empowered relationship is a partnership. There is mutual respect for the others skills and competencies and recognition of the advantages of combining these resources to achieve beneficial outcomes. The HCP is the expert when it comes to diagnostic techniques, the causes of disease, prognosis and treatment options and preventive strategies whereas the patient is the expert when it comes to his or her experiences of illness, social circumstances, habits, behavior, attitude to risks, values, and preferences [2–4]. Patient empowerment

Andrew Bate (ed.), *Evidence-Based Pharmacovigilance: Clinical and Quantitative Aspects*, Methods in Pharmacology and Toxicology, https://doi.org/10.1007/978-1-4939-8818-1_9,

has led to the situation today where patients can be and often are more involved in the decisions about their own care.

Patient reported outcomes (PROs) have become increasingly used in general healthcare and life sciences. PRO's is defined by the FDA as "any report of the status of a patient's health condition coming directly from the patient without interpretation of the response by a clinician or others, including self-perception symptom severity (absolute or relative to another report), and physical performance, but not information derived by others, e.g., physical examinations or performance assessed by healthcare professionals" [5] and the term is used similarly in other jurisdictions.

2 Patient Reported Outcomes of Adverse Events (PRO-AE) in Clinical Trials

Symptoms account for a large proportion of the adverse drug reactions listed in drug labels, but historically this information has largely been based on the clinicians' impressions of patients' symptoms, and not on patients' first-hand experiences. The advantages of using PROs for collecting information about symptoms in clinical trials, especially trials investigating the effects of cancer treatment, are plenty [6]. Studies of PROs in this area have shown that clinicians miss or underestimate a large proportion of the symptomatic adverse events experienced by patients [7–9]. Moreover clinician assessment of adverse events is relatively unreliable, meaning that if two different clinicians evaluate the same patient, they often disagree with each other's assessment [10]. Clinicians also downgrade the severity of patient symptoms [8].

By letting patients report these events themselves, the information comes first hand from those who have experienced the adverse events. Most patients are willing and able to self-report their experiences, feasibility studies demonstrate that when PROs are collected well (i.e., using contemporary electronic data capture collection methods and reminder calls to patients) compliance can exceed 95% in clinical trials and 80% in real world routine care settings [11]. An example of the latter is a study in which patients receiving chemotherapy were asked to self-report seven symptomatic toxicities via the web between visits. On average, monthly compliance was 83%, and weekly compliance was 62%, without attrition until the month before death [12].

With the evidence as to the advantages of using PROs in clinical trials, why has PROs not been wider implemented as a standard component of drug evaluation in clinical trials? A barrier for wider implementation of PROs in clinical trials is that researchers might not be convinced that PROs can provide valuable information which is relevant for the study. There is also a lack of validated questionnaires and standardization of outcome measures that can

be used. Data collection can also be problematic, in particular when it comes to missing data from hard-to-reach and ill patients.

Besides scientific challenges, there are also practical challenges, including logistics and the cost of implementing PRO programmes. However, in recent years technological advancements have made it easier to capture data from patients in an easy and affordable manner, which has prompted a renewed interest in the use of PROs [6, 13].

This chapter will mainly focus on how PROs are collected and used in safety surveillance of marketed products, their value and the possibilities new technologies create for capturing and analyzing the data.

3 Patient Reported Outcomes in Safety Surveillance of Marketed Products

Although patients can be a valuable source of information, the use of PROs in the safety surveillance of marketed products has been sparse. In many countries, the reporting of adverse drug reactions has been reserved for healthcare professionals. In 2007, the Erice Manifesto specified challenges to be addressed ensuring the continuing development and usefulness of the science of pharmacovigilance. A key issue mentioned in the Manifesto as a possible road to success was the active involvement of patients and the public in decisions about their own health and treatment of disease and discussions about benefits and risks of medicines [14]. The role of the patients as key players in pharmacovigilance was also acknowledged in the new pharmacovigilance legislation which contains several efforts to increase the involvement of the general public and it made patient ADR reporting systems mandatory [15, 16].

3.1 Patient Reporting to Spontaneous Reporting Systems

One of the first broader applications of PROs in the safety surveillance of marketed products was the introduction of the general public as reporters to spontaneous reporting systems. In some countries it is called patient reporting and in some countries it is called consumer reporting. The WHO has chosen to use the term "consumer reporting" since it is a broader term, as not all consumers of medicines are patients. A patient may be defined as a person who receives medical attention, care or treatment from a physician or other health professional [16, 17]. Throughout the text the word patient reporting will be used, as this is the term that is used at our center.

A patient report is a report of a suspected adverse reaction to a medicinal product as initiated by the patient and without interpretation by a healthcare professional. In some countries the actual reporting will be done directly by the patient themselves or by a person close to the patient (e.g., a relative), while in others

reporting can also be performed via a nurse or a pharmacist. In this case, a report is considered to be a patient report if the healthcare professional assisted the patient only in the submission of the report and did neither initiate the report, nor provided any additional information or interpretation to it. If a healthcare professional reports a personal experience of an adverse reaction to a medicine, this can be regarded either as a patient report or as a healthcare professional report depending on national interpretation [18].

Patient reporting has been possible for a long time in some countries (i.e., the US, Canada, and New Zealand) [19], however wider acceptance of patient repeporting was only achieved in the early 2000s. A key issue regarding the delay in wider acceptance of patient reporting in pharmacovigilance was the lack of (published) practical experiences and evidence of its usefulness [20]. In Europe, the Netherlands and Denmark opened their respective national spontaneous reporting system to accept reports from the general public in 2003, followed by the UK in 2005 and Sweden in 2008. Since then, more information about the value of the contribution of direct patient reporting to pharmacovigilance has become available [21–30].

3.1.1 What Do Patients Report

Underreporting of ADRs by healthcare professionals is an established characteristic of spontaneous reporting [31] that is that only a small minority of suspected adverse drug reactions are actually reported, and one of the initial aims by targeting the general public as reporters was to increase reporting. However, the contribution of patient reporting to pharmacovigilance goes beyond a purely quantitative contribution. Patients provide first-hand information about the ADRs, and these reports can lead to a better understanding of the patient's experiences of the ADR [32–34]. In the UK, patient reports on paroxetine were better at explaining the nature, personal significance, and consequences of ADRs than healthcare professionals' reports on similar associations [34]. Others found that patient reports gave more detailed information regarding quality of life including psychological effects and effects on everyday tasks [22, 35]. Information from patients may challenge the concept of what is considered a "tolerable" side effect of a drug [36]. The severity of the ADR is a main motivation for patients to report [34, 37]. As with the concept of "tolerability" of side effects it is important to be aware that the view of the concept of "seriousness" of a side effect in the medical community may differ significantly from the views of patients [38]. Many ADRs would be regarded as non-serious according to internationally agreed professional criteria while nevertheless being intolerable and considered serious and causing severe problems for patients, e.g., sexual side effects [38, 39]. That there are differences in the type of information reported between patients and healthcare professionals was also confirmed in a study. Patient reports are more focused on

patient-related information and the impact of the reported ADRs as described above, whereas reports from HCPs provide more clinically related information [35].

3.1.2 Contribution of Patient Reports to Signal Detection

One of the major aims of pharmacovigilance is to detect new signals. A commonly used definition of a signal is "information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action" [40]. Hence both previously unknown associations and new aspects about an already known association are considered to be signals. Since patients do not have a professional filter and being more unconstrained as regards probability and plausibility of causality between a drug and a perceived ADR compared to healthcare professionals, they may report events which to HCPs may seem unlikely to be related at first impression.

In the Netherlands a study was conducted to determine the contribution of patients' adverse drug reaction (ADR) reports to signals detection. The study concluded that the proportion of patient reports contributing to generate signals was equal to the proportion of patient reports in the database and that patients can provide a valuable contribution to the detection of signals in addition to healthcare professionals' reports [41].

In the UK a study was performed to investigate the relative contribution of patient reporting to signal detection through disproportionality analysis. The study concluded that patient reporting may make an important contribution by identifying different signals of disproportionate reporting (SDRs) not identified from HCP reports alone. The combination of reports from patients and HCPs, however, may result in the loss of some information [42]. These studies provide a reassurance regarding initial worries expressed in the literature that an increase in the number of patient reports would only increase distracting "noise" in signal detection [36].

Patient reports have been of crucial importance in identifying specific signals.

An example of this is a signal of electric shock-like sensations associated with the use of SSRIs [43–45]. This specific ADR is described by the reporters as shocks in the head, small electric shocks, feeling of electric current through the head, and extremities. As this is now a well-known ADR, there is also a MedDRA term to describe it "electric shock sensation." However, when the initial reports came, and the exact coding did not exist, the Netherlands Pharmacovigilance Centre Lareb coded these events as

paraesthesia and the signal was identified based on case by case review. The signal was further strengthened with patient reports [46]. This signal was also found in the UK where 23% of patient reports and 14% of HCP reports about citalopram, paroxetine, and venlafaxine included descriptions of "electric shock sensations" or similar reactions. Compared with the professional reports, patient reports were particularly vivid, comparing this reaction to a range of other extreme experiences and stressing the severity of the symptoms [22]. In 2011 electric shock sensations were detected in association with the use of duloxetine, a combined serotonin and norepinephrine reuptake inhibitor, almost exclusively based on patient reports [47]. Sexual dysfunction is an acknowledged ADR of SSRIs [48]. Although it has previously been assumed that patients always regain normal sexual functioning shortly after discontinuation of SSRIs, emerging evidence suggests that this may not be the case. In 2014, the Netherlands Pharmacovigilance Centre Lareb published a signal, mainly based on patient reports, of persistent sexual dysfunction in patients who had stopped using SSRIs for 2 months up to 3 years and who had not regained normal sexual functioning [49]. In the UK patient reports have contributed to the detection of signals as well, for example amlodipine and interaction with grapefruit juice, donepezil and unusual dreams including nightmares, medroxyprogesterone and infertility and fentanyl and product adhesion issues [50].

When patient reporting systems were introduced, it was thought that it could lead to earlier detection of signals. A small study indicates that reporting by patients can contribute to earlier detection of signals [51]. However since then no formal study has been conducted to investigate this, but in the case of duloxetine and electric shock like sensations and SSRIs and prolonged libido patient reports were key in detecting these signals, so one can reason that patient reports helped detecting these issues earlier [47, 49].

3.2 Intensive Monitoring

Another method used to monitor the safety of marketed products is intensive monitoring. In the late 1970s the Intensive Monitoring Medicines Programme (IMMP) was established in New Zealand [52] and since the beginning of the 1980s the Prescription Event Monitoring Programme (PEM) has been running in the UK [53]. The basis of these intensive monitoring systems is a non-interventional observational cohort where users of certain drugs are identified on the basis of prescription data. The prescriber of the drug is sent a questionnaire and is asked about any adverse events that may occur during the use of the drug being monitored. These data are collected and analyzed for new signals [51, 52].

3.2.1 Intensive Monitoring Using Patients as a Source of Information

In 2006, a web-based intensive monitoring system called Lareb Intensive Monitoring (LIM) was introduced using patients as a source of information. The choice of patients as reporters in LIM was based on the positive experiences from introducing patients as reporters to the spontaneous reporting system and the belief that patients would play a more important role in pharmacovigilance [20, 39, 54].

In the majority of studies conducted, patients eligible for inclusion have been identified using the first dispensation signal in the pharmacy [55–59]. However, inclusion is not limited to the pharmacy and studies have been designed where the general practitioner's office form the inclusion point [60, 61]. At the inclusion point, the patient is informed about the intensive monitoring study and is asked to participate. When registering online, the patient is asked for an e-mail address which will be used for further correspondence. In addition, information about patient characteristics and drug use is collected. After registration, the patient receives questionnaires by e-mail at specific points in time, allowing longitudinal data collection. In these questionnaires, questions are asked about drug use and possible ADRs. These data are coded and analyzed with the purpose of identifying new signals or obtaining information that will extend the knowledge about the safety of the drug under study [55–61].

For LIM, patient participation is of vital importance since the system can only be valuable and sustainable if patients actively choose to participate and share their experiences. In order to increase participation, patients' motivation for participation in LIM was investigated. The main motivation for participating could be classified mainly as altruistic reasons. Often experiencing ADRs or other negative experiences with drugs were not important as motivation [62]. In another study the reasons for non-response were investigated and the results from this study suggest that patients are willing to participate if they are asked and have the means to do so, i.e., Internet access [63].

Besides patient participation, web-based intensive monitoring also needs to be able to collect information which is relevant for pharmacovigilance. In the pharmacovigilance community there is a need for more information about adverse drug reactions such as the time course and management thereof. If it is clear when an ADR occurs, how long it persists and what actions can be beneficial in the management of the ADR, this knowledge can help optimizing pharmacotherapy for the individual patient. Because web-based intensive monitoring collects longitudinal data, it is possible to answer this type of questions [55]. Direct collection of information from patients also makes it possible to collect information regarding impact of an ADR [61]. In addition, although primarily not designed for this purpose, the system can also provide information about the use of the drug in daily practice such as age- and gender

distribution, drug dose, and indication for use. From these data, it is possible to see if the drug is prescribed off-label both with regards to the age as well as the indication and dosage [56].

3.3 Social Media as a New Source of Data

All the methods of collecting information from patients described above are dependent on the patient knowling where to report his ADRs. As most patients do not know where to report their ADR, the contribution of patient reported information to pharmacovigilance is not fully utilized at the moment. However, with emerging technologies, patients increasingly share their experiences of drug use and adverse drug reactions on social media such as forums, blogs, and social networks. Social or digital media tend to be umbrella terms used to describe often Internet-based systems allowing open discussion [64]. Consequently, very heterogeneous data sets are often discussed under the broad social media and digital media umbrella, including:

- Social media blogging type sites (e.g., Facebook, Twitter), Disease/product-specific discussion forums.
- Patient engagement programme data.
- Web search logs, e.g., Google and Bing.

Pew Research Centre's survey "The Social Life of Health Information" conducted in 2013 among 3000 adults in the US, found that 80% of Internet users had looked online for information about health topics such as specific diseases or treatments. Thirty-four percent of Internet users had read someone else's commentary or experience about health or medical issues on an online newsgroup, website, or blog and 4% of Internet users had posted their experiences with a particular drug or medical treatment online [65]. Due to quantity and near-instantaneous nature of data capture in social media, it provides potential opportunities for real-time monitoring of ADRs, greater capture of ADRs, and expedited signal detection [63, 66]. Figure 1 shows the different sources of social media being used for datamining.

In a review by Sarker et al. 22 publications were identified describing automatic methods for ADR detection from user posted data on social media. The earliest work dates from 2010, and the majority of work was published in 2014, showing the increased interest in this topic [67]. The process of using data from social media for ADR detection can be illustrated in Fig. 2.

One of the challenges with using social media as a source of information for pharmacovigilance purposes, is the classification of raw data. How do you know that a post contains information about a drug and an ADR? When reporting an ADR to a spontaneous reporting system, patients fill in a reporting form which allows structured collection of information. The data from the reporting form are reviewed and might be complemented (for example drugs

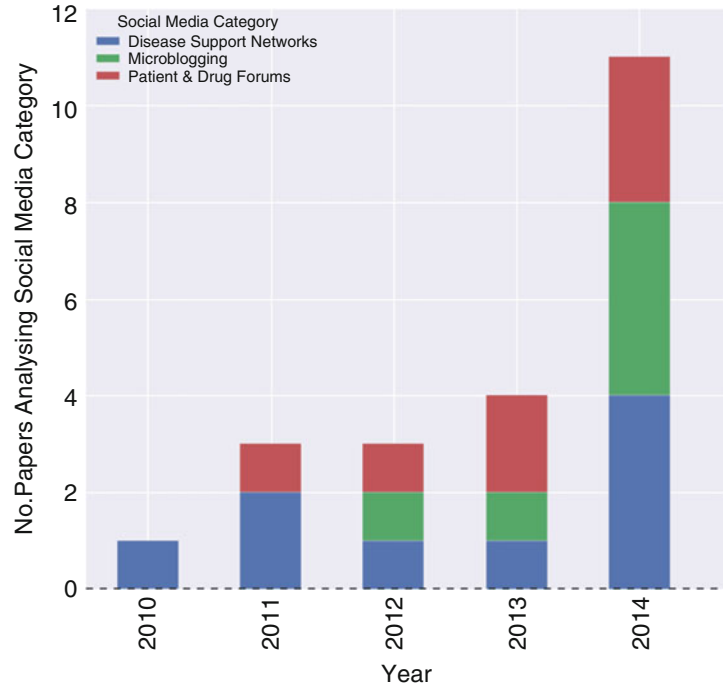

Fig. 1 The different sources of social media being used for datamining

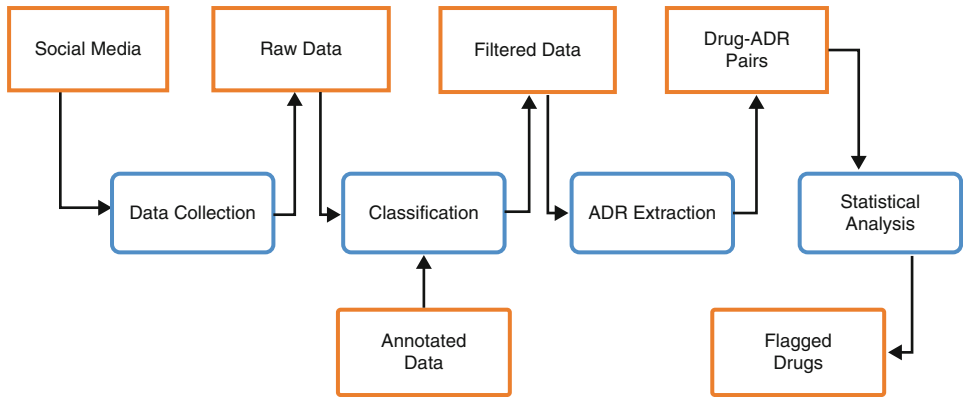

Fig. 2 Process of extracting data from social media data for pharmacovigilance purposes. Reprinted with permission from [67]

and ADRs can be coded using a dictionary) before it is entered into a database for further analysis [17], and while there is often an opportunity to provide free text as a clinical narrative, this is optional. Consequently, the vast majority of aggregate analysis of spontaneous reports has focused on the analysis of the structured data.

By contrast, information in social media largely consists of free text. Free text is unstructured, is subject to complexities and

variability of natural language, and abbreviations and therefore challenging to deal with algorithmically [68]. For social media to be a useful source of pharmacovigilance information, it is necessary to identify the information that relates to drug use and adverse events. In order to avoid confusion with the regulatory definition of an adverse event the word "Proto-AE" is used to describe social media posts with resemblance to AEs [69]. The major challenges in this area are that drugs names can be described in a variety of ways, an example of the named entity recognition (NER) problem. In studies this problem has been addressed by using search queries involving both brand and generic names of the drugs. Another approach is to use the drugs' phonetic spelling which addresses the issues associated with misspelling [66].

Identifying Proto-AEs in free text is even more challenging than identifying drug names as these also involve complex phrasing. In some studies, a predefined list (lexicon) of adverse drug reaction is used, such as MedDRA. However, this approach will have difficulties to capture cases where creative language is used to express an ADR [66, 67]. Another limitation is that MedDRA for example is only available in English and a restricted number of other languages, making it difficult to use this approach in countries in whose language the dictionary is not available [70].

Another approach to identify the relevant data is to develop supervised machine learning algorithms. Machine learning is the process of constructing algorithms that can learn from input data typically with a view to making decisions based on previously unseen data. Such an approach can be valuable where rules are not known, nor can be readily inferred, a priori. This is the case with unstructured data where each corpus of information can be very different and generalizability of specific rules from one corpus to another is challenging. Machine learning algorithms broadly fall within two categories: supervised learning and unsupervised learning. Supervised machine learning involves the process of a human "teacher" providing the desired outcome for each item of input data. This would typically involve a desired target variable for the data and within the context of pharmacovigilance could simply be a binary value indicating whether or not a specific sentence contains an ADR. These require a substantial amount of data to be manually curated, often by a domain expert, which makes it costly [66]. For example, in a study looking at the usefulness of Twitter as a source of information, 61,401 Twitter posts were manually curated [69].

Yang et al. describe a method that integrates both text and datamining techniques to automatically extract important text features from the posts first, and then classify the posts into positive/negative examples based on a few predefined ADR related posts. The classification process is based on a partially supervised learning method, which uses a small number of known positive posts to

identify other posts of similar text features from a corpus of unlabeled posts [71].

Nikfarjam et al. have developed the ADRmine method, a machine learning-based concept extraction system that uses conditional random fields (CRF). ADRmine utilizes a variety of features, including a novel feature for modeling words' semantic similarities. The similarities are modeled by clustering words based on unsupervised pre-trained word representation vectors (embedded) generated from unlabeled use posts in social media using a deep learning technique [72].

Most studies available of the use of social media in pharmacovigilance are focused on detected posts which contain Proto-AE information. However Powell et al. take this one step further and have also looked at statistical analysis of data from social media. By using natural language processing (NLP) each post (from Twitter and Facebook) was reviewed and the text was matched against a vernacular to regulatory language translation dictionary which contained over 5000 phrases matched to 1500 MedDRA preferred terms. Drug names were also standardized based on the Anatomical Therapeutic Chemical (ATC) classification system for drugs. Filtering step was applied to identify which posts were relevant for drug safety using a Bayesian probabilistic model which was developed through statistical machine learning computation. The dataset to train the model was developed manually coding more than 1,000,000 posts. The next step was deidentification of the post removing personally identifiable information. The social media data were supplemented with other sources of information such as process. The supplemented data included mention and sales data to be used as denominators in frequency calculations, the European medicines Agency (EMA) Important Medical Events (IME) terms list, drug labeling information and spontaneous AE data from the FDA AE Reporting system for comparison purposes, to help the review.

From these data, disproportionality was calculated using the proportional reporting ratio at the drug-event pair level. These analyses showed that the proto AEs with the highest PRRs were mostly known drug-ADR combinations or events relating to conditions for which the drug was indicated [73]. This is a nascent research field, and much research in the coming years to further articulate the scientific role of social media systems, can be anticipated.

3.3.1 Regulatory Framework

The use of social media as a source of information over the safety of drugs is in its infancy and there are no clear guidelines on how this information should be handled from a regulatory point of view. However, in the latest revision on the GVP 6 module in September 2014 from the EMA, guidance was provided on how MAHs should

treat information from Internet or digital media under their responsibility although the text leaves room for interpretation.

> Marketing authorisation holders should regularly screen Internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for, and/or controlled by the marketing authorisation holder. The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities within the appropriate reporting timeframe based on the date the information was posted on the Internet site/digital medium.
>
> In relation to cases from the Internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided) [74].

