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COMMENTARY

Fifty years of pharmacovigilance – Medicines safety and public health

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THE CURRENT EPIDEMIC OF DEATH, DISEASE AND DISABILITY IS A FAILURE OF MODERN MEDICINE

Adverse drug reactions (ADRs) are a major cause of illness and death. Around 25% of ambulatory patients in primary care suffer an ADR, which is serious in 13% of the cases.[1] ADRs cause 5–10% of hospital admissions.[2] In 2011, 2 to 4 million persons suffered serious, disabling, or fatal injury associated with prescription drug therapy in the USA, including 128 000 deaths.[3] Overall, in developed countries, ADRs can be the third[4] or the fourth leading cause of death (behind ischemic heart disease, stroke and cancer, ahead of diabetes, chronic obstructive pulmonary disease and traffic accidents). This figure, which was one of the results of a top-quoted systematic review of heterogeneous old studies,[5] was probably an underestimate, because in many of the original studies, only deaths that had been diagnosed as drug-induced were counted. The nowadays well-established etiological contribution of medicines to a variety of conditions with a relatively high incidence (e.g. hip fracture or traffic accidents associated with sedatives or antidepressants) was not counted in the estimation of the burden of drug-induced disease. On the other hand, in the last 15–20 years, heavy polypharmacy among the elderly has skyrocketed,[6] which makes drug interactions more likely, thus increasing the iatrogenic burden. Drug utilization studies have consistently shown that medicines are often prescribed and taken unnecessarily (e.g. statins in primary prevention), for unnecessarily long periods (e.g. double anti platelet treatment after myocardial infarction, bisphosphonates for more than 2 years), at unnecessarily high doses (e.g. ibuprofen 600 mg for pain), and to people for whom they are contraindicated. Unnecessary use of medicines is an especially worrying cause of disease, disability and death.

Certainly, ranking immediate causes of death (e.g. myocardial infarction) together with non-immediate (e.g. a medicine) causes of death may be ambiguously misleading, but nevertheless these figures reflect that drug-induced disease and death are a major and seemingly neglected public health issue. The medicines we rely on are a leading cause of death, disease and disability. This is a failure.

FIFTY YEARS OF PHARMACOVIGILANCE – FROM CASE REPORTS TO BIG DATA HANDLING

Spontaneous reports

Pharmacovigilance, the 'detection, assessment, understanding and prevention of adverse effects… of medicines',[7] was born 50 years ago,[8] as a reaction to the thalidomide tragedy. Phocomelia is an extremely rare malformation. This rareness was just what drew attention and helped to detect and establish the causal relationship with in utero exposure to thalidomide, albeit no formal surveillance systems were in place. In its first years, pharmacovigilance relied on anecdotal reports and case series. Spontaneous reporting is based on clinical judgement, which draws preferential attention to rare events, so that a rare disease is more likely to be reported than more common conditions. The conditions that topped the lists of spontaneous reporting in the sixties and in the early seventies were almost invariably type B ADRs with a low incidence (1 to 20 per million per year)[9] – blood dyscrasias,[10,11] acute hypersensitivity reactions,[12] acute liver failure, and severe cutaneous reactions.[13] Regulatory action also concentrated on rare type

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B ADRs.[14] Spontaneous reporting has identified many adverse drug effects, and it has helped to know their clinical course and their prognosis. It continues to do so. However, it is ineffective for detecting frequent and benign ADRs, and it does not provide any estimate of incidence or risk. **First-generation pharmacovigilance** was based on case reports and case series usually assembled through spontaneous reporting systems.