3.3.2 *Ethical Framework*

Using data that are not primarily shared for pharmacovigilance purposes raises a number of ethical issues. What measures should be taken to identify individuals by utilizing additional information such as the geocode location on posting, username, and other potentially personally identifiable information [66]? How would patient using social media react when approached for additional information by organizations that collect pharmacovigilance data? Not addressing these issues and being transparent about why and how social media is used in pharmacovigilance may affect trust in the system. Feedback mechanisms to try to contact reporters for required additional information when possible is a core benefit of spontaneous report systems—it will be interesting to see how this is addressed in social media, if at all, as the field develops.

The need for leveraging emerging technologies for pharmacovigilance was recognized by the Innovative Medicines Initiative, a public-private partnership between the European Union and the European pharmaceutical industry. WEB-RADR brings together academic- and industry researchers with the aim of developing new technical tools for data mining publicly available data shared on social media websites. Besides developing the technical tools to enable data mining of social media, a regulatory framework for social media mining for ADRs will be established, taking the ethical aspects surrounding this topic [75].

4 Engaging with the General Public

Raising the public's awareness of the existence and purpose of pharmacovigilance systems in general will presumably increase the number of patient reports to spontaneous reporting systems but it can also have a positive effect on the general public's perception of social media data mining if they are aware of why it is done. A recent survey conducted among the general public in the Netherlands showed that only 17% knew that adverse drug reactions could be

reported to Lareb [71, 76] and in the UK 8.5% of the general public knew about the Yellow Card Scheme for reporting ADRs [22].

In contrast to HCPs, the general public is more difficult to target regarding promotional activities, being a larger and more diverse group of reporters. One way to approach this problem, and involve other stakeholders in pharmacovigilance, is to form partnerships. Possible partners for promoting pharmacovigilance and the role of the patient herein are the patient organizations. By approaching patient organizations the general public is narrowed down to the drug using target population. In addition, members of patient organizations are also concerned and knowledgeable about their health status and hopefully more likely to report adverse drug reactions.

When raising the awareness about pharmacovigilance, it is important to show the general public what is done with their information and how that contributes to better pharmacovigilance, for example by sharing information about reports submitted and signals that have been raised on the basis of the reports. At the moment more and more organizations have opened up their databases to the general public [77, 78].

5 Summary and Personal View

With patient empowerment, patients are more informed than ever about their diseases and treatment options. Internet has facilitated searching for health related information and has also enabled social networking by patients [65]. Patients have the potential to play a vital role in providing information about the safety of the drugs they use, especially when it comes to increased knowledge over symptomatic adverse drug reactions. The occurrence of these symptoms, although not necessarily posing an immediate urgent medical problem, is strongly linked to a patient's treatment adherence and by either prevention or adequate management of these ADRs patient will experience more benefit from the treatment [79–81].

One of the major limitations of spontaneous reporting is HCP underreporting. The underreporting can have two reasons; the first is that patients do not discuss their ADR with health professionals, leading to signals being missed. Secondly, there might be discordance between what HCPs and patients believe is important, and that HCPs would not report something that they consider unimportant. Patient reporting can help minimize this limitation.

The contribution of patient reports to pharmacovigilance has been acknowledged in the new pharmacovigilance legislation and since 2012 all European countries must have implemented patient reporting. An overview of patient reporting in 50 countries

recognizes that 17 countries implemented their patient reporting systems in 2012–2013, probably as a response to the EU legislative changes. It also suggests that countries which quite recently started accepting patients as reporters, have lower reporting rates than countries that have accepted patient reports for a long time [28]. But implementing patient reporting systems does not necessarily mean that the value of patient reports has been acknowledged everywhere. In some countries, actively promoting patient reporting might not be done in fear of suddenly being flooded with reports in amounts difficult to handle. However, if we fully want to use the resource that patients can be to pharmacovigilance, active promotion is necessary and those organizations responsible for the processing and assessing these reports should be given the means needed to do this.

However receipt of large volumes of patient reports is not enough to contribute to pharmacovigilance. The reports also have to contribute to signal detection. Patients can, and more often do, provide detailed information about the duration and management of the ADR and its impact on the quality of life; information that until now has been scarce in pharmacovigilance [35, 55, 59, 61, 82]. However, the methods currently used to capture information from patients and the methods applied to detect signals are not fitted to make best use of the rich information that patients reports. Since patient reports contain information which cannot be easily captured in structural fields, new methods and measures should be developed which make better use of this information.

Mobile technologies can offer new possibilities for pharmacovigilance. In terms of patient reporting of adverse drug reactions, it offers the possibility of creating reporting forms that are easier to fill in than many of the paper- and electronic reporting forms available today. It also facilitates information exchange between the reporter and the one receiving the report. In the ADR app which was launched in the Netherlands as part of the IMI WEB-RADR project [75], focus was not on creating a reporting app only, but on creating an app where information about ADRs was available, and with the possibility of also reporting ADRs. Since awareness of reporting is quite low among the general public, it is only a minority of patients who will report an adverse drug reaction to a spontaneous reporting system.

In order to make use of the patient as a source of information, one must keep looking for the information where patients usually share it. Patients are increasingly using social media to search and exchange information about their health status. Due to the real-time nature of social media, it is possible that social media data mining can identify signals and generate warnings more promptly, allowing these to be acted upon before they would be with traditional pharmacovigilance practices [66]. In order to maximize the use of social media for pharmacovigilance purposes, it is important

to develop methodologies that can accurately capture data about drug use and adverse drug reactions accurately. A second step is then to develop methodologies on how to analyze this data and perform signal detection among this data. The real proof of the usefulness of social media is when it shows that it can detect signals which other methods are unable to do, or detect the signals faster and more reliably than other methods.

The use of mobile devices has created a new world of opportunities and has the potential to change the pharmacovigilance landscape. Through health apps patients have been provided with tools to monitor their own diseases and treatment. For example, an app for patients with epilepsy helps the patient to keep track of their seizures and has a medication list, including a schedule that reminds the patient to take the drug [83]. In the future, I believe that reporting of adverse drug reaction to spontaneous reporting systems will not be a standalone activity as it often is now, to have a special form, or have to go to a specific website to report and ADR. ADR reporting will be more integrated in tools that patient use for the management of their disease, for example apps. In the example given above, the app could also have a module of reporting an ADR coupled to the medication list.

A study among patients reporting an ADR to a pharmacovigilance center showed that almost 85% of the reporters were older than 35 years and 55% had a higher professional- or academic education [37]. Using social media and apps for collection of information can add a new source to pharmacovigilance, namely the younger and persons with a lower socio-economic standard.

To fully benefit from the patient reported information, new methods to capture and analyze these data need to be developed. At the moment there is much focus on social media data mining. However, I personally believe that patients are still willing to contribute to targeted data collection, such as described in Sect. 3.2. The increasing use of health apps can facilitate this data collection, and by integrating ADR data collection in tools already used by the patient in his disease- and/or drug management, it becomes a natural part of treatment. In the future pharmacovigilance will receive patient reported outcomes from multiple sources, including old-fashioned reports to spontaneous reporting systems, information from social media data mining and targeted data collection through apps and other electronic means. Although the proportion between the different methods will vary over time, I do not think that one of the methods will become obsolete within the near future.

But with what aim should patient reported information be collected? The primary aim of pharmacovigilance is to detect signals, a signal being defined as “information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a

known association between an intervention [e.g., administration of a medicine] and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [40]. In the past, focus has been on identifying the new ADRs, and less focus on new aspects of known ADRs. Research has proven that patient reports contribute to signal detection of new ADRs [41, 42], but I think that patient reported outcomes are extra valuable when it comes to identifying new information about known ADRs, such as time course, impact on daily functioning and management thereof.

Patient reported outcomes provide a number of advantages, including higher volume and richer context, leading to a better understanding of adverse events. Patients and carers can also give a better context than HCPs on the effects of treatment on patient's functioning and quality of life. At the moment the general public are increasingly becoming involved in all aspects of pharmacovigilance. The pharmacovigilance community needs to recognize the value of the information contributed by patients, and this value needs to be underpinned by research. The possibilities are endless but need to be further developed and evaluated.

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Chapter 10

Evidence-Based Pharmacovigilance for Medicines Used in Public Health Programs in Africa

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Abstract

Pharmacovigilance in Africa has grown sharply this millennium with the number of African countries joining the World Health Organisation (WHO) Programme for International Drug Monitoring having increased from just 5 in the year 2000 to 35 in 2017. However, published information indicates that Africa's contribution of individual case safety reports (ICSRs) to the WHO ICSR database (VigiBase) is paltry currently standing at less than 1% of the >14 million ICSRs in VigiBase. Moreover, there is little evidence of African countries collecting, analyzing, and using data from their settings to inform pharmacovigilance and drug safety decisions in their own countries. The huge doses of medicine and vaccines deployed for public health programs including those against malaria, tuberculosis, and HIV/AIDS as well as those for infant immunization against preventable diseases means that there is opportunity to collect real world data in relation to these medicines and vaccines. Spontaneous reporting may not necessarily be the best approach in the various African countries considering the high under-reporting associated with all spontaneous reporting schemes globally. However, there are opportunities to utilize more active pharmacovigilance approaches including cohort event monitoring and targeted spontaneous reporting to improve collection and use of safety data in Africa to improve patient care, especially in public health programs in Africa.

Key words Pharmacovigilance, World Health Organization (WHO), African countries, Cohort event monitoring, Targeted spontaneous reporting, Safety data

1 Introduction

The thalidomide tragedy and the resulting global actions spearheaded by the World Health Organization (WHO) led to World Health Assembly (WHA) Resolution 16.36 which invited "Member States to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use" [1]. This WHA culminated in the establishment of the WHO Programme for International Drug Monitoring (PIDM) in 1968 with ten participating full member countries. None of the ten founding members of the programme were from Africa and it took nearly a quarter of a

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century before the first two African countries (Morocco and South Africa) joined the WHO Programme for International Drug Monitoring in 1992. Currently, the PIDM has 125 member countries 35 of whom are from Africa. Figure 1 shows the growth of African membership in the WHO Programme since its inception. As shown in the graph, most of the countries from Africa joined relatively recently and the contribution of African countries to the WHO individual case safety report (ICSR) global database of spontaneous reports, VigiBase™, is extremely low with only 0.88% of the 11,824,804 reports being contributed by African countries as at the end of September 2015 [2]. Pharmacovigilance does not only involve the collection and submission of ICSRs to VigiBase™. It includes several other activities including signal generation and management, risk management and minimization, communication with the public, patient safety, medication errors prevention, and generally taking action to assure public health and safety in so far as the use of medical products is concerned. Studies however indicate that pharmacovigilance in Africa is weak—from all the perspectives including systems, legislation, structure, and activities [3]. It is important to highlight that prior to 2000, most countries in Africa had to contend with chronic shortage of medicines, weak and non-existent supply chains for medicines, and other health commodities and extremely limited financial resources to make any difference [4]. In such an environment, pharmacovigilance, however laudable it is, had to take a back stage: after all what is the point of starting a safety monitoring system if there are no products to be monitored? It was only when access to medicines started increasing that the stark reality of absent safety monitoring systems was identified leading to calls for collaboration to ensure that all developing countries including those in Africa develop pharmacovigilance systems to protect their populations from medicinal product associated harms [5]. The adoption of the millennium development goals by the United Nations in 2000 provided increased funding to tackle several health and social problems. Funding was therefore provided to several low and middle income countries to combat priority diseases. The growth in pharmacovigilance in Africa was therefore spurred by the increased funding for public health programmes, typically those designed to fight HIV/AIDS, tuberculosis, and malaria and the Global Fund Against HIV/AIDS, TB and Malaria (Global Fund) remains one of the main sources of funding for public health programmes and pharmacovigilance in Africa [6]. In addition, initiatives like the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the US Presidents Malaria Initiative (PMI) [7] have also provided huge financial support for public HIV/AIDS care [8] and for malaria control. The Bill and Melinda Gates Foundation has also been a good and stable source of financial support for public health programmes and for the projects to improve pharmacovigilance in Africa, a recent one

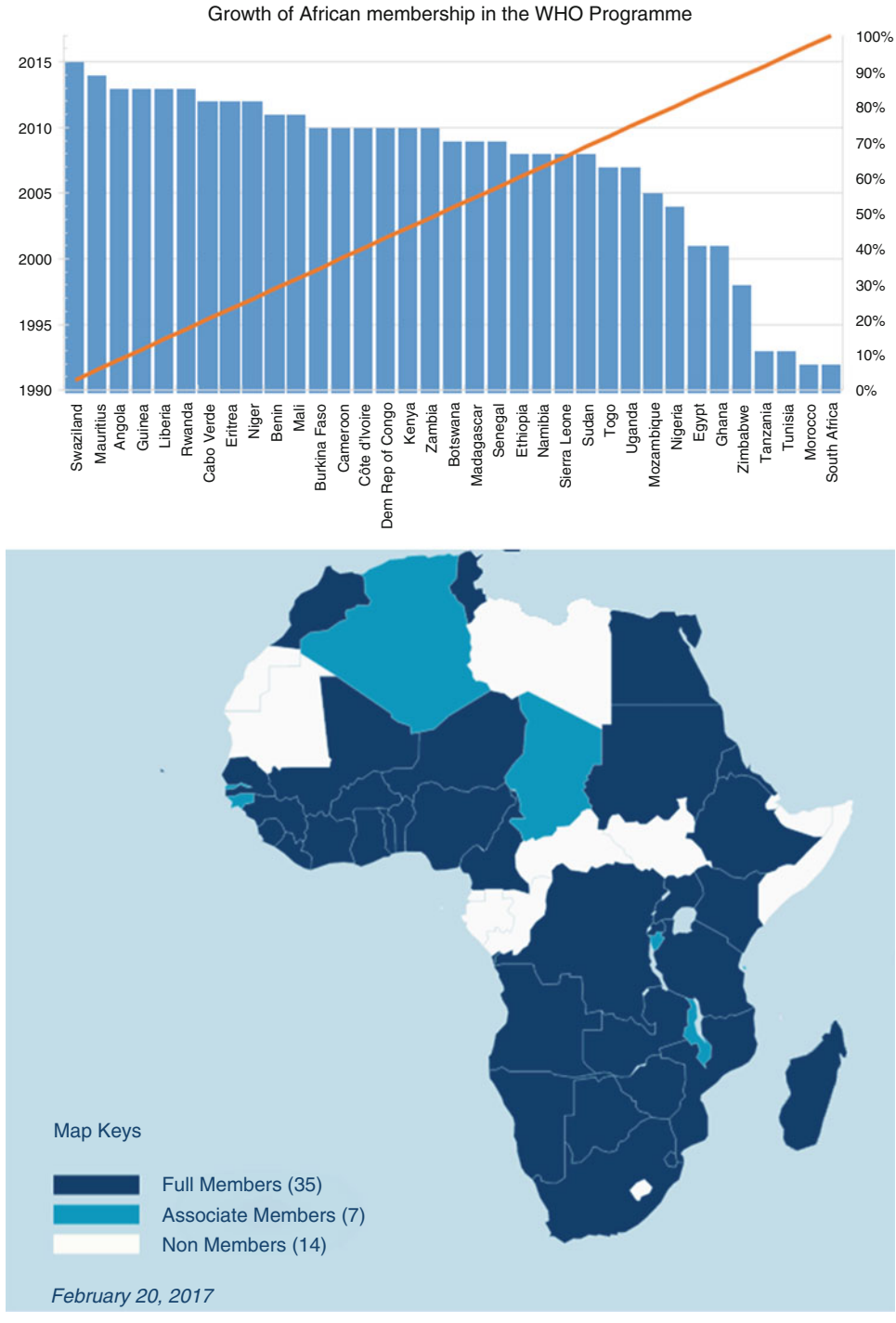

Fig. 1 The growth of African membership in the WHO Programme since its inception

being the INDEPTH Network for Effectiveness and Safety Surveillance (INESS) platform which undertook one of the few focused large-scale phase IV studies of antimalarials in Africa [9] . The interest of the BMGF for safety surveillance of products in Africa and other low and middle income countries (LMICs) led the Foundation to convene a Safety Surveillance Working Group (SSWG) which produced a report on how safety surveillance could be carried out in Africa and other LMICs. The SSWG poignantly recommends among other things that "approaches toward post-market safety surveillance in Africa need not mirror the approaches embarked upon by Western and industrialised countries" [10]. This is an acknowledgement of the fact that the systems in Africa have developed differently from those in developed countries and the continent most likely provides opportunities to develop innovative, cutting edge approaches for global pharmacovigilance based on the fact that it can learn from the history of failures and successes in existing developed country pharmacovigilance systems and then utilize the vast array of contemporary tools and technologies to develop responsive, cost-effective, as well as rigorous processes and systems for real-life safety monitoring of medical products. For example, the pharmacovigilance systems in Africa have already started relying on the use of cell phones to collect data from patients rather than rely on paper-based systems. The extensive use of mobile phones across Africa has already changed the way pharmacovigilance studies are undertaken with contact and follow-up occurring by use of cell phones rather than the traditional home visits that were expensive and challenging. Evidence from current studies shows that mobile phones are a feasible and realistic approach for pharmacovigilance and provide robust data in prospective studies [11]. These initiatives are exciting and the full array of tools and methods that can be used to generate robust post-marketing safety data in Africa is yet to be known. The full realization of the potential of Africa to provide innovative globally acceptable solutions for pharmacovigilance will take time to manifest, but it is important to analyze the current approaches toward pharmacovigilance in Africa with a focus of products used in public health programmes. Of relevance is the level to which pharmacovigilance decision making in Africa has been driven by evidence whether locally generated or foreign and to examine the way such evidence has been obtained—whether through traditional pharmacovigilance approaches or by the use of newer methods and tools.

2 Public Health Programs in Africa and Pharmacovigilance

In all countries in Africa, national governments, in collaboration with development partners like the WHO, have established formal public health programmes to spearhead the fight against endemic

diseases. Most countries therefore currently have National AIDS/HIV Control Programmes (NACP), National Tuberculosis Control Programmes (NTCP), and National Malaria Control Programmes (NMCP). In addition, these countries have Expanded Programmes on Immunization (EPI) which are responsible for national childhood immunization programmes. The EPI and the various disease control programmes are responsible for the deployment of hundreds of millions of doses of vaccines and medicines to hundreds of millions of people annually. However, most of these programmes and their activities are not associated with verifiable pharmacovigilance systems: concerns have therefore been raised on the ethics of deploying millions of doses of medical products to vulnerable populations without any robust safety surveillance programme. These concerns have led to several initiatives aimed at improving pharmacovigilance in Africa. This was definitely a factor that has led to increasing numbers of African countries joining the WHO Programme for International Drug Monitoring, and the relative sharp increase in the number of ICSRs from Africa in VigiBase [2] though the absolute numbers are still extremely low for a continent of nearly 1.5 billion people. In addition to the relative increase in the number of ICSRs being reported from Africa, there has also been an increase in the number of peer-reviewed publications relating to pharmacovigilance and/or the safety of medicines and vaccines used in public health programmes in Africa [12–16]. This chapter provides an overview of the state of play of pharmacovigilance and safety surveillance in public health programmes in Africa with a focus on four public health programme areas namely: malaria, HIV/AIDS; tuberculosis; and immunization. This does not mean that other public health programmes, e.g., those for the control of neglected tropical diseases or non-communicable diseases etc. are less important or do not require pharmacovigilance. Rather, it is to examine pharmacovigilance in these four major areas with a view to shedding light on the evidence that may exist and how that evidence is being utilized in pharmacovigilance in Africa. The high burden of malaria, HIV/AIDS, and tuberculosis in Africa means that most medicines are used to combat these conditions. Pharmacovigilance of these products is therefore key as is the safety monitoring of vaccines used in childhood immunization programmes since these vaccines are administered to nearly all children born on the continent making the need for a robust safety surveillance system critical and non-negotiable.