Observational research

In the seventies, several safety problems were uncovered by studies linking voluntary reporting data to consumption data, e.g. dose-related risk of thromboembolism with oral contraceptives (OCs)[15] and lactic acidosis with phenformin.[16] The risk of severe asthma attack and death related to high-dosage isoprenaline was uncovered by linking mortality statistics with sales data.[17] An extension of this strategy has been the case-population method, where the rates of exposure among incident cases of a particular condition are related to the rates of exposure in the general population.[18] These studies were soon followed by the first case-control studies, e.g. on vaginal adenocarcinoma and diethylstilbestrol[19] and also on more common conditions and exposures such as endometrial cancer and hormone replacement therapy (HRT),[20] gastrointestinal bleeding and acetylsalicylic acid,[21] hormone-dependent cancer and OCs,[22–25] road accidents and hypnotics and sedatives,[26] cholecystitis and thiazide diuretics,[27] and myocardial infarction and OCs.[28] Gradually, the interest moved from a clinical to an epidemiological perspective and from rare unexpected type B effects where drugs have a high etiological fraction (e.g. agranulocytosis,[29] acute hypersensitivity reactions[30]), to more common conditions with incidence rates of the order of 10^2–10^3 per million population per year, which are usually dose-related preventable type A ADRs, such as gastrointestinal bleeding in relation to non-steroidal anti-inflammatory drugs (NSAIDs),[31] or death from asthma with fenoterol,[32] apart from the glorious RCGP cohort study on OCs.[33] The relevance of incidence rates and relative and absolute risks was increasingly recognized. It became clear that if a single drug or group of drugs was responsible for 5% of all heart attacks (incidence of 1000–2500 cases per million and per year[34]), it would cause many more victims than a drug causing, say, 50% of cases of Stevens-Johnson syndrome (incidence of 1 case per million per year[35]).

In the late seventies and in the eighties, the first studies linking prescription records with individual patient files were published.[36–39] Since then, observational research on medicines harms has been mainly driven by the use of healthcare databases, which has paralleled developments in IT technologies. Associations with a particularly high impact on the public health are the increase in the risk of gastrointestinal bleeding with NSAIDs,[40] anticoagulants and antiplatelet drugs,[41] of sudden death with antipsychotics,[42,43] of falls,[44] fracture,[45] traffic accidents,[46] pneumonia,[47] and probably dementia,[48,49] cancer and overall mortality with hypnotic and sedative drugs,[50] of fracture and other adverse outcomes with antidepressants,[51,52] and the risk of fractures with proton pump inhibitors.[53]

In a historical perspective, observational studies have shaped **second-generation pharmacovigilance**. Observational research has made outstanding contributions to the knowledge of potential adverse effects of new and old medicines. However, the validity of its results is limited by the risk of misclassification of exposures and outcomes and their timing, bias and confounding. Not least, publication bias cannot be lessened or avoided by compulsory registration of studies, first because observational studies are in fact an extension of careful clinical evaluation, and second because as long as there is no public transparency on what is looked at in a healthcare database, pharmaceutical companies will be happy to disburse big amounts of money just to have the right to have a look at the database before a research protocol is registered. On the other hand, as long as pharmaceutical companies are the main sponsors of observational research, an industry priority bias tends to direct research to issues of commercial, rather than medical interest. Important progress has been made in the development of software and procedures compatible to the various existing healthcare databases.[54] However, while therapeutic innovation should be a primary interest of pharmacovigilance, the lack of healthcare-driven automated systems for the intensive surveillance of biotechnological products and other innovative medicines in hospital and specialized care in the European Union (EU) is paradoxical.

Clinical trials

Sometimes important adverse effects are discovered in RCTs. In 1991, the CAST clinical trial showed that, contrary to expectations and beliefs, prophylactic antiarrhythmic treatment after myocardial infarction increases mortality.[55] This was confirmed in a systematic review of clinical trials.[56] Other prominent examples have been an increased risk of heart failure with doxazosin[57] in the ALLHAT trial, and an increase in cancer mortality with ezetimibe in the SEAS trial.[58]

In 2002, an overview of randomized clinical trials (RCTs) showed that high-dose compared with low-dose

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epoetins increase mortality by 22%.[59] In the same year, two public-funded RCTs on hormone replacement therapy (HRT) had to be stopped because of an excess risk of breast cancer, cerebrovascular accident and myocardial infarction among participants randomised to HRT.[60] During the previous 8–10 years, HRT had been massively prescribed to menopausal women, in spite of weak evidence supporting its benefits. The population projections of these results suggested tens of thousands of breast cancer victims in the UK[61] and hundreds of thousands in the USA,[62] in a 10-year period. In 2004, after Vioxx had been pulled off the market, several meta-analyses of RCTs showed that other NSAIDs, particularly those with more COX-2 selectivity (e.g. celecoxib,[63] diclofenac[64]) also increase cardiovascular risk; the public health impact may be of the order of thousands of deaths each year in the EU. This underscores the need for routine cumulative individual patient-data meta-analyses of RCTs on new and perhaps on old medicines, and of course for clean and transparent clinical research. Given the evidence of common scientific fraud and selective reporting of results,[65,66] cumulative patient-data meta-analysis of RCTs should be a legal responsibility of EMA.