3 Pharmacovigilance of Antimalarials in Africa

In early 2000, the WHO and other agencies called for a change in national malaria policies and treatment options due to widespread parasite resistance to the main drugs being used in Africa—

chloroquine or a combination of sulfadoxine + pyrimethamine (SP) [17]. The new recommendation was to use artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria. This shift in malaria policy provided a need and also an opportunity to establish PV systems to monitor the safety of the ACTs particularly given the limited knowledge of the adverse drug reactions profiles of these products in Africa [18]. In the process, the PV of antimalarials became the pathway for several countries to establish national PV systems. Indeed, the first concerted African training programme on PV was held in 2003 in Lusaka, Zambia by the malaria and PV departments of WHO [19]. Though malaria was the pathway for the establishment of any pharmacovigilance system at all in most countries, the WHO and national authorities were naturally keen that any PV system served the whole country and not just malaria control programmes. In addition, the funds provided especially by the Global Fund for the policy change also represented an opportunity to obtain modest funding to start PV activities which had hitherto had no funds at all whatsoever. Subsequently, the US President's Malaria Initiative (PMI) as well as the Roll Back Malaria Programme (RBM) all contributed toward the building of PV centers and systems in Africa though uptake of these resources by countries was very weak [18]. In the past few years, it can be argued that PV of antimalarials has enabled PV in Africa to be firmly entrenched. The first signal from spontaneous reporting in Africa was in relation to an ACT—extrapyramidal symptoms in relation to the use of the combination of amodiaquine + artesunate [20]. This signal was raised solely from data from spontaneous reporting systems in Africa. The signal has since been confirmed and the summary of product characteristics now lists extrapyramidal symptoms as one of the expected adverse effects associated with the use of amodiaquine + artesunate [20]. The WHO has also provided support from active studies—usually cohort event monitoring (CEM)—in Africa and there are publications sharing the experiences gained in these studies [21]. The basis for the use of CEM is the fact that spontaneous reporting of ADRs provides very little individual case safety reports. Therefore, in order to obtain real world data relating to the safety of antimalarials as used in the general population the realistic option is to use active pharmacovigilance approaches including the recruitment and follow-up of patients as occurs in CEM. CEM, when undertaken in the African context, involves the prospective identification and recruitment of patients on the medication of interest and then recording any adverse events that occurred post medicine administration or intake. This is quite different from Prescription Event Monitoring (PEM) as in this case it is patients who are followed up. This is a pragmatic approach as record-keeping is poor in Africa making the traditional PEM all but impossible. CEM is therefore a more realistic and useful approach for collecting

safety data in Africa. Cohort [9, 22] and drug utilization [23] studies have been carried out in relation to antimalarials. However, when one examines the WHO ICSR database, VigiBase, it becomes very obvious that the data from most of these studies are not submitted to the WHO; hence there is much more safety information on antimalarials in peer-reviewed journals than there is in the WHO database. This may be because the regulatory environment did not impose mandatory requirements of ICSRs to the national drug regulatory authorities or, if they did then the enforcement is variable. The lower numbers of ICSRs in VigiBase compared to what is in the published literature may not just be an African phenomenon but rather global and need addressing especially as no published studies exist to quantify the scale of the issue. In relation to ICSRs to antimalarials in Africa, one study actually calculated that Africa contributes just over 1% of ICSRs to antimalarials in VigiBase [18], a situation that is worrying considering that Africa bears the greatest burden of malaria and most antimalarials are used in Africa. This poor reporting of ICSRs from Africa limits the ability of reporting systems in Africa to undertake systematic signal detection in stark contrast to systems in developed countries which are able to detect signals through their reporting systems. In addition to the increasing usage of ACTs to treat uncomplicated malaria, the use of antimalarials in Africa is increasing sharply as older products are being used for newer purposes. For instance, most countries now give SP to mothers as part of "Intermittent Preventive Treatment of Malaria in pregnant women (IPTp) [24] or infants (IPTi) [25]." A combination of amodiaquine and SP is also given to children as part of Seasonal Malaria Chemoprophylaxis (SMC) [26]. For severe malaria, a very serious condition that can be quickly fatal, the WHO now recommends the use of injectable artesunate instead of parenteral quinine due to safety concerns [27]. Despite these massive policy changes and increased usage of medicines outside their original licensed indications, safety data collection remains poor. It is not known to what extent these safety data have been analyzed by the global malaria community to inform policy though individual publications are emerging including those mentioned previously. The newer strategies for malaria elimination and changes in global malaria policy make it necessary and impose a high moral obligation to have systems to collect rigorous data on these products, especially when usage is for malaria prevention and not treatment. As more and more countries focus on malaria eradication and elimination antimalarial drugs will focus extensively and will need to be monitored closely. This is because as populations witness less malaria, they will become very intolerant of any ADRs to antimalarials and will have very high safety expectations of antimalarials—just as is occurring in the vaccine world. The WHO has demonstrated the importance the global community places on safety surveillance of

antimalarials and has insisted for more safety and programmatic data in relation to the novel malaria vaccine RTSS,AS01 (Mosquirix), even though the product has received a Positive Scientific Opinion from the European Medicines Agency (EMA) under the so-called Article 58 process [28]. The studies to be performed have been deemed as "post authorization safety studies" by the EMA and will focus on collecting data on both safety and effectiveness of the vaccine. When completed, these studies will constitute some of the most rigorous data-driven studies on antimalarial products in Africa and may offer an approach toward new products for malaria safety surveillance in particular and pharmacovigilance in Africa in general. Another example is the CEMISA study (clinicaltrials.gov identifier NCT02817919) which is funded by the Medicines for Malaria Venture (MMV) and sponsored by the African Collaborating Centre for Pharmacovigilance to collect real world medicine safety and utilization data in four African countries (Ethiopia, Ghana, Malawi, and Uganda) and which represents one of the first ICH-GCP post-approval real world studies on a product for treating severe malaria. Other studies are also getting underway including studies on Pyramax™, an antimalarial granted positive scientific opinion by the European Medicines Agency as part of its Article 58 procedure in support of the World Health Organization. The fact that injectable artesunate is being examined as an investigational new drug in the US [29] for the treatment of severe malaria shows how data from Africa will inform global policy. This makes it imperative for real world data collection and analysis systems in Africa to be rigorous and ICH-GCP compliant.

4 Pharmacovigilance and National HIV/AIDS Control Programmes in Africa

Africa bears the largest burden of HIV/AIDS in the world and, of the estimated 35 million people living with HIV worldwide in 2013, 71% were in sub-Saharan Africa [30]. Massive progress has been made in reducing HIV-associated mortality by the rapid scale-up of antiretroviral therapy. Since HIV is now a chronic disease and patients have to be on life-long treatment, safety monitoring has to be undertaken for the products used to manage the primary HIV infection as well as those used to prevent HIV-related opportunistic infections. In addition, there is also a need for pharmacovigilance of products used to treat other endemic diseases as well as those for treating the increasing cases of non-communicable diseases since interactions between these products and antiretroviral therapies can occur. Hence the pharmacovigilance of antiretroviral therapy in Africa has to include the safety monitoring of anti-retrovirals alone as well as monitor the safety implications of concomitant administration of anti-retrovirals and other medicines, e.g., anti-malarials, anti-tuberculosis, anti-hypertensive, and anti-diabetic

medicines. Safety surveillance of anti-retroviral therapy is perhaps the most intense pharmacovigilance activity in Africa. There are several publications involving the safety monitoring of products used for post-exposure prophylaxis in HIV/AIDS [31] and a lot more on the adverse events associated with anti-retroviral therapy in general [32]. In relation to the methods employed, both passive and active pharmacovigilance approaches have been used with spontaneous reporting and targeted spontaneous reporting as well as cohort event monitoring (CEM) being used [16, 33]. Most of the studies undertaken so far have been stand-alone with only the IeDeA consortium undertaking multi-country post-approval studies. The International Epidemiologic Databases to Evaluate AIDS(IeDEA) Collaboration is however not really focused on pharmacovigilance but rather on epidemiology and safety is not the primary endpoint in this collaboration even though the collaboration encourages treating physicians in the various IeDeA sites to collect adverse event information on its electronic capture tools. Very little of this data finds its way to the WHO database depriving the world of real world safety data from multiple countries and sites. Despite the intense research and publication currently taking place on the safety of anti-retrovirals in Africa, it appears most of the data is not shared with national authorities for onward transmission to the WHO database, VigiBase. While more than half of the ICSRs from Africa are in relation to products for managing HIV/AIDS, they remain a tiny fraction of the ICSRs in relation to these products. Thus, at the end of September 2015, there were a total of 2962 ICSRs in relation to nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and antivirals for the treatment of HIV infections in the WHO database compared to 105,089 for the same products for the rest of the world [2]. This is despite the fact that Africa has the largest global burden of HIV/AIDS and consumes the largest volume of these products. In relation to WHO policies for the treatment of HIV/AIDS, majority of the evidence has come from clinical trials rather than from post-market surveillance though post-approval clinical trials in Africa were key in changing treatment recommendations for children, e.g., early treatment of children [34] with HIV and early time-limited treatment of HIV in children versus deferred treatment [35]. In relation to safety, data from Africa seem to have contributed little in the signals raised in relation to several antiretroviral products whether used alone or in combination.

For instance, abacavir hypersensitivity appears to have been more and better described in studies from developed countries than from Africa. Similarly, the risks of myocardial infarction with nelfinavir, anemia with zidovudine, rashes with nevirapine, and lactic acidosis with stavudine appear to have all been identified from clinical trials and post-approval studies from outside Africa

[36]. Nonetheless, a few studies in Africa have attempted to provide local data to justify local policy, e.g., data showing the safety of post-exposure prophylaxis with anti-retrovirals [31] or the influence of modification of anti-retroviral therapy on the ADRs experienced by patients [32]. The large number of trials involving anti-retrovirals that has taken place in Africa gives the continent a good human resource base for clinical evaluation of products. However, it appears there is a dearth of published safety data when it comes to post-authorization safety surveillance. This may be due to several factors including lack of investment for human and technical resources to undertake routine pharmacovigilance and generate the evidence needed to assure a continuing positive benefit-risk ratio of marketed products. It may also be that national authorities in Africa rarely use their own data for regulatory decision making relying instead on the decisions of stringent regulatory authorities like the US FDA or the European Medicines Agency or on decisions made by the WHO. Whichever the case, there is the need for every country to undertake robust PV of all products used in public health programmes including those against HIV/AIDS.

5 Pharmacovigilance of Anti-Tuberculosis Drugs

Tuberculosis (TB) provides an area where PV data from Africa has had immediate impact on policy and will continue to do so for some time to come. Most drugs used to manage TB are quite old and in the late 1980s when thiacetazone (available since 1940s) began to cause severe cutaneous reactions in HIV positive individuals in Africa, the WHO recommended its replacement with ethambutol. Thiacetazone is currently no longer recommended by WHO as first-line therapy for TB except in rare and special situations but the experience it provided caused the WHO to call for increased investments in the PV of TB medicines [37]. There have been very few new products for TB and the management of TB, especially multi-drug resistant TB (MDR-TB), is extremely challenging especially in environments where HIV is also high. In 2012, the US FDA granted accelerated approval for the use of bedaquiline for managing MDR-TB based on data from phase IIb trials only [38]. This is a bold move because it goes against the traditional paradigm of drug development and suggests a new possibility for critical areas in public health. The need for an effective treatment for MDR-TB and the public health considerations allowed the FDA to approve bedaquiline. The WHO subsequently recommended its usage in national TB programmes but with a clear call for active and robust PV to ensure that more data is collected on its safety, benefits, and effectiveness in routine use. The current usage of bedaquiline in public health programmes is therefore essentially a large, global open-label nonrandomized phase III study. The

collection, sharing, and use of safety information in this phase will determine whether this approach of early product release associated with large post-authorization data collection is feasible, responsible, and useful for public health. WHO continues to encourage all national TB control programmes to undertake PV of drugs used in TB and has published guidance to assist in the same. However, compliance by national authorities is variable and there has not been an increase in the ICSRs in VigiBase in relation to anti-TB drugs though there have been a few publications in the literature from other regions of the world [39, 40]. Like malaria and HIV/AIDS, there is still a long way to go before real world post-approval safety data from Africa becomes widely available to inform local, regional, and global policy.

6 Vaccine Pharmacovigilance in Africa

Pharmacovigilance in Africa is in its infancy but it is far more developed than vaccine pharmacovigilance (Vaccine PV) in Africa. Vaccine PV is a new area, having only been recently defined [10] as an area similar to and yet distinct from "drug PV." The management of data on adverse events following immunization (AEFI) in particular and all data on vaccine PV in general varies from country to country with some countries having separate systems and some having the same. Vaccine pharmacovigilance falls in two broad domains in several low and middle income countries including most countries in Africa: the Expanded Programme on Immunization (EPI) which is responsible for national childhood immunizations and the national regulatory authority responsible for licensing vaccines and all other products [41]. Both of these agencies collect safety information on vaccines. Where the EPI collects AEFI, is expected that it will be shared with the national regulatory authority but this is rarely the case and the WHO ICSR database has very few AEFI data from Africa. Assessments by the WHO indicate that several countries in Africa do not have even the barest capacity for vaccine safety surveillance [42, 43]. The Global Vaccine Safety Blueprint has therefore been developed to ensure that all countries (especially the low and middle income countries of Africa) have efficient vaccine safety monitoring systems (Global Vaccine Safety Blueprint). Despite this weakness, there have been approaches toward real-life safety monitoring of vaccines used in Africa. For instance, in 2003, Dodoo et al. [44] undertook an active follow-up study to document adverse events following immunization after a change in EPI policy in Ghana to replace the trivalent Diphtheria-Pertussis-Tetanus vaccine with a pentavalent vaccine containing the following antigens: Diphtheria, Pertussis, Tetanus, Haemophilus influenza type B, and hepatitis B. In 2010, the rapid development and deployment of a vaccine (MenAfriVac) against Neisseria

meningitidis serogroup A, the major cause of meningitis outbreaks in sub-Saharan Africa, offered the opportunity to develop a responsive and pragmatic system for safety data collection in sub-Saharan Africa [45]. During the one-month period in which nearly 400,000 individuals aged 1–29 years (including pregnant women) were immunized in Niger, an enhanced spontaneous surveillance system was put in place to collect AE data during the campaign and up to 6 weeks later. This allowed the collection of 82 suspected AEFIs 16 of them being severe. The authors acknowledged the underreporting of AEFIs but also identified the opportunity that the campaign provided to develop PV in Niger to international standards. New or newly deployed vaccines in Africa is hence providing an opportunity to strengthen PV in Africa and active PV studies are currently being undertaken in association with the deployment of the rotavirus vaccine [46], the pneumococcal conjugate vaccine [47], and the human papilloma virus vaccine [48] in Africa. The very low number of ICSRs from Africa in VigiBase shows that the national spontaneous reporting systems in Africa are currently not receiving and/or sharing enough spontaneously reported ICSRs. So even though spontaneous reporting remains the bedrock of PV, other approaches have to be used in Africa. Active approaches, especially cohort event monitoring (CEM) appears to be able to provide rigorous data quickly. However, it appears that data from CEM is not being shared with national regulatory authorities for policy decision making. There is much more safety data from Africa in the published literature than in the WHO database a situation which must change and which requires collaboration between all stakeholders, especially researchers, academia, and national drug regulatory authorities.

7 Discussion and Conclusion

The pharmacovigilance landscape in Africa has changed remarkably since 2000. Although there were only five African countries that were members of the WHO Programme for International Drug Monitoring in 2000, there are now 35 countries. This increase has been accompanied by increasing establishment of national regulatory authorities as well as increasing passing of laws and guidelines for PV and product regulation. Some countries are already asking the pharmaceutical industry to provide periodic safety update reports or similar documents as they would do in ICH countries. In the past, industry could justifiably point out to the absence of structures and infrastructure for PV and hence state its inability to collect and submit African data to African regulators, as well as analyze themselves. That situation has changed rapidly and industry and regulators will have to find means of collecting and submitting safety data in Africa. Some countries including Ghana, Kenya, and

Nigeria are also demanding that all marketing authorization holders have Qualified Persons for Pharmacovigilance (QPPV) and also establish a complete PV system in line with the EU Good Pharmacovigilance Practice (GVP) guidelines. Clearly, there will be a lot of activity in the PV front in Africa. The gaps identified in this article—especially the low numbers of ICSRs in national databases compared to a high number of safety reports in the scientific literate—need to be bridged. This is important because ADRs from Africa can differ from those of the rest of world as shown by a recent study on angiotensin-converting inhibitors [49]. Enforcement of laws is important but it is just one option. Education, training, and development of a culture of safety reporting may hold the key to more sustainable success. Data driven PV in Africa is possible and desirable and systems capable of collecting longitudinal data are also needed urgently in Africa. With the deployment of some products for the first time ever in Africa, e.g., the malaria vaccine, it is clear that data from Africa will inform global policy and practice. It is therefore essential that the global community works with African countries and African partners to develop robust approaches for the collection and sharing of safety data for the benefits of Africa and the world. This is a responsibility for all stakeholders in PV.

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Chapter 11

Pharmacoepidemiological Approaches for Population-Based Hypothesis Testing

Olaf H. Klungel

Abstract

Pharmacoepidemiology aims to study the use and both the adverse and beneficial effects of drugs and vaccines in the population after market authorization. The efficacy of drugs is assessed in experimental studies before a drug is allowed on the market in a limited and usually selected group of patients. Therefore, after market authorization the focus is on serious and adverse effects in large groups of patients in daily clinical practice. Observational drug research is needed to establish and measure these effects. Observational research faces several challenges to minimize the chance of bias, including confounding by indication, which is caused by selective prescribing of drugs to certain patient groups. A comparison between treated and untreated subjects or between different drug regimens may be biased due to uneven distribution of risk factors for the outcome of interest. Important progress has been made during the past decade in controlling confounding by design and analysis in observational studies. The increasing accessibility of large electronic health record databases has fuelled various international initiatives to analyze multiple databases across countries using common protocols and common data models. Extensive sensitivity analysis across multiple designs, databases, and analytical techniques has provided more insight into causes of variation in results across studies and increases the confidence in findings of observational studies. Transparency of observational drug research through public registration of protocols and detailed reporting of methods should improve reproducibility and thereby reliability of pharmacoepidemiological studies.

Key words Confounding by indication, Immortal time bias, Study design, Type A adverse events, Type B adverse events, Channeling, Multi-database common protocol studies, ENCePP

1 Introduction

The discipline of Pharmacoepidemiology focusses on the study of the use and effects of drugs and vaccines in the population after they have been allowed on the market [1]. Before a drug is allowed on the market efficacy has to be demonstrated in experimental research. Once the drug is allowed on the market and the drug may be prescribed in daily practice studies will often be observational. This type of study is necessary because when drugs are allowed on the market efficacy is established by, at most, a few

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thousand patients. This is usually a selected group of patients avoiding high risk patient groups for example followed for a usually limited duration of treatment, often shorter than the time that patients use drugs in daily clinical practice—also in a controlled environment not necessarily mimicking real world use (e.g., drug utilization and adherence practices). At the time of launch of a drug it is known that the drug does what it is intended for, for example, lowering blood pressure, lowering of serum cholesterol, or reduction of symptoms in asthma. Furthermore, a number of side effects that occur fairly often and can be explained on the basis of the pharmacological effects of the drug, known as Type A side effects, will also have been established [2]. Examples of type A side effects are gastrointestinal bleeding due to aspirin use, or a dry mouth by antidepressant use. However, other effects, particularly rare unpredictable and potentially severe so-called type B side effects that occur in only 1 in 1000 or even 10,000 patients act, will not be known at that time. Examples of type-B side effects are allergic reactions, liver damage, and bone marrow suppression. Type-B side effects are reactions of the patient to the drug and can be detected, for instance, by means of spontaneous reporting systems such as those present in many countries and collected worldwide by the WHO Monitoring center in Uppsala. Spontaneous reporting of adverse drug reactions by patients and healthcare providers is important for generating a safety signal and hypotheses about a potential association between a drug and an adverse event (for more details see chapter on signal detection). Subsequently, pharmacoepidemiological studies are utilized for testing these hypotheses and this introduces a first important goal of a pharmacoepidemiological study, e.g., the quantification of the risk of type-B side effects in large numbers of patients. Study of drug effects in patients who have not been studied in pre-approval studies is an important second goal of pharmacoepidemiological studies. Patients in daily practice often differ from patients in the pre-registration studies. Women, elderly, children, patients with concomitant diseases, and/or medication use are often excluded from this type of research in order to obtain a valid estimate of the potential effect of the drug. However, the translation of the results of these studies to patients in everyday practice is getting more difficult. Consideration and development of a strategy for ongoing surveillance and study of a medicinal product after marketing approval is called Risk Management and this is discussed in detail in Chap. 12.

2 Observational Drug Research

Typical for observational drug research is that the choice of treatment is made by the physician and the patient in daily practice, and not by a researcher assigning patients (at random) to one or the

other drug or no drug (the term "drug" is being used throughout this chapter in the widest sense to represent any medicinal product). The investigator is in the first case, as it were, on the sidelines and observes the use of drugs in relation to their effects. In the latter case, in which the choice for pharmacotherapeutic intervention is determined by the investigator, one speaks of experimental drug research. The strength of the experimental drug trials in which patients on the basis of chance alone, are assigned to a treatment group, is that the treatment groups are similar with respect to reasons for the outcome of treatment to be studied. This leads to an overall equal distribution of risk factors, both observed and non-observed factors, and thus more or less equal prognosis of treatment groups that are compared, allows a reliable estimation of treatment effects—as the impact of these risk factors can be excluded and focus is solely on the differential impact of treatments to one another. Observational studies, where no randomization has been conducted, need to consider not only the impact of chance (as for any study) but also bias. The impact of chance can be addressed by quantifying the variability in effect estimates (e.g., confidence intervals). The purpose of sample size calculation in observational studies with large healthcare databases is somewhat different than for experimental studies and observational studies that involve direct data collection from subjects. When utilizing existing data sample size is already known and the purpose is to assess whether the study has sufficient power to detect an association of a certain size, whereas for studies that involve primary data collection the purpose is to calculate the number of subjects on which data has to be collected to assure sufficient power to detect the association of interest.

3 Confounding by Indication

Sometimes unintended and intended effects of a drug counteract against each other and the observational study of such effects is complex. This can be illustrated by a study by Bruce Psaty on the effect of antihypertensive drugs on the risk of myocardial infarction [3]. At the time of publication, only a few classes of blood pressure lowering drugs were known to lower the risk of cardiovascular disease. Calcium antagonists were known to lower blood pressure, however, while the lowering of blood pressure was expected to reduce the risk of cardiovascular treatment, the direct effect on the risk of cardiovascular disease, the ultimate goal of the treatment, had not been established. The calcium channel blockers primarily used in this study were short-acting. Previous research had shown that short-acting calcium channel blockers due to a rapid fall in blood pressure increased heart rate, and this could cause what is an

unintended effect that may increase the risk of myocardial infarction [4].

Psaty in his study among people with high blood pressure compared the use of different classes of blood pressure lowering drugs among people who had suffered a myocardial infarction and those who had not experienced a myocardial infarcion—a so-called case-control study. This study revealed that calcium channel blockers were used more often by patients who had experienced a myocardial infarction than patients who had experienced no myocardial infarction. A major criticism of this study was the examination of an outcome that was related to the reason for prescribing these drugs. An antihypertensive drug is indeed prescribed to reduce the risk of a myocardial infarction. Calcium antagonists are not only prescribed to lower blood pressure but also to treat the heart condition angina (caused by coronary disease and characterized by attacks of chest pain on exertion). Patients taking calcium antagonists are therefore more likely to have heart disease than those patients who receive, for example, a thiazide diuretic which are used mainly to reduce blood pressure. An increased risk of myocardial infarction among users of calcium channel blockers compared with users of thiazide diuretics is therefore to be expected due to its increased presence of angina among users of calcium channel blockers. This does not necessarily have to be caused by the drug, but may also be due to the type of patient the drug is prescribed. As stated by John Urquhart: "Did the product bring the problem to the patient, or the patient's did bring the problem to the product" [5]. This phenomenon of selective prescribing is a classic problem in pharmacoepidemiology and is also referred to as "channeling," and can be the cause of a major source of bias in observational drug, also known as confounding by indication [6–8]. Confounding or distortion of results of pharmacoepidemiological study occurs when a factor is present (e.g., the indication angina) which is both a determinant of drug use (calcium antagonists) as a risk factor for the outcome (myocardial infarction) (Fig. 1).

In order to avoid and correct confounding a variety of methods were used. The main method was as simple as it is effective, i.e., all patients who had a cardiac and/or vascular disease (including patients with angina) were excluded from this study. Subsequently

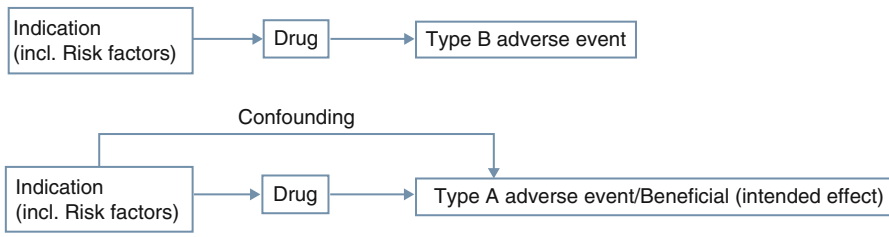

Fig. 1 Relation between indication, confounding, and type of event in pharmacoepidemiological studies

users of calcium channel blockers were compared with users of beta-blockers which are also indicated for the treatment of angina pectoris and thus comprise a comparable group of patients. The increased risk of a myocardial infarction remained present even after multiple methods to control for confounding such as restriction, matching, and multivariable regression were applied. An important strength of this study was the quality of data collection which involved secondary use of routine healthcare data (claims) and primary data collection (chart review and telephone interview of patients) allowing to control for many important risk factors (including lifestyle factors) of myocardial infarction. There are several published observational studies, some confirming, some contradicting this finding, but none with the same methodological quality as the original study [9]. Experimental studies have subsequently shown that certain types of long-acting calcium channel blockers reduce the risk of cardiovascular disease [10].

4 Inconsistency in Observational Drug Effect Studies

It is not uncommon that observational drug studies contradict each other such as the link between bisphosphonates to treat osteoporosis and the risk of esophageal cancer [11–13], and the use of statins, a group of cholesterol-lowering drugs, and fracture risk [14–16].

What these examples have in common is that individual studies often were not only carried out in different databases (for a discussion on longitudinal observational databases suitable for pharmacoepidemiology studies, *see* Chap. 7), they also differed in the methodology applied. This makes comparison and interpretation of results from observational studies very difficult, especially since the reporting of methods sometimes lacks sufficient detail for a proper comparison of studies. Following the STROBE guidelines for reporting observational epidemiological studies and the specific extension of the RECORD statement for reporting studies with routinely collected health data need to make improvement in this respect [17, 18]. When the same dataset is analyzed by various researchers to answer the same question it becomes clear what the impact if methodological choices on the results is. Tjeerd van Staa, for example, studied the link between the use of statins and the risk of a fracture in a large database of prescribing data and diagnoses of British GPs [14]. No association was found while a researcher from Switzerland in the same database did find a link, specifically a protective effect [15]. de Vries, van Staa, and others subsequently demonstrated that different methodological choices such as selection of patient populations, the definitions of drug exposure, and way of age adjustment could explain the apparent discrepancy in study results and in the end concluded there was insufficient evidence for a protective effect of statins on the risk of a fracture

[16]. Another major difference was that the initial investigation that found a large protective effect of statins was distorted by what is termed "immortal time bias" [19]. This form of bias is a major threat to the validity of observational drug studies. In a review of 20 observational studies that reported unlikely large beneficial effects of drugs, Samy Suissa showed that all these studies were to a greater or lesser extent distorted by immortal time bias [19]. This type of distortion is easily prevented by proper classification of exposure and selection of patients, although the complexity of databases and their data inclusion criteria, and drug-specific exposure variation make such classification challenging and careful study design an essential element of a pharmacoepidemiological study.

5 Observational Versus Experimental Studies

In addition to examples of conflicting results between observational drug studies, there are also differences in results between observational and experimental studies. For example, there are several observational studies on the effects of drug treatment of hypertension in daily practice and the risk of cardiovascular disease. Many of these studies have shown an increased risk which is curious because the effectiveness of this treatment in reducing the risk of cardiovascular diseases such as myocardial infarction and stroke is clearly demonstrated in randomized clinical trials [20]. Confounding by indication in observational studies is an important explanation for this discrepancy [21]. Persons who are being treated with blood pressure lowering drugs get these agents because they have an indication for the treatment, namely, an increased blood pressure, while individuals who do not get blood pressure-lowering drugs are also very likely not to have elevated blood pressure. Because high blood pressure is a risk factor for the development of cardiovascular disease, people who use an antihypertensive drug at this stage have a higher risk of cardiovascular disease compared to people who do not use antihypertensive drugs. Such a comparison is therefore not valid and has resulted in a number of observational studies with the misleading conclusion that drug treatment of hypertension in daily practice is not beneficial, or even harmful.

By selecting a similar group of individuals who have elevated blood pressure and also had additional cardiovascular risk factors, known as candidates for treatment, we were able to show that treatment with antihypertensive drugs in Dutch daily practice reduced the relative risk of stroke to the same extent as in the randomized trials [22].

Another example of a conflicting result from experimental and observational studies is that of the effect of oestrogen therapy in postmenopausal women at risk of coronary heart disease. In observational studies postmenopausal women who used estrogen

therapy compared with women who did not do so had a 35–50% lower risk of coronary heart disease was observed [23].

However, a few years later, the results from randomized trials on the effect of estrogen therapy on the risk of coronary heart disease revealed an increased risk during the first years of use compared to the women who had received a placebo [24]. An important difference between the observational studies and the trials was that in the trials, the women were followed from the time they started the estrogen therapy, while in the observational studies, the women were often tracked from a moment when they had already used estrogen therapy for a long time. These women were already beyond the time of an increased risk of coronary heart diseases such as was observed in the trials and were within a period of treatment in which the risk was lower. From a reanalysis of the observational studies in which the users of estrogen therapy were followed from the start of their therapy, the results proved to be similar to as seen in the trials, an increased risk of coronary heart disease during the first years of use and therefore consistent with the experimental studies [25].

Experimental and observational research are complementary with experimental research needed for the evaluation of the intended effects of interventions, while observational research is needed for detecting and explaining side effects that are unexplainable and cannot be predicted [26]. Unexplainable and unpredictable are important additional considerations because if a side effect cannot be predicted, a physician will not be able to consider patient characteristics when prescribing a drug. The indication for treatment is therefore not related to the study outcome, and therefore confounding by indication can be excluded. This dichotomy is an important basis for the added value of both types of research and a warning for the interpretation of observational research on Type A side effects and intended effects of drugs. Nonetheless, there are also exceptions where observational studies may lead to a valid estimate of these latter drug effects. Examples are for instance when multiple drugs are used for the same indication and the relative effectiveness can be estimated, or when the indication population that is untreated can be identified ("candidates for treatment") and accurate and complete information on potential confounding factors is available to assess and control for confounding.

6 Improving Consistency in Observational Drug Effect Studies

Results from observational drug studies are only useful for weighing benefits and risks of medicines if the results from these studies are valid. How can the reliability and consistency of observational drug studies be improved?

This question was one of the main drivers of the European PROTECT project coordinated by the EMA, the European drug registration authority. The project was funded by the European Innovative Medicines Initiative (IMI), bringing together public and private partners. Within the PROTECT project the impact of methodological choices on results of observational drug research was studied [24]. Based on a common study protocol, data from general practitioners, pharmacists, hospitals, and more than 20 million patients from the Netherlands, the United Kingdom, Spain, and Denmark were analyzed. All protocols were recorded in the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) register of studies before the analysis of the data. The results from the individual databases were unblinded only after all the centers had completed the analyses according to the protocol. In this manner, the risk of centers analysts being biased by knowledge of each other's results is minimized. Any changes to the protocol for reasons of clarification were also documented and recorded in the ENCePP register. An important aspect of the approach was that the impact of different methodological choices on the results of the study was studied within one study protocol. One protocol thus comprised several studies involving variations in the design, definition of drug exposure, the definition of outcome, and methods to correct for confounding. Five adverse events were chosen and all were examined prior to study initiation and considered relevant with respect to impact for individual patients and public health, and also included as they had led to regulatory decisions such as withdrawal of a drug from the market, restriction of the indication, or the inclusion of warnings in the leaflet. Further criteria were that a series of methodological issues could be studied. For example, acute events were chosen that could be measured relatively easy in a health care database such as myocardial infarction and hip fracture, acute events that are difficult to measure, such as liver damage, and suicide, but also a long-term outcome cancer. These events were examined for association with up to six different drug groups. It is important that knowledge of the biological mechanisms that underlie the effects of drugs is taken into account in the design and conduct of epidemiological studies. For instance to study cancer in relation to the use of calcium channel blockers cumulative exposure was considered over a long term, whereas with benzodiazepines use at the time of hip fracture was a focus.

Different types of study designs have their strengths and weaknesses (*see* Table 1). An important advantage of the case cross-over and self-controlled case series with respect to the case-control and cohort approach is that in the first two designs individuals are compared with themselves at different times (with a focus on comparing risk within patients of an outcome when exposed to a drug to times when the same patients were unexposed). A big

Table 1
Main study designs in pharmacoepidemiology

	Cohort	Case-control	Case-cross-over	Self-controlled case-series
Strengths	– Estimation of absolute risk...	– Efficient when primary data collection involved...	– Control for unmeasured confounding...	– Control for unmeasured confounding – Efficient (more power with fewer subjects compared to cohort)...
Weaknesses	– Analysis of time-dependent exposure and control time-varying confounding complex – Inefficient when primary data collection involved	– Sometimes difficult to select appropriate controls	– Multiple assumptions needed for valid estimation (e.g., acute transient events and variation in exposure)	– Multiple assumptions needed for valid estimation (e.g., acute transient events and variation in exposure)

advantage of this approach is that risk factors that do not change over time, and factors that are not measured, cannot have any influence on the association between drug use and the adverse effect. Factors that do change over time can however distort the relationship between a drug and adverse event. These so-called case-only studies are therefore primarily only applicable to acute events that are of a transient nature. If a link between the use of a drug and a adverse effect is found consistently in different countries, with a range of different methods confidence in and usefulness of results of observational drug investigations increases. In the PROTECT project, the increased risk of hip fracture associated with antidepressants and benzodiazepines was consistently found in three different databases from the Netherlands, United Kingdom, and Spain with four different study designs and different ways of correction for confounding [24, 27–30] (Figs. 2 and 3). The association between antibiotics and increased risk of acute liver damage, the absence of an association between long-acting beta2-agonists in the treatment of respiratory disease, and the risk of myocardial infarction was found consistently in different databases with different study designs. The risk of antiepileptic drugs on suicide was despite following the same common study protocol inconsistent in the United Kingdom and Denmark. Suicidality is a challenging outcome to study in observational databases and discrepant findings are reason to further explore explanations for these

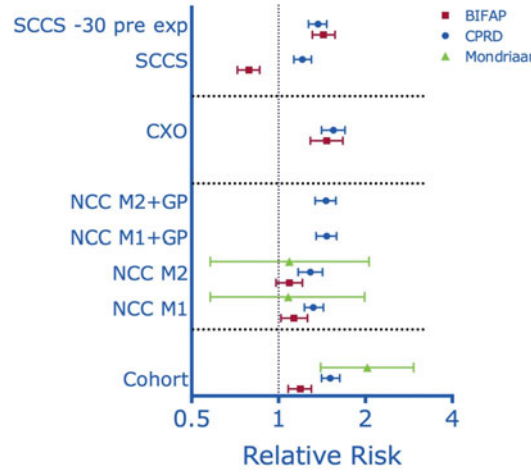

Fig. 2 Benzodiazepines and the risk of hip fracture. Impact of study design, database, and control for confounding (different matching strategies in case-control study). *SCCS* self-controlled case series, *CXO* case cross-over, *NCC* nested case-control, *M1* simple matching algorithm including sex, age (±2 years) and follow-up time, *M2* Euclidean distance matching algorithm including sex, age (±2 years) and follow-up time, *GP* general practice included as matching factor

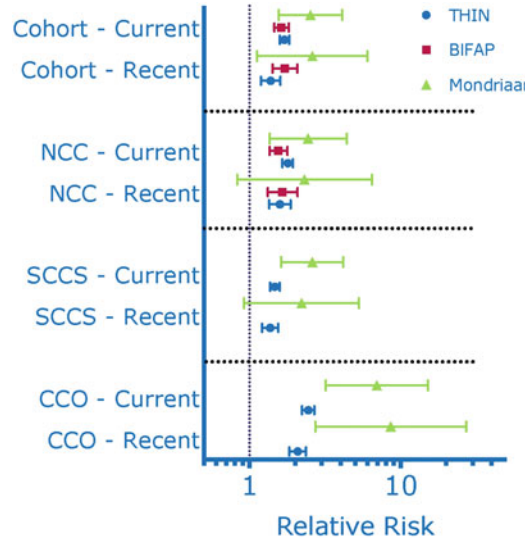

Fig. 3 Antidepressants and the risk of hip fracture. Impact of study design and database. *SCCS* self-controlled case series, *CXO* case cross-over, *NCC* nested case-control

differences. However, the results are currently not directly applicable to daily practice. Reuse of The PROTECT network of researchers and datasets can allow exploration of new safety signals in the future, and the capability to quantify associations [31]. The scope

and diversity of the populations across the PROTECT network also makes it possible to further examine specific products, rare disorders, and subgroups of patients.

7 Methods to Control for Confounding

As explained in the introduction of this chapter, confounding is a major threat to the validity of observational studies. During recent decades, the approaches to control for confounding have evolved greatly. A distinction can be made between methods that aim to correct for observed confounders, i.e., those that we have measurement of in a database, and methods that aim to correct for unobserved confounders, those that we do not have measurement of. Within the first category of methods, propensity scores are increasingly being applied [32]. The propensity score can be defined as the probability of getting a certain drug treatment which may be different for each patient and depends on the characteristics of the patient such as age, sex, additional diseases, and co-medication. In fact, all features which are considered risk factor for the outcome that is being investigated should be included in the propensity score calculation. The great advantage of this method is that all risk factors are reduced to a single variable, and thus the only confounder to be taken into account. Especially when the outcome is rare this has great advantages because the number of confounding factors which can be corrected for, depends on the number of outcomes/adverse events observed.

In addition to the prevention of unobserved confounding by design (e.g., self-controlled case series and case-cross over designs) the method of instrumental variables has been explored as a way to control for unobserved confounding. An instrumental variable is defined as a variable that is associated with the exposure of interest, but not directly, nor indirectly (e.g., through association with confounders) with the outcome of interest. Randomization in a randomized controlled trial can be considered a perfect instrumental variable. However, in observational studies one has to identify such a variable from the dataset that is available, and usually the conditions for a valid IV are not met [33]. This method is therefore not commonly applied.

Other important initiatives in Europe are the EU ADR alliance and the CARING project on safety of diabetes medications [34, 35]. The Canadian CNODES initiative is similar to that of PROTECT [36]. A joint protocol is executed in parallel in several Canadian provinces with their own data sets, and if results are consistent summarized in one overall effect estimate through a meta-analysis. In the future, results from one network could be more readily and often replicated in other networks so that confidence in results of observational studies can be further increased.

An important US initiative is the FDA Sentinel project in which data from 190M persons is combined through a common data model for the purpose of analyzing drug safety signals [37]. Besides the size of the population and the automated approach of analyzing data, an additional important strength of the program is the validation of various important health outcomes of interest.

Harmonization of data at the level of the least detailed database does not use the value of individual databases with the highest level of detail, although it holds some benefits for rapid query analysis capability. Meta-analysis techniques in which account is taken of this diversity may be able to offer a possible solution. In addition to these aspects of dealing with data from various sources and countries remain important to take existing knowledge of biological mechanisms in the design of observational drug analysis. Modeling as realistic as possible of exposure based on a drug data and biological mechanisms is an important focus of future research.

After the introduction of a new drug, benefits and risks in daily practice should be weighed continually and significant changes detected as soon as possible. Methodologically, it is a big challenge because new drugs especially in the early stages when newly introduced on to the market frequently are prescribed to a limited and selective group of patients. For instance, patients who have not responded to conventional treatments, or have experienced side effects, would be prescribed new drugs with the expectation that they would be more effective or may have fewer side effects. A comparison of patients who are put on the new drug with patients who do well on the standard will often be problematic in observational studies. It is important, therefore, in order to properly map these new users, to determine whether or not a fair comparison is possible with regard to the intended effects, but also the unintended effects. Randomizing patients in the daily practice without too much change to routine health care and minimal exclusions and following these patients through routine data collected from the field may also provide a solution for the study of the effectiveness of drugs in the daily practice [38].

8 Transparency and Independence

The debate between researchers, industry, and medicine authorities around controversies in drug research can be heated, the stakes are often high for each of these different parties. That is precisely why it is important to understand conflicting results and look to explain them.

In addition to applying the best methodology, transparency and independence of scientific observational drug research, it is very important to increase confidence in the results of observational research. Clear separation of the role of the sponsor of a study and

the executive researcher with freedom to publish must be guaranteed regardless of the outcome of a study. The recording of the protocol before the study is carried out with the public having access to such protocols.

These measures are now a precondition for observational drug trials that the EMA may impose on drug manufacturers and is enshrined in the so-called Code of Conduct ENCePP [39]. There are now more than 150 centers that have joined this European network. It should be emphasized that the purpose of registering protocols of observational drug research is greater transparency and that the methodological quality and reliability of such studies are not guaranteed. To achieve this goal, it is especially important to promote and follow guidelines for the proper execution of pharmaco-epidemiological studies and to all parties concerned to improve education in pharmacoepidemiology. An important prerequisite for reliable pharmaco-epidemiological study in addition to the correct application of the optimal methodology, is a solid infrastructure in which access to valid data on drug use, risk factors, and outcomes such as side effects is well organized.

9 Conclusion

Different methods of approaching a problem can lead to new insights and these different methods of approaching different sources of data should already be considered and articulated (and appropriate registrations obtained if necessary) from the beginning, actually at the study design stage. In this way, the time-consuming process of years in which one study is followed serially by another should be avoided as far as possible, so situations where the field must explain why similar studies with years in between have contradictory results could be reduced significantly, perhaps to less than a year—supporting public health and also increasing credibility of the field by more capability of discovering and understanding across study discrepancy. A thorough knowledge of pharmacoepidemiological methods and understanding the context of the use of drugs ensures the value of observational drug research, and the added contribution that such work adds to that of experimental drug research. Transparency of observational drug research through public registration of protocols and detailed reporting of methods should improve reproducibility and thereby reliability of these Pharmacoepidemiological studies further reinforcing their contributory role in combination with experimental drug research in better understanding the risks of marketed medicinal products.

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Chapter 12

Risk Management and Minimization

Yola Moride

Abstract

Therapeutic risk management aims to improve patient safety by assessing and monitoring the risks, and by developing risk minimization interventions to reduce or mitigate such risks while maximizing benefits. Throughout the lifecycle of drug development, risk management broadly includes the surveillance and detection of previously unknown risks, evaluation of potential risks or key safety concerns, as well as minimization or mitigation of identified risks. Assessment of effectiveness of risk minimization is methodologically challenging in the absence of an "unexposed" population and clear outcome definitions. Of concern also is the undue burden for healthcare professionals and healthcare systems that may be generated by risk minimization, which remains inadequately explored to date. A framework for the different components of risk management and minimization, as well as practical examples for the evaluation of effectiveness of risk minimization interventions, are presented in this chapter.

Key words Risk management, Risk management plan, Risk minimization, Risk Evaluation and Mitigation Strategy (REMS), Post-authorization safety study (PASS), Drug utilization study (DUS)

1 Introduction

1.1 Scope of Risk Management Planning

Risk management is a process to improve patient safety by assessing the risks of a medicinal product and devising interventions to reduce or mitigate such risks while maximizing benefits. These interventions, also called risk minimization interventions (RMIs) or risk minimization measures (RMMs), are those that extend beyond the product label [1, 2]. Although the majority consists of communication materials [3], more extensive interventions have been implemented, such as mandatory training of prescribers and/or patients, prescriber certification, patient informed consent, restricted distribution in particular pharmacies or hospital settings, dispensing following evidence of safe-use conditions, or registries to track patients, prescribers or pharmacies, to name a few. In the US, RMIs are referred to as Risk Evaluation and Mitigation Strategies (REMS) and components that involve more extensive interventions, such as the ones listed above, are those with Elements to

Andrew Bate (ed.), *Evidence-Based Pharmacovigilance: Clinical and Quantitative Aspects*, Methods in Pharmacology and Toxicology, https://doi.org/10.1007/978-1-4939-8818-1_12,

Assure Safe Use (ETASU). These intend to either restrict access to the drug to those patients for whom the benefit-risk is highest or to ensure safe prescription and/or monitoring practices. Examples of ETASUs include mandatory laboratory tests or investigations prior to prescribing the drug to the patient. In some programs, actions may also be required in order for the patient to continue on treatment, such as specific monitoring tests. In the community setting, verification of these tests is generally done by a central pharmacy. In the absence of RMIs for similar products already on the market, RMIs implementation and evaluation studies are often the results of negotiations between the drug manufacturers and the regulatory authorities.

Over time, implementation of RMIs for brand and generic products has become challenging. Regulatory authorities require that generic products have the same RMIs as the brand product. Two historical pre-REMS shared risk management programs with elements now deemed to be a REMS with ETASU are isotretinoin for the treatment of severe acnea, and clozapine, an atypical antipsychotic indicated for the treatment of refractory schizophrenia. Some of the REMS components for newer drugs are patented, which creates an additional challenge for generics that enter the market.

1.2 Stakeholders of Risk Management Planning

Risk management spans the entire product lifecycle in a continuous and uninterrupted manner from the pre-approval to the post-approval or commercialization phases. As an emerging discipline, it has, since the early 2000s, had tremendous impact on drug development, regulation, as well as the delivery of care and medicinal products. It draws together multiple stakeholders and cross-functions, including drug manufacturers, regulators, public health officials, healthcare professionals, and patients. Regulators such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have released respectively, draft guidance documents or implemented legislation that provide a framework for the development of risk management and minimization strategies. Since then, other regulatory agencies around the world have followed in these footsteps and implemented risk management officially or unofficially. In 2014, the Council for International Organizations of Medical Sciences (CIOMS) published Working Group IX on the « Practical Approaches to Risk Minimization for Medicinal Products », which provides a roadmap for the selection and evaluation of effectiveness of RMIs [4]. These guidances are all driven by the same overarching principles: improvement of public health and accountability. In this chapter, research methods applied to the various components of risk management and minimization will be discussed, followed by an expert view on limitations and future directions.

2 Risk Management: An Emerging Discipline

2.1 Rationale

Like many disciplines, the emergence of risk management stems from the realization of gaps in the process of drug development. At one end of the spectrum, randomized clinical trials (RCTs) in the pre-approval setting are conducted in a highly scrutinized environment, with restrictive and captive populations who are followed regularly and adverse events (AEs) recorded in a comprehensive and systematic way. Adverse events, when observed are, by design, rarely missed in RCTs. In patients being followed closely, any AE will be documented and processed accordingly. At the other end of the spectrum in the post-approval setting, pharmacovigilance systems, relying mainly on spontaneous reports, cast the broadest safety net for drug safety surveillance. While RCTs are evidently robust for the close follow-up of patients, their environment is too restrictive to provide an overall and comprehensive assessment of safety in all sub-groups of patients treated in the real-world clinical practice setting. Conversely, spontaneous reports, with their well-known limitations described elsewhere in this book, cover very large and heterogeneous populations and are designed to identify signals of previously unknown drug effects. But, what about those effects that may be suspected based on pharmacokinetic or clinical data but that have not been observed in RCTs because of insufficient sample size, restricted patient populations, short durations of follow-up or for which the number of cases observed is so small that results are inconclusive? For example, a few cases of liver enzyme elevations may have been observed during the clinical development of a product that includes analysis of data from a total of 4000 patients. In the real world, hepatitis may therefore be a potential risk for all patients or for a subgroup of patients. Further data would therefore be needed in order to substantiate this risk and identify subgroups of patients or conditions of drug usage (i.e., dose and/or duration) with a risk that may be unacceptable. Previously, regulatory authorities may have opted for postponement of the drug approval until further clinical studies be conducted, thereby postponing access to a beneficial drug for some patients. On the other hand, commercialization of the drug with these existing data gaps may result in signals of hepatitis that would have been detected perhaps months if not years later. By conducting studies or surveillance activities specifically to address the key safety concern of hepatitis as soon as possible after product launch should provide answers much sooner, leading to label modifications for example.