Since 2004, several important adverse effects have been uncovered through the systematic review and meta-analysis of RCTs. Examples with a particularly important potential impact on public health include an unexpected increase in suicidal ideation and behaviour from 2% to 5% per year in children and adolescents with depression on SSRI antidepressants,[67] suicide attempts in adults with paroxetine,[68] myocardial infarction with rosiglitazone,[69] cerebrovascular disease and death in the elderly with neuroleptics,[70] heart attack and cardiovascular death with inhaled anticholinergics,[71] atrial fibrillation with bisphosphonates,[72,73] a 10–12% increase in the risk of diabetes with statins,[74] or the adverse gastrointestinal and cardiovascular effects of NSAIDs.[75] Meta–analyses of RCTs can also be used to confirm the safety of a particular medicine or group of medicines when a signal arises from other methods. The magnitude of the risks recorded in RCTs may not necessarily be the same as in clinical practice. In principle, a higher incidence and poorer prognosis is to be expected in real clinical practice. The signals uncovered or evaluated in meta-analyses of RCTs refer to relatively common potentially life-threatening conditions and to commonly prescribed medicines; hence, they have a relevant public-health impact. The meta-analysis of clinical trials is **third-generation pharmacovigilance**: it has greatly contributed to the knowledge of the causes of the present epidemic of death and suffering caused by medicines.

Big data handling

In recent years, important progresses have been made in widening the potential for research based on healthcare databases. Two initiatives deserve particular attention, one in a country with a state healthcare system with universal coverage and the other in the USA. In Denmark, the Danish National Prescription Registry (DNPR) provides individual-level high-quality information on dispensed prescriptions, including those to residents of long-term care institutions.[76] Importantly, the DNPR is linked with other data sources equally covering the entire nation (e.g. population registry, patient registry on all hospital admissions, causes of death, psychiatric conditions, births, dialysis and transplantation) through a unique patient identification number.[77] However, it only contains aggregate data on sales of over-the-counter drugs, on drugs dispensed at hospitals for outpatient treatment (such as anti-neoplastic drugs or HIV drugs) and on drugs for inpatient use. Spreading the Danish model to other EU countries in the next future is urgently needed.

The Mini-Sentinel Project led by the US FDA is an effort for an expanded secondary use of electronic health records (EHR) and medical insurance claims. Mini-Sentinel is a nationwide (non-universal) system where each partner healthcare organization develops and maintains its own data, formatted according to a common data model. Patient privacy is protected, protocols are posted for public comment and investigators are free of conflicts of interest. Queries can be made to gather information from the data partners about any utilization or safety outcome.[78]

On the other hand, there is recognized need to harness non-traditional resources that are generated by patients via the Internet, including online social media – patients' experiences explicitly shared via online health forums,[79] Twitter, Facebook, and patients' blogs – and implicit drug information contained in the logs of other popular search engines.[80] An FDA's scientific committee recommended the need to augment pharmacovigilance with safety evidence from search logs.[81] This strategy was used in a study on drug interactions leading to hyperglycemia.[82] More recently, a study on 181 drugs and four outcomes has shown that jointly leveraging data from the FDA's AERS database of spontaneous reports and search logs can improve ADR detection by 19%.[80]

Every new strategy in the historical development of pharmacovigilance has been built on the knowledge and experience accumulated in the previous steps. Spontaneous reporting gives clinical insight into signs and symptoms, time course and prognosis. Observational research provides relative risks and, in

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prospective studies, incidence rates. Meta-analysis of RCTs provides incidence rates and absolute risks, but in generally healthier populations, compared with those of clinical practice. Recent research shows the complementarity of spontaneous reporting, observational data and search logs. **Fourth-generation pharmacovigilance** will probably take advantage of big data by adding search log signals to existing methods.

EUROPEAN UNION PHARMACOVIGILANCE LEGISLATION IS TWO GENERATIONS BEHIND SCIENCE

The concepts of the new EU-wide legislation[83,84] most directly related to public health protection are a broadening of the definition of ADR to include medication errors and off label use, establishing uniform criteria and procedures with standard format and content for the electronic transmission of reports, the Eudravigilance database as the single spontaneous reports database, the promotion of reporting by patients[85] and company-driven risk management plans (RMP). The 2010 Directive did not set any obligation for the EMA to perform or to promote independent observational research and cumulative meta-analyses of RCTs in collaboration with academic centres, neither to collaborate with other institutions in the development of new methods such as big data handling. The EU legislation on pharmacovigilance is therefore two generations behind science.