The science of clinical pharmacology has received great recognition in the process of ascribing a drug effect to a treatment, also referred to as causality assessment or imputability [5]. But this can only be achieved once a drug effect has occurred and has been

observed and reported. In the ideal world, such cases should be avoided altogether. Clinical pharmacology as a science to predict potential drug effects before they occur and therefore acted upon before tragic events happen did not seem to be part of the regulatory process until about 2005. For example, a new biologic anticancer drug may lead to dermatological reactions, especially if it is an antiepidermal growth factor inhibitor. Therefore, risk minimization or mitigation strategies to promote the recognition, prevention, and management of the dermatological AEs, through for example communication materials to prescribers and/or patients, can allow successful continuation of therapy, and minimize patient distress.

Conversely, secondary malignancies are long-term risks associated with new anti-cancer drugs, such as etoposide, and may occur between 10 and 25 years after treatment. However, if the patient population treated with this agent is composed mainly of elderly patients, their life expectancy may not be sufficient to experience secondary malignancies. This risk may therefore not warrant further interventions beyond routine pharmacovigilance activities.

2.2 Regulatory Considerations

Prior to the introduction of risk management planning, regulators needed to make decisions mainly based on clinical trial data which only provide a glimpse of the safety of the drug, knowing that in the post-approval phase, surveillance would be reactive as opposed to proactive; thereby highlighting gaps in the surveillance process. Faced with this somewhat inefficient paradigm, the first Agency to formally act upon those gaps was the FDA with the issuance of the FDA Draft Guidance Documents in March 2005 [2, 6, 7]. Shortly thereafter in 2008, the European Medicines Agency (EMA) finalized its Guideline on Pharmacovigilance for Medicinal Products for Human Use. Also known as Volume 9A, a template for risk management plans was introduced, which led to regulatory requirements at the time of product submission and in the post-approval phases. Since then, Volume 9A has been replaced with the Guideline on good pharmacovigilance practices (GVP), including modules on risk management systems and post-authorisation safety studies [8, 9]. These documents are useful for addressing knowledge gaps on the safety of a new product, thereby supporting strategies for the development of risk management activities. However, they provided limited guidance either for the selection of risk minimization tools to address these risks or the assessment of their effectiveness and burden.

Risk management has since become an integral part of the lifecycle approach to product development leading to the broadening and enrichment of methods for the detection, evaluation, and minimization of risks toward a continuum of evidence generation. In addition to clinical trials and spontaneous reporting which are still the mainstay of drug safety surveillance, methods such as active

surveillance, pharmacoepidemiology, and quasi-experimental designs are being increasingly used to fill the knowledge gaps. Risks must be better defined at the time of approval, and, where preventable risks exist, interventions to minimize their occurrence must be put in place. For risks that are not preventable or cannot be predicted, then interventions to ensure their detection, and mitigate their impact can also be implemented.

3 Risk Management: At the Crossroads of Methodologies

3.1 Alignment of Methods with Risk Management Objectives

In the EU risk management plan, whether Volume 9A or the modular approach of the EU Pharmacovigilance Legislation (2012), synthesis of knowledge about a drug including preclinical to clinical data leads to a set of *identified* risks, *potential* risks and *important missing information*. Such classification drives the risk management strategy in the post-approval setting. Identified risks that are deemed important may lead to the implementation of RMIs while potential risks or missing information will be further examined or addressed through the conduct of post-approval safety studies (PASS) as soon as possible after launch. Other types of risk, such as those that are still unknown, will continue to be monitored through the traditional spontaneous reporting system but in a more systematic and pro-active manner such as quantitative signal detection methodology. Risk management is dynamic since risks may change from one category to another with the generation of new evidence. For example, a few cases of hepatic enzyme elevations observed during the clinical development may have been considered a potential risk in the initial RMP. Consequently, a PASS study would be conducted as soon as possible after product launch as a commitment to regulatory authorities. Following the findings of a positive association between the drug and the risk of hepatitis, the risk may now be considered as identified which will invariably result in label modifications and, where appropriate, in the implementation of RMIs such as periodic liver enzyme tests. Conversely, if further studies show no risk of hepatitis, monitoring through the traditional pharmacovigilance systems may be appropriate. The iterative process and methodological strategies of risk management are illustrated in Fig. 1.

3.2 Methodological Considerations

A framework for the selection of the most appropriate RMI has been provided by CIOMS Working Group IX [4]. In general, it can be observed that one RMI can apply to more than one risk but not all RMIs apply to all risks. For example, communication materials may address risks of QT-prolongation, dermatitis, and gastropathic effects, while the accompanying RMI consisting of mandatory prescriber certification may only apply to the most severe type of AEs, such as QT-prolongation. Additionally, several RMIs may be

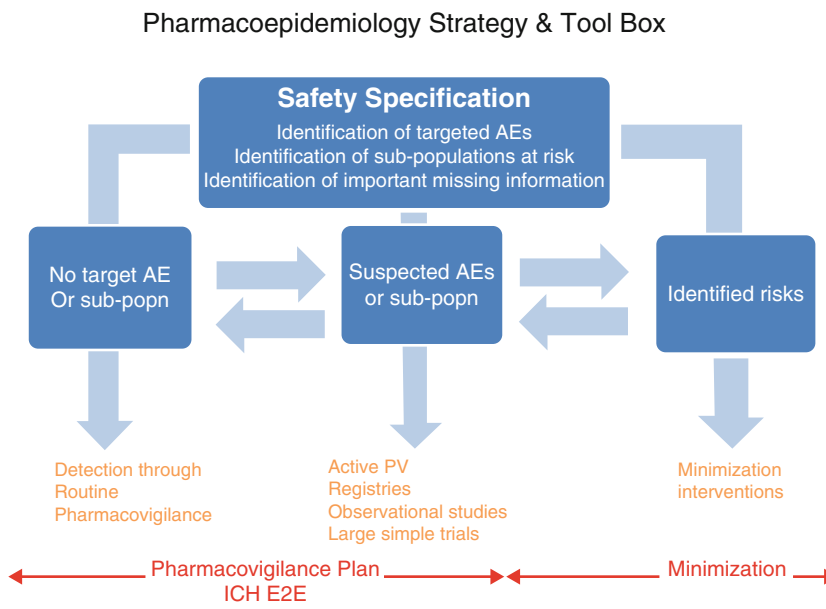

Fig. 1 Iterative process for risk management planning

contemplated to address a given risk; the selection of the most appropriate should be risk-proportionate. For example, to implement a restricted distribution program to address a non-serious risk that could be appropriately managed through communication would not be considered appropriate because of the resulting burden to patients, healthcare professionals, and the healthcare system.

As part of risk management planning, the effectiveness of RMIs must be evaluated, and protocols for evaluation appended to the RMP or agreed with regulatory authorities. Two levels of evaluation must be considered: *implementation* and *effectiveness*. While the former refers to a process evaluation, the latter addresses impact on actual risk(s). Implementation may be measured using metrics such as the number of pamphlets shipped to prescribers, number of hits on education websites, etc. This information is routinely recorded by marketing departments of pharmaceutical companies but a key challenge is the timing and frequency of data collection. For example, implementation may need to be evaluated quarterly during the first year post-launch but marketing data may only be available on a yearly basis.

Evaluation of effectiveness, i.e., whether the intervention is effective in minimizing or mitigating the risks, is more challenging. It would be useful to know which interventions work best for which types of risk and populations. However, as shown by a literature review [10–12], it appears to be too early to be able to produce guidance on this topic. CIOMS Working Group IX provides a framework for selection of RMI tools and evaluation. Published data on the effectiveness of RMIs remain scarce in the

literature. According to a systematic review of the literature [8], only 34.6% of RMIs published mentioned an evaluation component at the time of publication. For one-third of those that did, the effectiveness measure did not correspond to the aim of the intervention. Such misalignment likely stems from the absence of a conceptual framework that could shape the evaluation study with a more robust and valid evidence. Example of misalignment would be the conduct of a drug utilization study to assess effectiveness while the RMI aimed at enhancing monitoring through laboratory tests. A framework for the evaluation of effectiveness, inspired by the uptake of clinical guidelines, has been proposed by Gridchyna et al. and depicted in Fig. 2 [10]. Basically, the three levels of implementation include: (1) knowledge, (2) attitude, (3) behavior. On the other hand, the effectiveness component of evaluation relates to the ability of intervention to achieve intended effect. For example, is a weekly monitoring of liver enzyme effective in preventing hepatitis?

The evaluation of effectiveness of risk minimization should follow best practices in hypothesis-testing research, such as those published by the ENCePP [13] or the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE) [14]. The first step is to define the research question, highlighting the importance of a supporting conceptual framework. To further strengthen the research process,

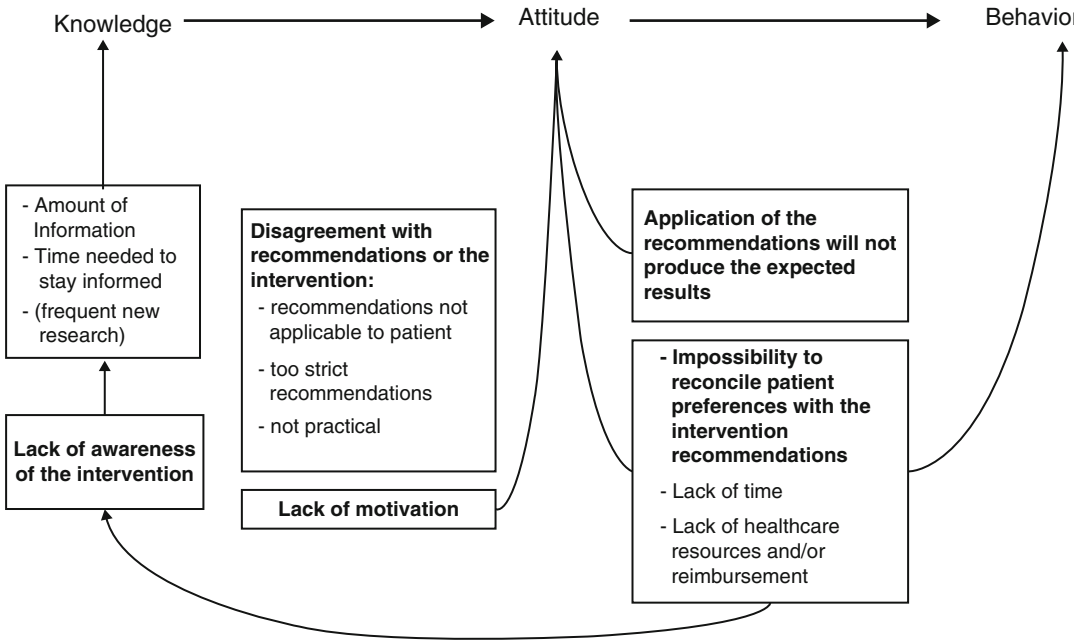

Fig. 2 Theoretical framework. From [10]

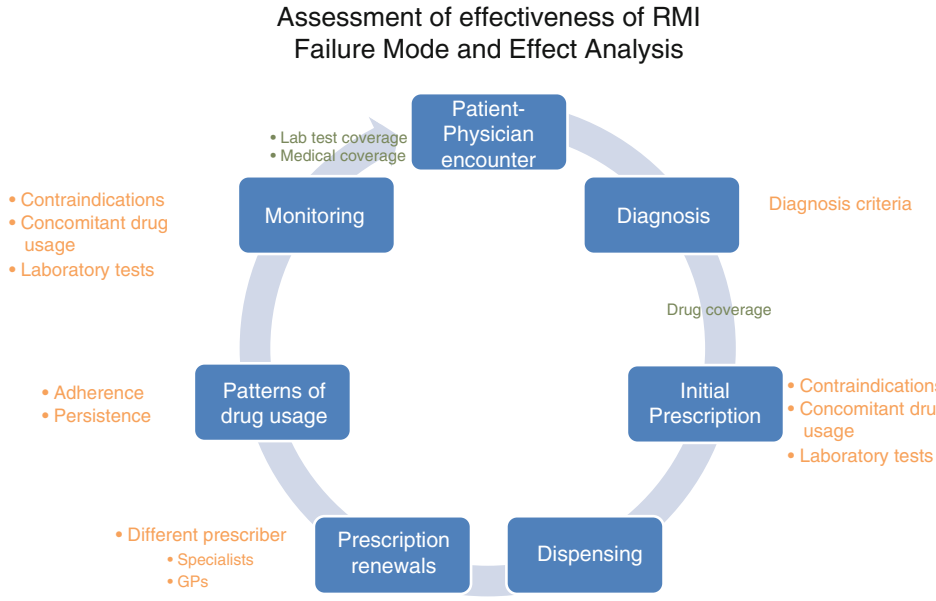

Fig. 3 Failure mode and effect analysis

a failure mode and effect analysis could be conducted highlighting the elements of implementation and effectiveness where gaps may exist and therefore should be formally evaluated. For example, if off-label use is a key safety concern and communication materials address specifically this issue, a study would be conducted to determine if physicians know about the approved indication(s) and if all patients receive the drug for the approved indication. Similarly, if QT-prolongation is an identified risk then a study may be conducted to assess whether patients have received an electrocardiogram (ECG) at the time of treatment initiation and throughout treatment. A framework for a failure mode and effect analysis is provided in Fig. 3.

For new products, a major methodological challenge with evaluation studies is the absence of a parallel or historical group of prescribers or patients "unexposed" to the RMI, given that RMIs are usually widely implemented at the time of product launch. Most evaluation studies therefore rely on a "threshold" of acceptable practices or risks. For example, surveys of knowledge and understanding of key safety messages will be powered to be able to detect a percent adequate knowledge with a lower bound of 95% confidence interval that is superior to 60% [15, 16]; active surveillance of a risk will be powered to detect a risk that is not superior to the "expected" value in the target population. Obviously, the latter is a concept that is difficult to implement in practice given that published data on specific subpopulations are rarely available or the potential risk is so infrequent that it will likely not be detected in the study.

Findings from evaluation studies, however, may be confounded by external factors that could also act as RMIs, even if unintended. Prescribers may be "exposed" to other sources of information that may also affect prescribing and monitoring practices, such as articles published in the literature, clinical practice guidelines, conferences, coverage restrictions, local online decision tools. Especially for very expensive drugs, the role of third-party payers in restricting access is important. In this context, third-party payers may restrict reimbursement to those patients who meet specific diagnostic criteria, which will by itself greatly reduce off-label use, or only in circumstances when the drug is shown to be effective in a given patient (e.g., in several Canadian provinces, public coverage of cholinesterase inhibitors for the treatment of dementia is available only to those patients whose disease has not progressed/deteriorated while on this drug). Hospital formularies or protocols are another type of decision-making process that may restrict the prescriptions of drugs. For example, tumor boards in tertiary care centers determine the eligibility of patients to potentially beneficial but risky treatments.

To assess the effectiveness of RMIs, one or more component of the theoretical framework (Fig. 2) may be evaluated through multiple studies. For example, a knowledge and understanding survey may be conducted to assess whether the communication has reached the target and whether key safety messages have been understood, and drug utilization studies (DUS) to determine whether this has translated into appropriate prescribing or monitoring behaviors. While RMIs and evaluation studies are respectively implemented and planned at the time of product launch, there is no strict guidance on how long the RMI should remain in place, and what are the triggers for discontinuation. Examples of RMIs, which have been "released" or discontinued, may be found on the FDA website [17]. Many studies designed to evaluate effectiveness of RMIs will be conducted at various points in time in order to account for changes in prescribing practices, attitudes, and information available to the various stakeholders. While FDA typically expects such studies to be conducted at 18 months, 3 years, and 7 years after product launch, many regulators are not so explicit with the timelines.

3.3 Knowledge and Understanding Surveys

The prescriber survey is the most frequent method of evaluation of effectiveness of RMIs [18]. A survey sets out to assess the understanding of appropriate prescribing of a specific product. Such a survey may be repeated at several predefined time points after product launch in order to target all potential types of prescribers. Typically, shortly after launch, a new drug tends to be mainly prescribed by specialists and then may expand into the general practice setting. A convenience sample of key opinion leaders, while adequate for market surveys, is not a representative study

population for the assessment of effectiveness of RMIs. The study sample should be as representative as possible of the target population of prescribers and therefore should follow best practices of surveys and use appropriate sampling strategies [19]. As a first step, a sampling roster of prescribers should be constructed. Administrative claims databases or electronic medical records (EMRs) may be used to identify and sample prescribers for participation in a survey. However, for privacy reasons in most jurisdictions, custodians of these secondary data sources do not disclose nominal information on the identity of the prescribers or are unable to send them questionnaires. A more resource-intensive alternative would be to use a directory of medical practitioners of the relevant specialties, such as those that are commercially available, in order to identify "potential" prescribers and screen them until actual prescribers are found for appropriate sampling. Relevant specialties can be determined using marketing data. Simple random sampling or stratified cluster sampling (according to specialty and region for example) should be used. As previously mentioned, in order to take into consideration the dynamic nature of the characteristics of prescribers, sampling may be repeated over time with time-varying sampling strategies (different clusters and strata) to reflect the population of prescribers. Appropriate a posteriori sampling fractions can therefore be used to obtain valid estimates of knowledge and understanding of key safety messages. Non-response is a threat to the validity of any survey and, as much as possible, protocol should include a comparison of responders and non-responders.

3.4 Drug Utilization Studies

Drug utilization studies (DUS) are often conducted to evaluate the effectiveness of RMIs by addressing the third component of the theoretical framework, i.e., behavior. Such studies aim at assessing prescribing practices in relation to indication (i.e., off-label use), patient characteristics, medical history, contra-indicated concomitant drug usage, depending on the nature of the safety concern and the RMI. As data are often expressed as dichotomous variables (i.e., adequate or inadequate prescription practices), these DUS are often referred to as being qualitative. Claims databases would be, for many of those factors, an adequate and timely source of data but very often cannot be used. In fact, due to the frequent lag between drug approval and formulary coverage, it may be years before a drug appears in the database. In addition, the diagnostic codes recorded in those databases may not be specific enough. For example, moderate or severe forms of hemangioma may not code differently than milder forms. Concomitant drug usage may also not be adequately assessed if contra-indicated drugs are also available over-the-counter (OTC). Electronic medical records (EMRs) do offer a more extensive description of indication, especially through the physician notes, but depending on the extent of coverage of the EMRs in a given region, they may not be representatives of all prescribers (most EMRs include GP practices only) or of all patients

(some only cover specific regions within a country). For these reasons, DUS conducted for risk management purposes often involve primary data obtained through the review of medical charts or pharmacy records. In rare instances, it may be possible to identify prescribers through secondary data sources, such as claims or EMRs. Because DUS aim at evaluating prescription and/or monitoring behaviors, it is important that the conduct of such studies does not influence behaviors, and therefore become a RMI in itself. For example, if a physician is invited to participate in a study that will involve prospective collection of information on prescription and monitoring behaviors in case report forms (CRFs), it can be envisaged that he or she will not report off-label prescribing and may therefore select the patients who will be included in the study. Physicians may also conduct more laboratory tests because of a CRF that is documenting the number of visits or tests during treatment. In epidemiology, changes in behavior because of a study conduct are a well-known source of bias, referred to as the Hawthorne effect [20]. For these reasons, it can often be preferable to conduct retrospective DUS where the prescription and the follow-up of patients have already occurred, and to use existing sources of data. This, however, is only possible in circumstances when data collection can be postponed to a few years after market launch. If the safety issue is an important concern and effectiveness of RMIs must be assessed at frequent time points as soon as possible after market launch, then retrospective data collection would likely not be feasible.

Sampling of the study population to assess the effectiveness of RMIs is also critical for the validity of the study. For example, to select only hospital centers with the largest number of patients may be normal in clinical trials in order to optimize patient recruitment, but may jeopardize the validity of a study designed to measure prescription behaviors. Consequently, a cluster stratified sampling strategy with cluster corresponding to regions and strata to types of hospital (e.g., primary, secondary and tertiary care) or types of prescribers (e.g., specialist, general practitioner) may be used. Over-sampling may also be considered for the smallest strata. A posteriori sampling fractions could then be calculated and estimates weighted accordingly.

Ethical requirements and legislation for the conduct of DUS also seem to vary from one country or institution to another. While informed consent requirements for the prospective follow-up of patients are well defined, those related to DUS remain heterogeneous. In fact, some institutional review boards (IRBs) consider that while chart review may be necessary, the study really targets the prescribers; hence, no individual patient informed consent would be required [21].

4 Risk Minimization: Between the Devil and the Deep Blue Sea

While the potential benefits of risk management and risk minimization are undeniable, a concern is the undue burden that may arise from their implementation. Some RMIs may be redundant when compared to existing routine RMIs, and so, generate an undue burden on the various stakeholders [22, 23]. As a consequence, RMIs can potentially limit or reduce access to drugs for patients who could benefit from their valuable use, such as those who do not respond well to the alternative therapies available on the market and that do not have RMI [24]. Although RMIs have the potential to improve drug usage and patient safety, their development and implementation in real-world practice may be time-consuming, and impose financial and administrative burden to various stakeholders including healthcare professionals (HCPs), patients, and the healthcare system as a whole [25].

In an attempt to address this issue, the FDA has sponsored an online survey designed to obtain additional information on the impact of REMS on the healthcare system and on physician practices [26]. A total of 150 full-time professionals who were familiar with REMS participated. Questions focused on identifying which features of REMS are the most effective and least effective to assure safe use, and what was their impact on medication selection. Most of the physicians surveyed stated that REMS do not have an impact on the selection of medication when they prescribe. However, a majority still preferred prescribing a non-REMS medication. In addition, a public meeting held in 2013 on "Standardizing and Evaluating REMS", was hosted by the FDA to gather approaches and feedback from stakeholders on how to measure the impact of REMS. It was mentioned that observational time-motion studies, or computer-simulated modeling exercises can be appropriate methods to evaluate REMS-related burden. However, these methods do not appear to have been implemented, according to literature findings.

One example that can be cited is that of isotretinoin, which is used for the treatment of severe acne, also known to cause major birth defects if used by pregnant women [27–31]. In order to reduce this risk, many RMIs have been implemented over the years. The Isotretinoin Pregnancy Risk Management Program (iPLEDGE, 2006) consists of specific requirements for prescribing and dispensing the drug, and was implemented to keep the drug on the market and to prevent inappropriate drug use by pregnant women. However, iPLEDGE was found to be unduly burdensome following the feedback obtained from stakeholders through call center interactions, iPLEDGE Scientific Advisory Board (SAB), letters and meetings with the manufacturers and the regulatory authorities, as well as from testing the usability of that program

[32, 33]. Also, there was no significant reduction of the pregnancy rates compared to the previous System to Manage Accutane Related Teratogenicity (SMART, 2001). In fact, a decrease in the quantity of prescriptions was observed [34, 35]. Over the years the interventions became more restrictive, yet the pregnancy rate was not significantly reduced, and through the stakeholder feedback, iPLEDGE was found unduly burdensome.

In settings where the drug is also on exception lists for coverage, that is the product can only be covered under specific circumstances (e.g., non-response to other available treatments, specific patient characteristics, etc.), administrative burden may be overwhelming since forms need to be filled for reimbursement as well as for access if there is a restricted distribution program in place for risk minimization. Although the type of information required may be similar (i.e., confirmation of indication, age, some medical history), forms and periodicity of submissions often differ (e.g., monthly for the restricted distribution program and quarterly for the reimbursement). Also, in a hospital setting, many centers already have protocols in place for the prescription and monitoring of drugs that have important risks. It is therefore important to identify activities that may be duplicated in order to properly quantify the burden associated with RMIs.

As recommended by the CIOMS Working Group IX, RMIs should be developed in collaboration with all stakeholders (HCPs and patients) in order to assess feasibility, acceptability and avoid duplications or redundancy between routine healthcare and RMIs.

5 Future Considerations

Risk management and risk minimization have evolved extensively in the regulatory environment in many parts of the world, at a rate that appears to exceed that of methodological developments. Several methodological gaps currently exist on how to measure effectiveness and burden associated with RMIs. Although best practices for the design and conduct of non-interventional studies or surveys are available in public sources (i.e., literature, web sites of regulatory agencies or learned societies), their implementation for risk minimization may not be mandatory in all regions, which results in heterogeneity in the quality studies being conducted . Regulatory authorities and the scientific community are nevertheless addressing such gaps by conducting further research in this area. The other main component of risk management, which is transparency, appears to be somewhat lagging behind. Data on RMI effectiveness remain scarce in the literature and greater transparency can be achieved through appropriate dissemination of results.

Furthermore, risk management planning is often conducted globally by drug manufacturers, with the challenge that each

protocol needs to be adapted to a variety of countries and healthcare settings. While some RMIs may be implemented in some countries, it may not be possible to do so in others. For example, restricted distribution programs are more frequent in North America than in Europe for feasibility reasons. Drug prescribers and coverage status may also differ from one country to another. Although such differences make the implementation of interventions ever more challenging, there is an opportunity to compare the effectiveness of different types of RMIs applied to one drug.

Some products, such as vaccines, may first be marketed in countries with no formal risk management regulations and with healthcare systems that may not be conducive to the implementation of traditional RMIs. Further tools or types of RMIs may therefore need to be customized to those settings in order to better communicate and ultimately minimize the risks. In addition, these same countries often do not have administrative claims databases or EMRs that would allow the evaluation of the effectiveness of the risk management strategies through surveys or drug utilization studies.

As patients and patient groups are becoming more involved in their health care and are now being considered a key stakeholder in the decision-making process, to involve them early on in the planning and design of the RMIs as well as in the evaluation process will optimize alignment between regulation, interventions, and target.

Compared to other industries, such as aviation or engineering, the uptake of risk management has been very late in the pharmaceutical, and even later in the device industry. This could be perceived as an advantage moving forward as pharma can move faster up the learning curve, provided that lessons learned from these other industries be taken into account. However, formal interactions between the various stakeholders involved in therapeutic risk management and those of the other industries appear to remain somewhat isolated instances. Through concerted efforts, one may avoid "re-inventing the wheel" and achieve robust practices sooner, which will in the end benefit all stakeholders, especially patients.

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Chapter 13

Benefit-Risk Assessment in Pharmacovigilance

Ola Caster

Abstract

Benefit-risk assessment is an important component of Pharmacovigilance: it is used to support regulatory and clinical decision making affecting vast populations of patients. Transparent and robust assessments require the use of structured methods, which has sparked lots of research involving both academia and regulatory bodies in recent years. The main aim of this chapter is to provide an overview of the conceptual thinking behind present methods for benefit-risk assessment of medicines, with a more detailed description of some important approaches including multi-criteria decision analysis (MCDA) and decision tree modeling. Also, a few examples of real assessments are briefly presented to enhance and concretize the methods discussion. The expectation is not to provide the reader with an exhaustive account of the field, but rather to support further exploration and stimulate critical review. The chapter concludes with a personal outlook on future challenges and opportunities.

Key words Benefit-risk, Risk-benefit, Decision analysis, Multicriteria decision analysis, Stochastic multicriteria acceptability analysis, Decision tree, Markov model, Discrete event simulation, Quality-adjusted life year, Stated choice

1 Introduction

Nearly everybody concerned with medicinal products—manufacturing, regulating, researching, prescribing, dispensing, or consuming them—understands that their use not only brings the potential to cure, prevent, or alleviate disease, but also carries a risk to do harm. Medicines can hugely impact the length and quality of people's lives, both positively and negatively. Therefore, the importance of assessing which medicines should be available, or what medicine to use in a specific patient, cannot be overestimated. For marketed medicines, this activity of benefit-risk assessment falls within the realm of Pharmacovigilance.

The notion that the treatment for a disease could itself be harmful, and that this needs to be accounted for, is probably almost as old as the practice of medicine itself: already Hippocrates alluded to it [1]. At the population level, such considerations must have

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been made at least since the 1960s, when drug regulation as known today really started to evolve [2]. Simple quantitative benefit-risk assessment methods for single drug effects emerged in the 1980s [3], and were followed by more comprehensive methods around a decade later [4, 5]. The mid 2000s saw the advent of advanced methods [6], and the latest trend has been more collaborative efforts toward developing and evaluating structured methods for benefit-risk assessment [7–9]. Most of this development has been driven by academia, though regulators and manufacturers have started to take a more active role recently, in particular as regards pre-marketing benefit-risk assessment.

There are several perceived advantages with using structured methods for benefit-risk assessment, most notably increased transparency and consistency. This chapter attempts to describe the concepts of such methods, with the understanding that most of them are still considered experimental and have not yet reached widespread practical use in drug licensing and other related activities. This and other challenges for the future are discussed further in Sect. 5.

1.1 Terminology and Scope

Benefit-risk assessment is an ill-defined concept. A recent survey found severe disagreement on the interpretation of the words "benefit" and "risk," even among experienced professionals in medicines regulation [10]. Part of the confusion may be related to an apparent imbalance between the terms "benefit" and "risk." Whereas the former is usually understood as a positive effect that already has occurred or will occur with certainty, the latter typically refers to the potential for a negative effect that might or might not substantialize [11, 12]. Arguably "effectiveness-risk assessment" would be more appropriate in the context of Pharmacovigilance, or even medicine generally. Nevertheless, this chapter will conform to the standard terminology.

Here, benefit-risk assessment is to be understood as any analysis that aims to appraise the usefulness of a medicine in a given indication, jointly accounting for favorable and unfavorable effects. In most cases, not only the indication is specified, but also the dose and the route of administration of the medicine. This is quite natural considering that effectiveness and risk are often dose-dependent.

While this description may refer to general usefulness in a patient population or to usefulness in a specific patient, the former aspect is emphasized here. Benefit-risk assessment for populations is tightly connected to regulatory decisions, e.g., on initial or continued marketing, although several other applications exist. Whereas benefit-risk assessment for specific patients is practically quite different, several of the concepts discussed in this chapter apply partly or fully in that context also.

Pharmacovigilance revolves around the discovery of adverse effects with medicines, and benefit-risk assessment fits naturally as follow-up to signal detection [13]. This chapter focuses on the post-marketing setting; however, many of the principles discussed are equally relevant to pre-marketing benefit-risk assessment. In any case, it is essential to realize the intrinsically dynamic nature of benefit-risk assessment: not only may new effects of a medicine be identified, but the knowledge about established effects increases over time as new data appear. Further, alternative treatments can both emerge and disappear, which may significantly influence the relative usefulness of a medicine in question. Accordingly, global regulatory guidelines prescribe that a medicine's benefit-risk balance be reassessed after the identification of new important information [14].

2 Core Concepts and Properties for Benefit-Risk Assessment Methods

This section provides an introduction to some general concepts and properties of benefit-risk assessment methods, which facilitates the upcoming in-depth discussion of specific methods in Sect. 3, and the brief presentation of some real assessments and their challenges in Sect. 4.

2.1 Frequency and Desirability of Drug Effects

For a benefit-risk assessment method to have real practical utility, it needs to be able to accommodate all relevant effects of a drug. In general, at least on the risk side, there will be several. Of equal importance is the ability of a considered method to account for the two intrinsically different aspects of drug effects here referred to as *frequency* and *desirability*.

2.1.1 Frequency

Of the two, frequency is far easier to appreciate. Intuitively, it is better for a medicine to cure 80% than to cure 40% of patients. Similarly, it is better if an adverse effect occurs in 1 of 1000 patients than in 1 of 100 patients. Because frequency is measured on a well-defined scale with a natural zero, the 80% cure rate is twice as good as the 40% cure rate, and the adverse effect incidence of 1 in 1000 patients is ten times better than the incidence of 1 in 100.

An important point is that generally in benefit-risk assessment one needs to measure absolute rather than relative frequencies. Conceptually this seems uncontroversial: when comparing two medicines, it makes a huge difference whether their respective frequencies of some serious adverse effect like liver failure are, say, 50% and 25% or 0.0050% and 0.0025%. Nonetheless, traditional pharmacoepidemiology is very much focused on estimating relative risks [15], although recent developments indicate that perspectives are widening [16]. A similar conceptual argument as for relative

frequencies can be made to claim that differences of frequencies also are insufficient substitutes for the actual absolute frequencies. Formal analysis affirms these statements [17].

2.1.2 Desirability

Although frequencies can be very difficult to estimate well in practice, they are conceptually straightforward. They are *objective* in the sense of typically being derived from observational or experimental data on the outcomes resulting from various treatments. Desirability, in contrast, is fundamentally *subjective* in nature: different people may make wildly different value judgements about entities like adverse effects and disease states. And even though some preferences are closer to the norm, it makes little sense to classify deviances as incorrect.

There is at least one compelling argument why desirability must be accounted for in benefit-risk assessment: if it were disregarded, all effects would be assigned the same importance, and only their frequencies would matter. For example, one patient's saved life would in essence be cancelled out by another patient's headache. Accepting desirability as one aspect to be considered implies accepting benefit-risk assessment as a partly subjective endeavor. This also means that the conclusions from an analytically sound assessment cannot be classified into terms like "right" or "wrong," and one's expectations on methods for benefit-risk assessments should be adjusted accordingly.

Apart from its subjective nature, another complicating property of the desirability dimension is the difficulty of measuring it. Both ordinal and quantitative scales can be employed, but regardless there is no obvious way of doing it. Lots of different approaches exist [18], the overview of which is beyond the scope of this chapter.

Importantly, the intrinsic nature of a drug effect or a disease state is not the only aspect of desirability that matters. Most notably, duration is at the same level of significance, and so must be accounted for as well [4]. Unless the duration is specified for a beneficial or adverse effect in an assessment, it becomes almost impossible to gauge its desirability.

Finally, a crucial question is for whom desirability is to be evaluated. In benefit-risk assessments aimed to support treatment decisions in individual patients, it seems clear that the only preferences that should matter are those of the concerned patients. In regulatory decision making, however, the answer may sometimes be less obvious. A reasonable guiding principle is to make such decisions entirely on behalf of the concerned patient population, with the ultimate aim of maximizing their health. If so, it is the desirability for those patients that should be considered, assuming they are mentally and physically capable to appraise desirability and communicate their views.

2.2 Recommendable Properties of Benefit-Risk Assessment Methods

It is very difficult to present a set of absolutely mandatory properties for benefit-risk assessment methods. Section 2.1 introduced two highly recommendable properties: the ability to first of all accommodate all relevant drug effects, and then to account for their respective frequency and desirability. Yet there are methods still in use, e.g., the standard formulation of the number needed to treat (NNT) [3], that possess neither of these properties. This underscores the current lack of maturity and consensus of this field, and the best that can be offered are recommendations coupled with arguments, with the understanding that some degree of subjectivity is unavoidable. For reference, previous initiatives have produced property lists similar in spirit to the below, with partly overlapping content [8, 19].

2.2.1 Comparative Assessments

All benefit-risk assessment methods should permit comparison to the choice of giving no treatment at all, i.e., allowing the disease to follow its natural course. Sometimes, it is preferable to compare also to other relevant treatment options, most importantly alternative medicines for the same indication. Therefore, it is recommendable for methods to accommodate such comparisons as well.

2.2.2 Integration of Available Information

The different types of information that need to be considered in a typical benefit-risk assessment are numerous and disparate. Important examples include pre- or post-marketing controlled trials and observational studies, findings based on individual case reports, and preference elicitation studies. Sometimes an assessor may need to generate necessary information from raw data such as that available in databases of health records, insurance claims, or individual case reports. When it comes to the desirability dimension, information may even come in semantic form like "X is less desirable than Y" [20, 21]. While it is clearly better the more types of information a method can sensibly integrate, it is nearly impossible to offer general guidance; the requirements will depend on the purpose and the particulars of the assessment at hand.

2.2.3 Uncertainty

In practice, several aspects of a benefit-risk assessment are fraught with uncertainty. For example, true frequencies of drug effects are not known and must be estimated. Sometimes, like with early signals, there can even be uncertainty whether there is a causal link between the drug and the effect in the first place [22]. Preferences will vary across a population, and even a single individual may express uncertainty with respect to her preferences [23]. Information can be missing altogether. Consequently, any method that can naturally accommodate uncertainty will offer a much more realistic perspective than one that cannot, but will also inevitably be more challenging to interpret.

2.2.4 Other Important Properties

Apart from the three recommendable properties discussed at some length above, there are many more that are of similar importance. The following list covers some of these without any claims of completeness:

- Transparency: It is clear to the user which inputs are being used, how they are being used, and how the output is to be interpreted.
- Soundness: The results generated by the method follow logically from the information fed to the method.
- Practicality: The method is easy to use and comprehend, and expedites rather than delays assessments; also, it supports decision making.

Table 1 provides a summary of the properties discussed in Sect. 2.2.

Table 1
Overview of recommendable properties for benefit-risk assessment methods, as introduced in Sect. 2.2. This collection of properties is not intended to be exhaustive

Property	Explanation	Motivation
Capacity for multiple drug effects	More than one beneficial and one adverse effect can be jointly assessed	There are generally several effects that are of importance to a benefit-risk assessment
Incorporation of frequency and desirability	The method accounts not only for how frequent a drug effect is, but also for its (un)desirability	Different effects generally vary greatly with respect to seriousness, severity, and duration, and therefore will not be equally desirable to patients
Integration of disparate information types	Information of several different types can be used in the same assessment	This is generally required to be able to consider the whole body of available relevant information, and so arrive at a representative result
Uncertainty handling	The method can handle the uncertainty attached to the available information	This is required to understand how robust the results are, and to appreciate the value of decreasing the uncertainty related to a given source of information
Transparency	It is clear which inputs are being used, how they are being used, and how the output is to be interpreted	The user is more likely to trust and use a method that is transparent; also, communication and reproducibility is facilitated
Soundness	The results generated by the method follow logically from the information fed to the method	This is required to justify any action based on the results of the method
Practicality	The method is user-friendly, expediting assessments and supporting decision making	The more practical the method, the more likely it will actually be used

3 Critique of Existing Methods

In line with recent years' increased interest in methods for benefit-risk assessment, substantive efforts have been made to list and classify all available approaches [7–9, 24]. Interestingly, the Pharmacovigilance community provided important pioneering work of the same kind, dating back to the late 1990s [5]. While these references are very useful, it is important to note that their respective lists are not exhaustive, and their selected method classes do not represent any kind of general standard. It is far beyond the scope of this chapter to repeat those exercises; rather, some of the more promising and interesting methods will be briefly introduced and discussed, hopefully equipping the interested reader to further explore the field constructively and critically.

3.1 The Hierarchy of Benefit-Risk Assessment Methods

In Sect. 1, benefit-risk assessment methods were defined broadly to include any method that supports analyses aiming to appraise the usefulness of a medicine in a given indication. To be able to discuss and compare methods, and to practically choose and apply methods in a given situation, it is useful to divide them into two main categories that are hierarchically related to each other.

Methods from the upper category will be referred to as *frameworks*. A framework could for example stipulate a set of general principles to select relevant treatment alternatives and corresponding drug effects, gather the necessary information on them, and generate an interpretable overall result. Each framework is dependent on supporting methods from the lower category that enable the constituent variables of the framework to be estimated. To use a real historical example, a framework method would have been required to assess the overall usefulness of clozapine in treating schizophrenia, following its signal of myocarditis and cardiomyopathy [25]. However, to be able to reach the overall result, methods aimed at the underpinning variables are required. An obvious example in this particular case would be the estimation of the risk of myocarditis and cardiomyopathy with clozapine.

The framework sets the general boundaries for what the assessment can and cannot do, and determines its general properties. In the same applied example as above, a comparative framework would have the benefit of enabling a comparison between clozapine and alternative anti-psychotics. At the same time, the result generated within the framework will be of no better quality than that of its supporting methods, which makes their selection crucial. Most basically they must be compatible with the selected framework. For example, so called tree-based frameworks (see Sect. 3.2.2) require absolute risk estimates, which makes case-control analyses not particularly useful from a benefit-risk perspective.

3.2 Frameworks

Two general types of framework methods for benefit-risk assessment are brought up for discussion: those based on criteria, and those based on decision trees. Both have been recommended for practical use [8, 9], and together they are useful to highlight and put into context the properties and concepts introduced in Sect. 2. Both types of frameworks are rooted in decision analysis, i.e., the scientific discipline to formally address important decisions [26]. This reflects the main application of benefit-risk assessment, which is to support decision making on the use of medicines in populations or individuals.

All frameworks discussed in this chapter are summarized in Table 2.

3.2.1 Criteria-Based Frameworks

These frameworks are all based on the common workflow of decision analysis, which starts by the identification of the decision problem and its objectives. This will define the purpose and the time horizon of the benefit-risk assessment, and whose preferences to consider. Thereafter comes the identification of the relevant options, which are typically the medicine of interest, the no treatment choice, and possibly other active comparators.

The next step, which is essential, is the identification of drug effects to consider. These are formulated as criteria—hence the proposed name—which are commonly modeled in a hierarchical structure. Using again the historical example of clozapine, "Risks" could be one major criterion with "Myocarditis" as one of its sub-criteria. To further illustrate the concept, Fig. 1 shows a typical such criteria tree for a simple fictional example. (Sometimes the terms "value tree" or "decision tree" are used instead; however, the latter is *not* appropriate in this context. Cf. Sect. 3.2.2.)

The presentation of criteria-based frameworks thus far is generic. It applies to descriptive, i.e., qualitative, criteria-based frameworks including the specific examples PrOACT-URL (Problem, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainties, Risk, Linked decisions) [36, 37] and BRAT (Benefit Risk Action Team) [38], as well as quantitative frameworks such as MCDA (Multi-Criteria Decision Analysis) [6, 39] and SMAA (Stochastic Multicriteria Acceptability Analysis) [21, 40]. Despite this broad range of methods proposed, practical application of criteria-based frameworks in benefit-risk assessment is still relatively infrequent. Three examples include glatiramer [28] and natalizumab [27], respectively, for multiple sclerosis treatment, and venlafaxine versus fluoxetine in depression [21].

Descriptive Frameworks

In descriptive criteria-based frameworks like PrOACT-URL, the selection and modeling of criteria is followed by presentation of the available information on the alternatives' respective performance on those criteria. An important example of such information

Table 2
Framework methods mentioned in this chapter, with examples of applied use

Framework	Brief description	Applied examples
PrOACT-URL (Problem, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainties, Risk, Linked decisions)	Generic decision-analytic framework that supports selection, modeling, and possibly weighting of criteria in a structure like that in Fig. 1. Also supports collection of data relevant for those criteria, though alternatives are not quantitatively scored and compared	Natalizumab in relapsing-remitting multiple sclerosis [27]
BRAT (Benefit Risk Action Team)	Conceptually and practically very similar to PrOACT-URL, though BRAT was developed specifically for the purpose of benefit-risk assessment	Natalizumab in relapsing-remitting multiple sclerosis [27]
MCDA (Multi-Criteria Decision Analysis)	A quantitative extension of frameworks like PrOACT-URL and BRAT. Weighting of criteria and scoring of alternatives are mandatory components	Glatiramer in relapsing-remitting and clinically isolated syndrome multiple sclerosis [28]
SMAA (Stochastic Multicriteria Acceptability Analysis)	Criteria-based framework where uncertainty is handled through probabilistic modeling. Allows for incomplete information on preference weights	Venlafaxine versus fluoxetine in depression [21]
Decision tree	Generic decision-analytic model, which in benefit-risk assessment outlines a number of possible courses of events from the patient perspective. Each such course is described as a branch, for which a probability is computed and a utility assigned	Alosetron for irritable bowel syndrome [29]; methylprednisolone in multiple sclerosis management [30]; and antiplatelet therapy in acute coronary syndrome [31]
Markov model	Extension of decision trees, where the distribution of a fictional patient cohort across various possible health states is recomputed in even time intervals	Natalizumab in relapsing-remitting multiple sclerosis [32]; and isoniazid for latent tuberculosis infection [33]
Discrete event simulation	Extension of Markov models, where the course of each individual patient of the fictional cohort is simulated over time	Alosetron for irritable bowel syndrome [34]; and rofecoxib versus naproxen in rheumatoid arthritis [35]

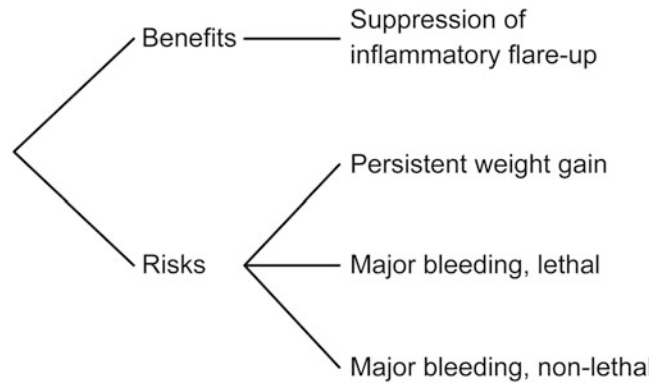

Fig. 1 Criteria tree for a fictional benefit-risk assessment of some anti-inflammatory medication. There are two main groups of criteria, one for benefits and one for risks. The latter consists of three specific criteria, one relating to the adverse effect weight gain, and two relating to the adverse effect major bleeding. If this tree were to be used in a quantitative framework, e.g., MCDA, the considered alternatives would have to be scored on the lowest-level criteria, and all criteria would have to be assigned weights. See section "Quantitative Frameworks" for more details

is tabulated or visualized frequency estimates for the effects reflected by the included criteria. With the aid of the criteria themselves, possibly a criteria structure model, and the alternatives' respective performance information, the assessor reaches a conclusion on the relative merits of the alternatives.