Member states have no responsibility for monitoring national drug utilization patterns. There is not even a reference to the need of intensive monitoring systems for innovative biotechnological and other products, which is in the hands of the sponsoring companies through their RMPs.

The advantages of a central EU database can be lost if it is not easily accessible to health professionals, scientists and the public.[86] On the other hand, a review of 15 RMPs concluded that several activities appeared to be inadequate with respect to the potential medicines risks and that transparency was poor.[87] Similarly, the US FDA has admitted that only 30% of requests for trials are fully adhered to by companies.[88]

The legislative framework of EU pharmacovigilance builds on spontaneous reports and on inadequate and often opaque industry-sponsored studies. This does not take advantage of new methods (e.g. meta-analysis of clinical trials and big data handling), it is not evidence-based and it grants the industry an undue role, considering that reiterated fraud has been documented.[4,89,90] It is an inadequate system for protecting the public health.

ADVERSE DRUG REACTIONS OCCUR IN A CONTEXT WHICH IS FAR AWAY FROM REGULATORY AGENCIES

Medicines of general use in primary health care (e.g. PPIs, statins, antiplatelet agents, hypnotics and sedatives, and antidepressants) may have acceptable safety margins for the unrepresentative patients included in the short-term clinical trials on which regulatory approval is based. However, their benefit/risk ratio is less favourable in low-risk patients with high NNTs (e.g. statins in primary prevention and acetylcholinesterase inhibitors for dementia), where the drug is ineffective (e.g. antidepressants in mild or moderate depression), or when it is used for unnecessarily long periods (e.g. bisphosphonates[91] and double antiplatelet aggregation[92]). They are particularly risky in elderly patients taking multiple medications, because of drug interactions and more medication errors. Patients' safety is the priority, and this can only be evaluated in the context of real practice. It is noteworthy that inadequate utilization of medicines is rarely a reason for regulatory action at European level; member states have occasionally found difficulties in taking national action because of constraints imposed by European legislation (e.g. the misuse of cyproterone as an oral contraceptive in France[93,94]). From a public health perspective, the epidemic of ADRs, and particularly of ADRs caused by unnecessary medicines and in overmedicated patients, can only be faced by promoting a healthier use of medicines.

Type A ADRs are those with a highest public health impact. They can be largely prevented by promoting a healthy prescribing and use of medicines. This depends on the priorities of the health system, the regulation of the pharmaceutical market, the quality of the information on therapeutics available to prescribers, continuing education and other factors. The priorities for promoting medicines safety lie in the health system, rather than in the interaction between regulatory agencies and pharmaceutical companies.

On the other hand, observational studies and clinical trials usually focus on one exposure variable and one outcome, while patients generally have more than one clinical problem and they are exposed to multiple drugs. Real-life monitoring at local level is crucial. The engagement of healthcare organizations to this end is essential, because not only they produce and they have the data but also because their commitment in promoting patients' safety should boost a healthier prescribing.

CONCLUSIONS

Fifty years after the birth of pharmacovigilance, the current epidemic of death, disability and suffering

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caused by medicines calls for a critical review of the aims and results of the activities to promote a healthy and safe use of medicines.

Pharmacovigilance is only one of the many components of any pharmaceutical policy. For example, if new medicines were only approved if they offer convincing evidence of some advantage in terms of efficacy, safety, convenience or cost, many unnecessary ADRs would be avoided. At the same time, a more cautious use of medicines, tailored to patients' needs and social context, would also contribute to avoid suffering, death, disability, and economic burden for the health system.

The mandate of public health protection of regulatory agencies compels them to widen their activities and to set up other strategies that are complementary to spontaneous reporting. Legislation should mandate a widening of EMA's and national agencies' responsibilities, namely, coordination of observational research and cumulative systematic review and meta-analysis of clinical trials with individual patient data, at least on medicines with less than 5 years in routine use. Openness to independent academic researchers and collaborating networks with national health systems is essential to these ends.

In recent years, it became clear that scientific fraud in the pharmaceutical industry is not an exception.[4,90] Risk management plans in the hands of pharmaceutical companies are unreliable for protecting public health. The planned studies should be designed, performed and analysed by researchers free of conflicts of interest, in collaboration with health regulatory authorities, the interested company, and healthcare provider organizations. They should include patient-oriented and population-oriented observational studies in real practice, in particular on new medicines and on those with a narrow therapeutic margin, those which are often used for non-approved indications, those whose use concentrates in vulnerable patients (e.g. the elderly), and those which are merely misused.