Desirability could be incorporated either explicitly—in case external preference information is presented prior to arriving at the conclusion—or implicitly, in case the assessor's own preferences help shape the conclusion.

Quantitative Frameworks

Quantitative criteria-based frameworks like MCDA are more explicit in the latter stages of the process. A major extension relative to descriptive frameworks is that each alternative is scored on each of the considered criteria. When a hierarchical criteria tree is used, like in Fig. 1, only the lowest-level criteria are scored.

For the majority of criteria, scoring is based on some type of frequency information. Scales are arbitrary in the sense that they have no corresponding entity in the real world: low and high scores are simply to be interpreted as poor and good performance, e.g., high and low incidence, respectively, of an adverse effect. In particular, scores should not be confused with actual frequency estimates. Numerically, scales often range from 0 to 1 or from 0 to 100.

Furthermore, the considered criteria are given numerical weights that reflect the preferences of whomever the assessment is made for. Hence, quantitative criteria-based frameworks explicitly account for desirability. As the scores, these weights generally lack

natural interpretation. In the case of a hierarchical criteria tree, like in Fig. 1, weights are usually assigned level by level from right to left. Each lowest-level criterion then obtains an aggregated weight by multiplying weights along each branch of the tree.

The overall result for an alternative is generated by multiplying the scores of the lowest-level criteria with their corresponding aggregated weights, and then summing up a total weighted score. This yields a quantification of the respective merits of the considered alternatives, to support the benefit-risk assessment at hand.

Uncertainty

Descriptive frameworks generally conclude with some sort of qualitative sensitivity analysis, whereby one considers how the identified uncertainty in the performance information could affect the conclusion. Possibly, the decision supported by the benefit-risk assessment at hand is compared to previous similar decisions as a basic control of consistency.

Naturally, sensitivity analysis is an integral part also of the quantitative frameworks. Here it becomes more explicit, in the sense that for example altering a weight over an interval will immediately affect all alternatives' overall weighted scores.

Some quantitative criteria-based frameworks accommodate uncertainty in a probabilistic sense. SMAA is one such example [21, 40], although the approach is generally applicable [39, 41]. The principle is to feed the framework not single point values for scores and weights, but rather probability distributions thereof. The distributions show the likelihood of a certain score or weight to lie within any possible range of interest. By sampling from these distributions over a large number of iterations, one obtains resulting weighted total scores that also take the form of distributions. One can then infer how likely these total scores are to deviate from their point values by any difference of interest.

Traditional sensitivity analysis can also be combined with probabilistic sensitivity analysis. For example, there could be uncertainty with respect to the inclusion of some specific effect in the assessment, and the top-level sensitivity analysis would then pertain to using two different criteria trees—one with and one without this specific effect—and both scenarios could be probabilistically analyzed, as outlined above.

3.2.2 Decision Tree Frameworks

The use of decision trees in medical decision making dates back at least to the early 1980s. One early example is the formal analysis of the decision whether to start a pregnant woman diagnosed with deep vein thrombosis on anticoagulant therapy [42]. Whereas the application of decision trees to benefit-risk assessment has been recently proposed and recommended [8, 43], decision tree frameworks do not currently appear to receive as much attention as for example MCDA. Like the criteria-based frameworks such as

MCDA covered above, decision tree frameworks too rely on decision analysis. Naturally, therefore, the two approaches share some common features, although there are also distinct and important differences. (See Sect. 3.2.3 for a discussion of this.)

There are several examples where decision trees have been used practically in benefit-risk assessment. These include alosetron for irritable bowel syndrome [29], methylprednisolone in multiple sclerosis management [30], and antiplatelet therapy in acute coronary syndrome [31].

With decision trees, the perspective is generally that of a concerned patient: the decision relates to choosing among treatment alternatives—active or inactive—and the uttermost objective is to maximize health for that patient over the considered time horizon. In benefit-risk assessments supporting policy or regulatory decision making, there is no actual patient, but rather an implicit hypothetical representative of the target population.

Like with the criteria-based approaches, modeling of the decision tree must be preceded by the important step of identifying what drug effects to consider in the assessment. Beneficial effects, e.g., prevention of disease or improvement over the natural course of disease, and adverse effects are included through so called chance nodes. Each such node is associated with two or more possible events, of which the patient will encounter exactly one. A trivial example is whether or not the patient will experience a certain adverse effect, such as myocarditis in the clozapine example. The tree as a whole outlines a number of possible branches, each consisting of a unique collection of events. Figures 2 and 3 display two different decision tree models for the example previously considered in Fig. 1.

Decision trees offer a very natural way to incorporate absolute frequencies for the included drug effects. Each possible event linked to a chance node is assigned a probability, whose value should be set to the corresponding frequency estimate. For example, if the frequency estimate for an adverse effect is 1%, the probability for the event of experiencing that adverse effect should be set to 1%. Consequently, the probability for the event of not experiencing that effect should be set to 99%.

Desirability is handled by assigning each branch a value that should reflect the preferences of the concerned patient or patient population vis-à-vis the collection of events represented by that branch. In classic decision analysis, that value would be called a *utility*. By definition, utilities are numeric values assigned by a rational decision maker, where rationality is defined by a specific set of rationality rules [44]. This construction assures that the alternative with the highest expected utility is the most preferred one. An alternative's expected utility is obtained by first computing the overall probability of each branch through multiplication over

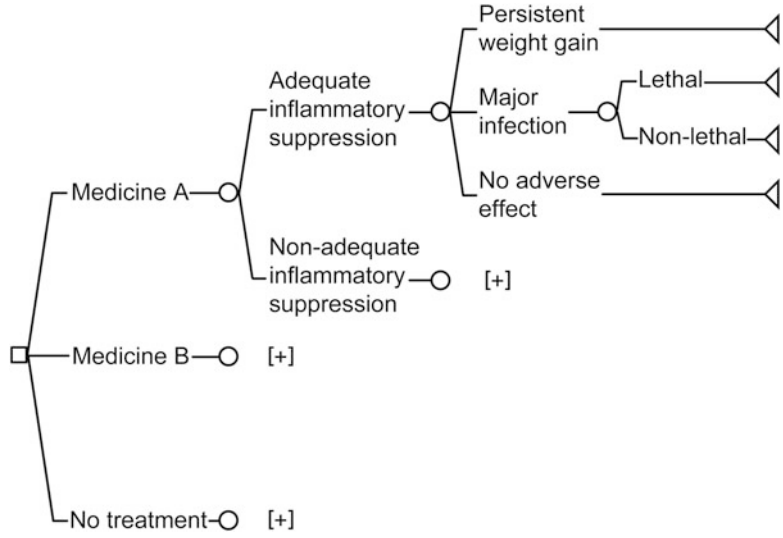

Fig. 2 One possible decision tree model corresponding to the criteria tree presented in Fig. 1. Here it is assumed that the medication of interest (Medicine A) is compared to one relevant alternative active treatment (Medicine B) and to the no treatment alternative. In the diagram, circles represent chance nodes and triangles represent leaf nodes. The symbol [+] has been used to indicate a sub-tree that is identical to the one immediately above it. Hence, there are really eight possible branches for each alternative, and 24 branches altogether. An assumption made in this model is that weight gain and major infection cannot occur together

all its constituent event probabilities. Then the utility of each branch is weighted by its overall probability, and finally the probability-weighted utilities of all branches are summed up.

Whereas this concept of assigning utilities to whole branches has been used for benefit-risk assessment [20, 30], it is more common to compute quality-adjusted life years (QALYs) for the branches [29, 31, 43]. This is further explored in Sect. 3.3.

Uncertainty

The approaches to handling uncertainty that were described for the quantitative criteria-based frameworks in subsection "Uncertainty" of section "Criteria-based frameworks" apply equally to decision tree frameworks, both conceptually and practically. Obviously, however, the types of model parameters are different: for example, criteria-based frameworks such as MCDA use scores to account for frequencies, whereas the decision tree frameworks use probabilities instead.

3.2.3 Comparative Overview

Unsurprisingly, both of the considered types of frameworks possess many of the recommendable properties introduced in Sect. 2.2: both account for frequency as well as desirability, both permit comparative assessments, both are generic and put no hard requirements on the type of information, and both can sensibly

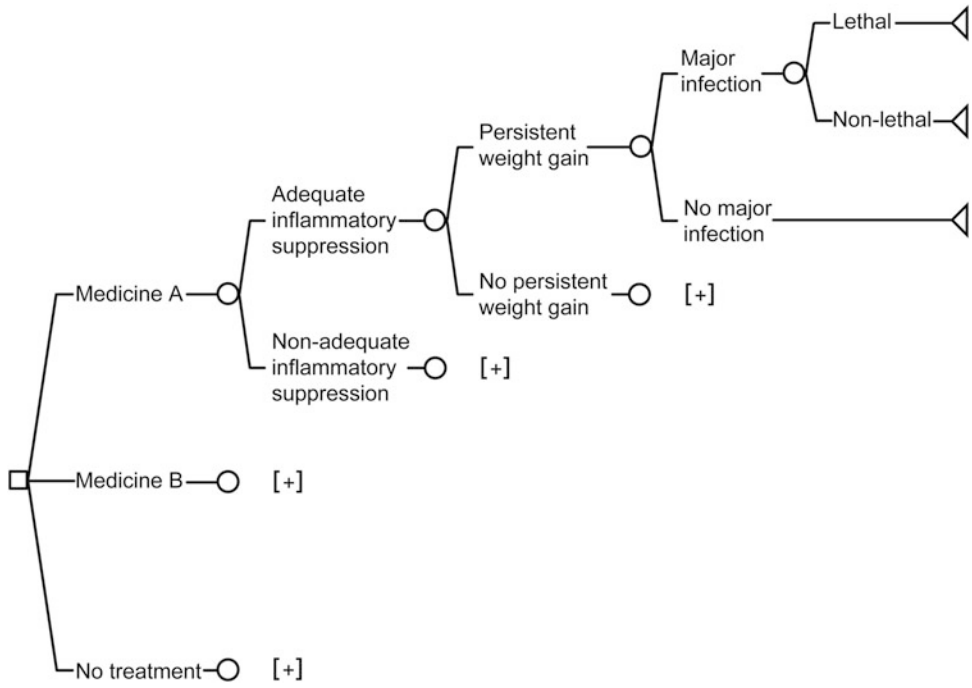

Fig. 3 One possible decision tree model corresponding to the criteria tree presented in Fig. 1. Here it is assumed that the medication of interest (Medicine A) is compared to one relevant alternative active treatment (Medicine B) and to the no treatment alternative. In the diagram, circles represent chance nodes and triangles represent leaf nodes. The symbol [+] has been used to indicate a sub-tree that is identical to the one immediately above it. Hence, there are really 12 possible branches for each alternative, and 36 branches altogether. In contrast to the model in Fig. 2, this model allows for the possibility of weight gain and major infection to co-occur

accommodate uncertainty. As for the other properties, they are fulfilled to varying degrees, and this is where the interesting differences emerge. The below discussion reflects how these approaches have been used in benefit-risk assessment thus far, and clearly does not exhaust all relevant aspects.

Practicality

On the whole, criteria-based methods like MCDA are more practical. They generate considerably smaller and therefore simpler models, which is clear even from the very limited example considered in Figs. 1–3. When many effects are considered, model size could become a severe issue with decision trees, and certain simplifying assumptions may need to be made. One example is to assume mutual exclusiveness of adverse effects, as illustrated in Fig. 2.

Explicitness

The practicality advantage of the criteria-based frameworks primarily relates to being less explicit. However, this feature might compromise soundness in some situations, in particular due to inadvertent multiple inclusion of considered effects. This could

possibly happen when two or more criteria directly or indirectly correspond to the same effect. Decision trees require all relationships to be explicitly modeled, which reduces the risk for errors of this nature.

At the same time, this explicitness required in decision trees could be a disadvantage in other situations. In particular, the need to categorize possible outcomes from each chance node could pose a limitation if the node in question corresponds to an effect normally measured numerically, e.g., blood pressure. The need to discretise a numeric variable causes an undesirable information loss.

Transparency

Both approaches are transparent in the sense that the assessor must clearly report what aspects were considered, what type of information was included, and how that information was used. However, the aggregate results might not be all that transparent, and an entity like expected utility is likely to be complex to grasp for non-specialists. On the other hand, the criteria-based frameworks appear even worse in this respect, as there is not a single and immediately natural way to perform the scoring. And further, when scoring reflects frequency, there are no explicit rules that disallow the use of relative risks or risk differences. This arbitrariness promotes flexibility but hinders interpretation. It may also compromise soundness.

Since decision trees are more explicit, they carry more information, and so in a sense are more transparent. The model in Fig. 2 clearly assumes weight gain and major infection cannot co-occur, while the alternative model in Fig. 3 clearly takes this possibility into account; for the corresponding criteria tree in Fig. 1 this is ambiguous.

Time Handling

Decision trees have been criticized for not being able to handle assessments that cover extended time horizons, for example with chronic illnesses that fluctuate in intensity [45]. The main reason is the virtually endless number of possible configurations of events and durations one might encounter over time, each essentially corresponding to a very convoluted branch of the tree. Practically managing the resulting models becomes very cumbersome, and comprehending as well as finding data for each of the branches is challenging. Feasible alternative methods in such situations include Markov models [46] and discrete event simulation [47], both of which have been utilized practically in benefit-risk assessment [32, 35]. (For method descriptions, see Table 2.) Even though criteria-based frameworks are more rarely criticized in this regard, they are actually less apt to handling complex time patterns than are decision trees. After all, a stated criterion is usually a very high-level description that does not permit much flexibility at all.

Some further aspects of time handling more specifically related to the desirability dimension are discussed in Sect. 3.3.2.

Non-Patient Related Benefits

The strong focus in decision tree frameworks on the health of the patient considered for treatment could pose a disadvantage in situations where a medicine might bring benefits for others. Some plausible examples include overall reduced antimicrobial resistance thanks to a new antibiotic, or herd immunity following high levels of vaccination. Criteria-based frameworks should be able to more easily accommodate such effects, simply by including a suitable high-level criterion group to be weighed against the benefit and risk criterion groups corresponding to effects among those actually treated.

3.3 Accounting for Desirability

Methods to estimate frequencies of beneficial or adverse effects—for subsequent use within some framework method—will not be discussed here, since this is an extensively covered topic in Pharmacovigilance. Note, however, that rare and serious adverse effects are very problematic in this respect, yet of considerable importance in benefit-risk assessment [48].

In contrast, some more attention will be given to methods to account for desirability, as they appear much more infrequently in other Pharmacovigilance contexts.

3.3.1 Preference Elicitation

Eliciting preferences for various health states in terms of so called quality weights has long been a primary concern in the area of health resource allocation [49]. As mentioned in Sect. 2.1.2, there are many approaches available for the purpose of elicitation [18]. Some hope that publicly available collections of quality weights [50–52] will be sufficient to support expedited benefit-risk assessment [43]. However, given the vast number of different beneficial and adverse effects that exist, and given that preferences are likely to vary by patient characteristics and by indication, this may be too optimistic. The post-marketing setting often requires urgent decision making, so specifically designed elicitation studies that are likely to require relatively long time for planning, realization, and analysis may not always be sufficient. Hence, there is a role for methods that can more quickly generate at least some imprecise information on the desirability of the considered effects [20, 21].

Stated-choice elicitation is a general method that has quite recently entered the medical domain [53]. It seems quite well suited for benefit-risk assessment, since patients' preferences are estimated by analyzing their choices in a series of direct comparisons between hypothetical treatments with well-defined beneficial and adverse effects [54, 55].

3.3.2 The Dimension of Time

In health technology assessment, quality weights are generally aggregated over time to yield QALYs. For example, if preference elicitation results in a weight of 0.85 for a certain severity level of Crohn's disease, a patient living with that disease for 2 years would be accounted 1.7 QALYs.

The QALY paradigm is now commonplace also in benefit-risk assessment, most frequently within frameworks based on decision trees, Markov models, or discrete event simulation, as mentioned in section "Time Handling". Its advantage is that it more easily permits complex time modeling. For example, in discrete event simulation the status of each patient of a simulated cohort may be updated weekly, even for assessments that span months or years in total.

However, the use of QALYs in benefit-risk assessment also has clear disadvantages. Apart from the basic practical limitation that all relevant quality weights simply may not be available, there are more conceptual objections. Simply put, if quality weights are elicited in the right way, and if a range of assumptions are valid, QALYs represent utilities [49]. In that case, expected utility (i.e., expected number of QALYs) is an appropriate principle for selecting a most preferred option. However, some of the required assumptions are very strong and unlikely to hold in practice, for example so called "additivity over time": the preference for a health state is assumed to be independent of what precedes, co-occurs, and follows that health state, as well as its duration. And if the assumptions are invalid, the theoretical basis for recommending the alternative with highest expected number of QALYs is much weakened.

Using QALYs in benefit-risk assessment has several questionable consequences [20]. For example, short-term adverse effects will always have negligible impact on assessments with medium or long time horizons, no matter how terrible they are. Also, an alternative carrying risk of causing a lethal effect is penalized only on the grounds that the affected patients would lose time, not that they would lose life itself.

The obvious alternative to the QALY paradigm is to assign utilities to entire collections or sequences of events, so that time is accounted for as part of the utility assignment. While this may be impractical in some situations, particularly with large models, there should be no reason to not do so whenever possible [20, 30].

4 A Practical Example: Alosetron for Irritable Bowel Syndrome

Alosetron is an interesting example since its history reflects a real Pharmacovigilance controversy. It was approved in the US in 2000, and then voluntarily withdrawn later that year following reports of serious complications such as ischemic colitis, of which some were lethal. It was then reintroduced to the market again in 2002, with a narrowed indication and a rigorous risk management plan [56]. Alosetron is not available in Europe.

There are at least three publicly available benefit-risk assessments of alosetron: Ladabaum in 2003 [29], Lynd et al. in 2010 [34], and Caster et al. in 2012 [20]. Of these, the latter two publications are primarily methodological. Table 3 provides an overview of the key features of these assessments.

4.1 Results and Conclusions

Interestingly, although the assessments differ in many ways, not least in terms of methods used, their results are very consistent. Ladabaum and Lynd et al. both found alosetron preferable in close to 100% of the iterations of their respective probabilistic analyses. Caster et al. found generally the same thing. However, their assessment included an additional level of sensitivity analysis that essentially corresponded to the level of risk aversiveness for lethal outcomes, and when that was set high enough, the usefulness of alosetron dropped rapidly. Notably, such penalization of alternatives carrying higher risks of lethal adverse effects is not possible in the QALY paradigm, used by both Ladabaum and Lynd et al., as explained in Sect. 3.3.2.

4.2 Practical Considerations

These benefit-risk assessments certainly demonstrate both the need to accommodate different kinds of information, and the common practical limitation of not possessing the kind of information one would ideally like to have. For example, all three assessments used clinical trial efficacy data as a surrogate for real world effectiveness data. And they all used relative reporting rates from spontaneous reporting to estimate the conditional probabilities of serious outcomes from the considered adverse effects; this will likely cause overestimation, since serious outcomes are more prone to be reported [57].

In terms of desirability, several assumptions had to be made as a result of missing information. Ladabaum used publicly available quality weights and had to assume, as an example, that the quality of adequate relief from treatment was the average of that for irritable bowel and that for non-irritable bowel.

The assessment by Lynd et al. may be the most accurate one, given that it was based on desirability information elicited using a tailored stated-choice study in the target population, and given the complex and detailed discrete event simulation framework. However, it is unclear whether this approach would be the most useful in a prospective setting, at least initially, since stated-choice studies may require considerable time until results are available.

Finally, it is interesting to note the differences in the selection of effects between on the one hand Ladabaum and Caster et al., and on the other hand Lynd et al. For example, the latter used overall a considerably larger set of effects, with benefit split over abdominal pain, urgency, and diarrhoea. This selection step is difficult, but immensely important since it will predicate all subsequently generated results.

Table 3
Key features of three publicly available benefit-risk assessments of alosetron for the treatment of irritable bowel syndrome

Study	Overall comparison	Framework	Desirability measure	Time horizon	Effects	Main information sources	Uncertainty handling	Overall conclusion
Ladabaum [29]	Alosetron or standard care for female patients with IBS	Decision tree	QALY	6 months	Adequate relief from IBS, ischaemic colitis, severe constipation	RCTs for frequencies; spontaneous reports for conditional frequencies of serious adverse effect outcomes; literature estimates for quality weights and durations	Probabilistic sensitivity analysis and separate one-way sensitivity analyses	Alosetron strongly preferred
Lynd et al. [34]	Alosetron or no treatment for patients with IBS	Discrete event simulation	QALY[a]	12 months	Abdominal pain, urgency, diarrhoea, constipation, moderate colitis, severe colitis, impacted bowel, perforated bowel	RCTs for frequencies; spontaneous reports for conditional frequencies of serious adverse effect outcomes; stated-choice elicitation of quality weights	Probabilistic sensitivity analysis stratified by baseline quality of life	Alosetron strongly preferred
Caster et al.[b] [20]	Alosetron or standard care for female patients with IBS	Decision tree	Utility, per whole branch of decision tree	6 months	Adequate relief from IBS, ischaemic colitis, severe constipation	RCTs for frequencies; spontaneous reports for conditional frequencies of serious adverse effect outcomes; qualitative utility relations	Probabilistic sensitivity analysis stratified by risk aversiveness for lethal outcomes	Alosetron strongly preferred, *except for very risk-averse patients*

IBS irritable bowel syndrome, *QALY* quality-adjusted life year, *RCT* randomized clinical trial
[a]Strictly, a measure called relative value-adjusted life year (RVALY) was used; however, they are conceptually equivalent and differ only in the way the quality of a health state is measured (see column 'Main information sources')
[b]This study was intentionally designed to be identical to the one by Ladabaum, with the exception of the approach to accounting for desirability

5 Future Opportunities and Challenges

Pharmacovigilance always has been and likely always will be primarily concerned with the risk side of medicinal products. However, the current very sensible trend is to put greater emphasis on benefit, and the weighing of the two against each other. The act of balancing benefit and risk is nothing new, of course, neither in the regulatory nor in the clinical setting. But the increased demand from the public for openness and engagement, and the increased willingness from decision makers to be transparent, does bring new requirements. Benefit-risk assessments must be robust and transparent, and this inevitably requires some kind of formal, structured, approach. The Pharmacovigilance setting, with medicines already in the market place and potentially huge populations exposed, also calls for urgency in the face of newly discovered adverse effects about which we may know very little.