Pharmacovigilance should not be regarded as an exclusive responsibility of regulatory agencies. By their nature, regulatory agencies perform product-oriented pharmacovigilance. They may contribute to protect the health of the citizens, but they are only one of the many steps of the medicines chain.[95] ADRs occur as a result of the policies, priorities, practices and perceptions on medicines safety and effectiveness in each society and in each healthcare organization, which contribute to shape wide international variability in the patterns of drug utilization across the EU member states.

At present pharmacovigilance is mostly medicines-oriented, that is, it focuses on the health status of medicines: a medicine becomes ill if unexpected ADRs appear and are publicized, it suffers a major disease if a drug safety committee is appointed in a regulatory agency and it dies if it is withdrawn from the market. On the other hand, when 'benefit/risk' is evaluated in a regulatory setting, it is generally assumed that the 'benefits' shown in clinical trials directly translate into clinical practice. In contrast, public health-oriented pharmacovigilance should focus on the patients' and citizens' health, rather than on the health of medicines. This is genuinely a responsibility of each national health system.

National systems of pharmacovigilance and their regional centres should play an active role in the promotion of a healthier use of medicines. Their primary objective should be to prevent ADRs, rather than to count a high number of them. In developing a centralized and purely quantitative approach to pharmacovigilance, there is a risk of compromising the clinical and pharmacological analysis of spontaneous reports by independent teams, especially in pharmacovigilance centres. Regional centres should be deeply rooted into healthcare-provider organizations, the health system and the society at large. They should not only ensure an accurate evaluation of reports but also be close to prescribers and give support to them. They should offer routine feedback to reporting professionals. They should critically monitor local drug utilization patterns and contribute to detect and eventually correct inadequate or suboptimal patterns of use. Other suggested activities could be the dissemination of independent information on medicines and therapeutics (bulletins, social networks and the networks of the health system linking electronic health records) and of the EMA's and national agencies safety alerts, therapeutic consultation,[96] participating in independent continuous medical education activities (including training on the diagnosis and reporting of ADRs and even financial incentives),[97,98] promoting patients reporting through social networks, patient associations and clinical consultations, and collaborating with the health system drug and therapeutics committees and their working groups.[99] Healthcare-provider organizations should be legally responsible for close follow-up of the patterns of medicines use, including monitoring of the effectiveness and safety of new medicines. A European network observatory on medicines utilization, collecting continuously updated data, should be set up, to support pharmacovigilance decision-taking and to monitor the patterns of medicines use.

Modern pharmacovigilance benefits from various complementary methodological strategies. Since its origins in the sixties of the last century, pharmacovigilance has mainly relied on spontaneous reporting.

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Spontaneous reporting has saved thousands of lives and continues to do so. However, observational research since the eighties, and the meta-analysis of clinical trials since the 2000s, have shown the value of incidence rates and of relative and absolute risks for a better understanding of the main causes of the epidemic of drug-induced death and suffering. Regulatory agencies should collaborate among them and with other global agencies in the development, evaluation and implementation of current and new methods, and on the ethics and the cost-benefit of the new opportunities offered by modern IT technologies and by the use of big data.

Legislation and regulations must protect the public and support health professionals, rather than the industry.[86] Transparency in all regulatory and decision-making procedures should be the norm.[100] As recently urged by the Parliamentary Assembly of the Council of Europe,[103] Manufacturers should be required by law to submit all the evidence collected during the development of new medicines, in particular individual patient data from clinical trials. The data should be accessible to any interested party. Conflicts of interest should be avoided at all the stages of medicines' evaluation and at all levels of the pharmacovigilance systems.[101] Any funding for pharmacovigilance from pharmaceutical companies should not be collected by the EMA but by the EU Commission, which should grant EMA financial support independent of the activities undertaken, the products and the companies involved.[102] Regulatory decisions should be based not only on efficacy and safety considerations, but also on need.

Key Points

- Adverse effects of medicines are a growing cause of illness, disability and death. They are an important public health problem in need of preventive action. Medicines safety – or rather unsafety, or harm[103] – depends on how medicines are prescribed and used within and outside the health systems and also on the actions of regulatory authorities and pharmaceutical firms.
- Much harm could be avoided by promoting a healthier use of medicines. We need pan-European initiatives linking a coordinated action among healthcare systems and national and regional centres of pharmacovigilance. The European legislation should be updated to be science based.

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