Recent history also shows that we have quite a long way to go. For example, as rofecoxib was withdrawn after concerns about cardiovascular adverse effects, one can seriously question whether fundamental principles [5] of benefit-risk assessment were overlooked: was a comparative assessment against other viable options performed, and were all important aspects such as gastrointestinal adversity and effectiveness considered [58]? The results of subsequent assessment underline these question marks [35].

Without doubt, benefit-risk assessment poses a great challenge to Pharmacovigilance, not least in the area of method development. At the same time, the current climate is one that offers great opportunities. If the right developments are made, public trust is for the Pharmacovigilance community to earn. And most importantly, there is a great potential to support more rational use of medicines, for the benefit of all.

5.1 Subjectivity

One of the commonest mental fallacies in research and development in this area, in my view, it to picture benefit-risk assessment as purely an act of objective data analysis: with infinite amount of data about the effects of medicines, and with the best available methods to analyze that data, we would be able to assess the usefulness of any medicine in any given scenario. This does not make sense, since people always will have variable preferences even if faced with deterministic choices. Hypothetically, would it be worth to take a medicine that is certain to cure one's arthralgia, but instead induce diabetes? There is no objectively right or wrong answer. The following authentic quote from an elderly woman is very telling in this regard. Upon having been told that the medicine she was using to prevent urinary incontinence, terodiline, had been withdrawn due to a risk of fatal arrhythmias, she said: "Young man, I would rather die dry than live in a wet hell."

This fallacy to disregard the subjective component of benefit-risk assessment might stem from a strong belief in objectivity and scientific reasoning among professionals in Pharmacovigilance, or even medicine generally. But instead of fearing subjectivity, the way forward may be to *embrace* it. The first step would be general acknowledgement of the importance of subjectivity in benefit-risk assessment, and eventually we might see cross-scientific endeavors that include systems scientists, behavioral scientists, and other professional groups that are currently rare or absent in Pharmacovigilance.

5.2 Directions for Methods Research

The lion's share of this chapter concerns proposed methods for benefit-risk assessment: what are the concepts that underpin them, how do they work, and what are their advantages and disadvantages? Yet the discussion here has only been able to serve as an introduction, leaving many important methods behind, and failing to exhaust several very important aspects, both theoretical and practical.

A major challenge ahead lies in properly evaluating existing approaches. The evolution of the field thus far has shown this to be far more difficult than presenting new methods, and there are good explanations for this. The first is very much related to the above discussion on subjectivity. Pharmacovigilance is used to settings where methods provide results that can be classified as right or wrong, for example when it comes to statistical methods for signal detection. And even in those situations, method evaluations are far from straightforward [59, 60]. Then, obviously, this becomes so much more difficult in benefit-risk assessment, when methods are not primarily there to provide an objectively verifiable result, but rather to help decision makers structure complex assessments, and reach conclusions coherent with both data and preferences.

Secondly, as mentioned in Sect. 3.1, there are so many different kinds of methods. It seems quite apparent that we must compare only those methods against each other that aim to do the same thing. But currently even the domain experts have widely different systems to classify methods and define their main purpose. This needs to change in the future.

Finally, proper method evaluation requires test cases, both retrospective and prospective. However, this field seems to possess far fewer such test cases than other fields, and there has been little work done toward agreement on how or where to collect them. Again, signal detection is an interesting field for comparison that seems to lie far ahead [61]. The likely explanations for this deficiency are the modest number of cases to begin with, and the difficulties involved in defining and collecting their key properties in a structured manner, and the complexity of issues, sparsity of data, and non-transparency make definitive knowledge difficult to determine.

Another area in methods research that requires more attention is the selection of what actually goes into an assessment. This concerns primarily the selection of adverse effects, of which there will be many more than can practically be handled. Many method descriptions acknowledge this as a crucial step, yet offer very little guidance on how to do it. And actual proposals [4, 30] have never been properly evaluated. Similarly, much more work is required to be able to give solid practical recommendations on what data to use with a particular type of method in a given situation.

At the other end of the spectrum, good visualization techniques will be key for the future, as they will greatly help practitioners interpret data and assessment results. More research should go into this area, where previous work in areas like engineering or statistics should be considered.

My expectation is not that there will eventually be a single best method identified, not even in a quite narrowly defined situation. Much like in other subfields of Pharmacovigilance, the task of advancing the science and practice of benefit-risk assessment amounts to compiling a solid toolbox: removing methods that work suboptimally, keeping a reasonable number of promising methods, and developing clear user instructions for those methods that are retained.

5.3 General Directions

From a long term perspective, I hope and believe that benefit-risk assessments will be used routinely for all important decisions related to a medicine, including development, initial licensing, subsidization, surveillance, and individual therapy. I envision that such assessments will become a very natural component of the regulatory life of a medicine, much like pre-marketing clinical trials and post-marketing spontaneous reporting of suspected adverse drug reactions are today. Several decades from now, the aforementioned toolbox should be mature and generally accepted, and we should know much better what data we need and how to generate it.

Obviously, changes will not occur overnight. One prerequisite for moving the methods discussed in this chapter into mainstream use is confidence. Researchers must gain confidence in what methods to recommend, and better understanding how to measure and demonstrate performance will take us a long way toward that goal. Subsequently, practitioners, e.g., regulators, will gain confidence as they get more accustomed to using the recommended methods. This process must be allowed to take time.

However, methods cannot operate in isolation. A major issue today is the lack of appropriate and reliable data, particularly on real world use of medicines, but also on their targeted diseases. Structured methods have the advantage of revealing what required information is missing, but that property alone can only take us so far. What data to generate and how is a somewhat independent

question from what method to apply, and one that must be tackled before any major changes can take place.

Finally, the interplay between benefit-risk assessment and pharmacoeconomic analyses, such as in health technology assessment, warrants more consideration. The two areas have a lot in common [62], but their respective decision processes are often very separate in practice.

5.4 Conclusions

Benefit-risk assessments are important to support robust and transparent regulatory and clinical decision making on the availability and use of medicines. They are an integral part of Pharmacovigilance, naturally suited to make use of newly generated information on marketed medicines, not least concerning previously unknown adverse effects. There is a plethora of methods available to support the benefit-risk assessment process in different ways. Currently, the relative usefulness of these methods is evaluated primarily through conceptual argumentation and application in isolated examples. Although highly challenging, future research must address this by providing practical and empirically well-grounded recommendations, for the ultimate benefit of patients worldwide.

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Concluding Thoughts

Andrew Bate

To do everything possible to ensure patient safety through the appropriate use of medicinal products is the ultimate and core remit of pharmacovigilance. The field has never had a wider profile than it has now and is both a relatively young and tremendously wide discipline as the chapters throughout this book demonstrate. Pharmacovigilance draws on the developments of many other fields of work and endeavor. On occasion, scientific approaches well established in other fields have only recently been applied to pharmacovigilance. For example, the use of instrumental variables, an approach to minimize unobserved confounding in analyses, has been well established as a core approach in economic theory for many decades [1], but their use in Pharmacoepidemiology studies has only recently been explored (*see* Chap. 11 for a brief discussion). Multi-criteria decision analysis (MCDA) is extensively used in engineering, but assessment of its applicability for risk benefit assessments in pharmacovigilance is more recent [2] (*see* Chap. 13 for an extensive discussion on risk benefit.) As such approaches feed into pharmacovigilance, the field undergoes great change. While core elements of pharmacovigilance have remained and will remain for the most part unchanged, the scope of pharmacovigilance is likely to continue to evolve dynamically. For example, modern pharmacovigilance is now widely considered to include identification of medication errors and substandard medicines and other general aspects of patient safety [3], adverse event preventability [4], indicators of drug dependence [5], and assessment of the economic impact of adverse events [6]. There are many more lessons to be heeded from other fields of work [7].

The chapters in the book highlight many of the fields where most change is occurring, or needs to occur. The reader should be aware that the subject matter covered in this book is necessarily just a selection of examples of fertile and active research subdisciplines within pharmacovigilance, and in brief some other areas of PV research and development are covered below.

An area of research that should not go unmentioned is personalized medicine, given the amount of recent discussion on this topic. Many will argue that the attention heaped on personalized

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medicine has not so far really lived up to the hype overall; particularly in pharmacovigilance, we are however beginning to see examples of such a focused approach in parts of healthcare delivery and drug development. For example, in the area of oncology, there is the development of targeted therapies of tumor-specific oncogenic drivers. Improvements in genomic technologies have greatly advanced the understanding of the genomic alterations that contribute to lung cancer [8]. Personalized medicine offers the potential for improved health outcomes by targeting more on tumor-specific oncogenic drivers as we move potentially into an era of biomarker-based treatment decisions with drugs, for example, used to treat patients with late-stage (locally advanced or metastatic) non-small cell lung cancer (NSCLC) with an abnormal anaplastic lymphoma kinase (ALK) gene [9]. Another example is in the treatment with ivacaftor of cystic fibrosis patients with the G551D mutation in the Cystic Fibrosis Transmembrane Regulator (*CFTR*) gene. This mutation has been estimated to be present in some 4% of the Cystic Fibrosis population; recent studies have shown in vitro efficacy of ivacaftor on other different gating mutations in cystic fibrosis resulting in a widening of indications for the product by the FDA [10].

In terms of specific impact on pharmacovigilance, the HLA gene complex is linked with immune-modulated hypersensitivity reactions for some medicinal products, increasing patient disposition for getting adverse reactions. One of the more well-known examples being reporting of carbamazepine-induced Stevens–-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with the *HLA-B*15:02* allele in some Asian patients [11]. This reported association has impacted routine healthcare practice with recommendations for testing for the presence of the HLA-B*15:02 prior to the prescription of carbamazepine [10]. Consider, for example, the association between HLA *B*57:01* and abacavir hypersensitivity syndrome [12]. While the challenges in successfully converting a genome discovery into a tangible clinical endpoint should not be understated [13], as examples like the above potentially become more widespread, one can anticipate that the advances in pharmacogenomics will increasingly influence more and more of routine pharmacovigilance [14, 15].

Specific therapeutic solutions can bring their own tailored PV challenges and therefore approaches: Surveillance of vaccines [16, 17] is an area of research where different approaches and techniques to those of drugs have often been deployed. There are of course clear differences in the utilization of vaccines compared to drugs including the prophylactic use of vaccines in large, healthy and often young populations, and differences in their more commonly used routes of administration. These differences greatly impact pharmacovigilance strategies. For example, the focus on injection as a frequent route of administration means clearly that surveillance for injection site reactions is important. The common

one-off use of vaccines also makes for differences in the analytic approaches that can be deployed or may be most effective. For example, within patient control, epidemiological methods will obviously be more effective than for patients with long-term transient medical use. Similarly rechallenge, a core component of clinical review of spontaneous reports for causality assessment [18, 19], is clearly not possible. More recent therapeutic options such as biological agents [20] bring new challenges and may have quite different ADR profiles to other drugs. Similarly consideration needs to be given to biosimilars and whether different ADR profiles to the related reference biological product occur [21], perhaps due to differences in the manufacturing process. Device pharmacovigilance also brings with it unique challenges [22].

As well as considering a given medicinal product, its anticipated use, most likely adverse effects, and our ability to capture relevant data on exposure and health outcomes, one must also consider how effectively one captures other data of importance for effective pharmacovigilance activities. In addition to herbals (discussed in Chap. 3), food interactions with drugs are being considered and studied more and more, for example, the reported interaction of cocoa on ACE inhibition [23], or the effect of grapefruit juice on drug efficacy [24], as well as the role that excipients can play in the safety of products rather than a sole focus on active ingredient [25]. These examples and similars are far from new and yet still our ability to consistently and routinely capture data on exposures other than conventional medicine is still very limited and is a significant limitation in modern PV. Perhaps in the era of "Big Data"-enhanced routine systematic data capture of such data types will allow still more focus on the impact of diet, etc., on health outcomes of relevance to pharmacovigilance.

A clear change in pharmacovigilance, evident throughout this book, is the wider existence, availability, diversity, and size of electronic data sources that might or do have more relevance to pharmacovigilance than ever before. Traditional data sources (clinical trial data, spontaneous reports, registries, medical literature, electronic medical records, and private and public transactional insurance claims data sets) are now widely available in electronic format and are more widely used. Such data sources have now been supplemented by other forms of data including, as discussed in Chap. 9, social media (Facebook, Twitter, patient group web chat forums, etc.) and automated data upload from electronic devices or wearables, so-called "mdata" such as heart monitors, mobile phones, and "Fitbits". With such mobile data streams, we potentially may be getting hundreds of thousands of data points rather than the hundreds we rely on for analysis often currently, frequently in near real time. The potential new capability incurred by this rapidity of data availability as well as data volume has led to a whole new terminology: the "internet of things," "big data," "data democratization," "deep learning," etc. Emphasis has

moved from data collection capability to ensuring rapid effective generation of actionable insights from large volumes of disparate data. Where previously electronic data was converted into structured data for analysis, now the advent of Natural Language Processing means that analysis of unstructured data in the form of, for example, free text clinical narratives can be conducted effectively, often in combination with structured data [26]. An example of a healthcare surveillance tool is GPHIN [27], which is a general surveillance tool for internet media, such as news wires and websites, in multiple languages in order to help detect and report potential disease outbreaks or other health threats around the world and would also have applications in pharmacovigilance. Google flu trends are another example where internet search activity is used to monitor for unexpected spikes in particular searches, particularly of course medical symptoms, which in near-real-time monitoring can provide insight into flu outbreaks (when linked to geographical region) [28]. Internet analysis through "Web scraping" of medical literature websites such as Pubmed is also proving a promising emerging source for data discovery and potentially signal detection [29]. However under-recording of data is always a challenge in all data sources developed specifically for use in pharmacovigilance, or otherwise. While there is much discussion of how well-structured data captures specific health outcomes of focus and how unstructured data can support this, there is less about how selective under-recording or accuracy of coding varies by situation (general and specific for a given patient) or also in the phrases or terms used in free text fields: More sophisticated pattern recognition is needed to tackle this challenge.

Use of terminological vocabularies to ensure we capture and cluster conceptually similar healthcare outcomes is critically important to the effectiveness of the pharmacovigilance enterprise. With the advent of more and more data streams, different terminologies are used with varying level of specificity. The ability to not only effectively use a given terminology for a given data set but also to understand the assumptions and errors that can occur at data entry and output stages, as well as to map and therefore analyze across disparate data streams with different terminologies, are all important. Informatics approaches leveraging ontologies can help with this, and promising research is going on in this area (see e.g. [29]). Natural Language Processing, mentioned above, when used to better leverage unstructured data may also provide an alternative approach to bypass information loss of data entry in structured formats and other problems with the current terminologies used in modern data sources or of use in pharmacovigilance.

Linkage across often apparently disparate existing data streams can also contribute greatly to increasing our inferential capabilities. This may be more detailed or granular information on data captured for or about healthcare use, such as medicinal product

information, or other information about the patients captured in health data but from elsewhere, such as transport or mobile phone data. While data linkage is clearly beneficial from an information theoretical basis, privacy concerns are paramount and need to be considered in what data can be linked, in what way and how such data is stored and analyzed. Transparency of data use, including details of how and why data is linked, the process undertaken and the usage of data, are all critical components for ensuring widespread trust in the use of real world data.

More detailed information on medicinal products could and should be linked to healthcare data streams and used routinely in analyses such as QSAR [30] and other chemical structure representation [31]. Information such as receptor activity and selectivity potentially allows more sophisticated analyses than merely considering medicinal products as binary variables, i.e., listed as present or not. Some work has been done, but it is less routinely used in pharmacovigilance than might be anticipated. Over two decades ago, Alvager et al. [32] conducted a small study attempting adverse event prediction for antidepressants using neural net-based analysis on chemical structural properties and receptor activity, attempting to show the ability to predict AE profiles based on a given antidepressant's receptor activity fingerprint. More recently, Almenoff et al. [33] looked at chemical structure and chemical and biological property linkage and the correlation with spontaneous reporting. Linking spontaneous reports to CYP 450 activity information for drug–drug interaction signal detection has also been conducted [34]. Basic spontaneous report analysis process linked to EHR data and systems biology, with experimental validation of outputs, is also being explored [35]. In terms of linkage to other data sources, the importance of road traffic data for pharmacovigilance is not immediately obvious. Yet in a study in a region of Scotland with particularly strong data linkage systems in place, such a linkage to healthcare data allowed researchers to look at the impact of benzodiazepine use on driving [36].

Pharmacovigilance can also be considered to include the analysis of poisoning data [37]. Indeed similar methods to those used in the detection and analysis of ADRs and adverse events following vaccination can be used in the analysis of international poison case data. A pilot example of such an analysis was the use of a feed forward neural network, Bayesian Confidence Propagation Neural Network (BCPNN) [38], adapted from that used in quantitative signal detection in drug and vaccine safety surveillance [39] on organophosphate poisoning data collected in a multicentre international study involving eight countries [40]. The IPCS (International Programme on Chemical Safety) "Toxscore" [41] was used by emergency hospital staff to score clinical variables on 537 reported poisoning cases; a subset of the patients died and the majority survived. The research examined the clinical variables

that predict mortality either singly or together, as well as considering the effect of treatment. Grouping of treatment variables totalled 66 types, the majority of cases with (386) antidote plus gastric intestinal decontamination. IPCS Toxscore covered 33 clinical variables in addition to many other factors (e.g., weight, height, occupation code, and hospitalization). The most reliable predictive single variables, in order, were found to be Coma scale, Peripheral motor activity, Peripheral sensory activity, Respiratory rate and Pa CO_2. Arrhythmia predicted the patient would die, but the reverse was not true. However, the Coma scale and arrhythmia, together, indicated the worst chance of a fatality. We see machine learning approaches like the above beginning to be more widely applied in healthcare.

While the field strives to take maximum benefit from existing data for pharmacovigilance and other applications, the demand for strong inference lays bare more clearly than ever before when existing data is insufficient for the desired purpose, either because the data types needed are not present or because of likely biases that make the study question hard or impossible to appropriately investigate. A challenge is therefore when an observational data source, alone or linked, is near ideal for a given study, but there are a few key pieces of information that are missing. In such situations, some prospective bespoke data collection component may be embedded in the routine data collection. We are increasingly seeing examples of such data fortification studies. For example, a study assessed prescriber attitudes by embedding a prospective survey in clinical practice software thereby ensuring survey outputs were linked to the EMR data collected routinely [42]. Similar approaches are used for pragmatic or large simple trials where randomization is conducted but in a "real world data" setting. Examples of such studies include ZODIAC, an open-label, randomized, postmarketing study enrolling patients with schizophrenia in naturalistic practice in 18 countries with the primary studied endpoint being the rate of non-suicide mortality in the year after initial recommendation for therapy [43] and the Salford Lung Study which conducted a pragmatic randomized clinical trial of asthma and chronic obstructive pulmonary disease (COPD) that was a clinical study embedded in routine healthcare delivery [44]. We anticipate more data fortification and data augmentation studies as the field continues to develop.

Much of the above has focused on how we better understand population risk and benefit. Efforts are also very much underway to harness advances in pharmacovigilance and other disciplines to help in the care of individual patients through information sharing, supporting healthcare delivery, and prevention and prediction of future healthcare outcomes. For example, with appropriate data and patient privacy protection, tool-based advice provision to healthcare professionals around managing care can be undertaken

[45]. Such tools can also facilitate safety data uploads such as for spontaneous reporting [46, 47], and hold promise in the potential for interactive real-time secure privacy protecting interactive discussion between HCPs and pharmacovigilance experts. This could be beneficial in order to request extra data that would be useful for individual patient treatment but also highly informative, for example, in refining overall pharmacovigilance knowledge rapidly. Information observed in a healthcare encounter may not be considered important to report or record at the time without prompting but may ultimately be crucial for accurate diagnosis, and therefore vital to whether or not a medicinal product were likely to have had a causal role (such as drug-induced skin reactions).

Ultimately might one envisage a nearing and potential merging of spontaneous reports and electronic medical records? Could this lead to spontaneous reports no longer being collected and reported but instead becoming a detailed near real-time questionnaire description of a healthcare encounter where a suspected adverse drug or vaccine reaction occurred for an HCP in order to communicate situation-specific data and receive related information and potentially guidance? All of this we have done as part of a repeating iterative patient-specific learning cycle—naturally with appropriate privacy protection in place—and is of benefit to both the patient and also the wider treated population. Efforts must continue to more effectively solicit and better capture patient data. The recent attention on Patient Reported Outcomes is gratifying to see.

Enhanced IT capability and more data allows and requires on occasion more novel approaches to data analysis in general, exemplified by the enhanced interest in Machine Learning and Data Science as disciplines. Such analytic developments have been arguably more sporadic in pharmacovigilance and related fields; this may be in part due to the sparse, noisy, and sometimes biased nature of healthcare data, as there are certainly many analytical problems that demand methodological developments. A recurrent Bayesian confidence propagation neural network BCPNN, related to the Information component analysis used for routine quantitative signal detection, has been used for syndrome detection in spontaneous report [48] and other cluster detection algorithms approaching a similar problem [49]. Analytic approaches like Random Forests [50], deep learning, hit miss models for assessing record similarity for subsequent clustering [51], and other machine learning algorithms for unsupervised pattern recognition are all being developed, tested, and improved. Much routine analysis currently focuses on detection and evaluation of signals. In the future perhaps as data becomes ever richer, we might see more patient-level disease impact and healthcare outcome prediction analysis, as well as treatment pathway investigations; our ability to make patient-specific inference from population-based assessments is a clear need for further development. Efforts to apply other methodological

approaches like data capture recapture [52] are to be encouraged, rather than focusing on a narrow suite of tools and approaches.

As patients become rightly more and more engaged with pharmacovigilance and the impact it has on their personal choices around healthcare, the discipline of risk communication becomes ever more important, and there are several efforts to assess and improve how risk benefit information is communicated [53]. Measuring the impact of pharmacovigilance for individual patients and on a public health level and how evidence supports our decision making, such as in Vermeer et al.'s article [54], is also being increasingly prioritized.

Pharmacovigilance is very much an international discipline these days with important research and activity occurring around the globe, e.g., Argentina [55], Japan [56], and Qatar [57]. As pharmacovigilance becomes increasingly important and generates increased interest, teaching in the core principles and training strategies will become ever more important [58], using more novel and creative mechanisms for training such as crowd sourcing to take advantage of technological advances and valuable attitudinal changes [59].

It is most certainly an exciting time for pharmacovigilance. While we have come far since the start of organized drug safety surveillance in the 1960s, this book shows that in all disciplines there is some ways to go, and only by considering both clinical and quantitative aspects will our capability grow as it should.

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INDEX

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