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History of pharmacoepidemiology

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Summary

Pharmacoepidemiology, in the sense of the study of the reciprocal interactions between drugs and populations, was probably conceived far before being named so. However, the modern era started in 1985 with the birth of the International society of pharmacoepidemiology and the development of specific methodological approaches and large databases. This advent of pharmacoepidemiology resulted from a long period where the actual target of medicines, i.e. patients in real-life settings, was not considered, the truth being provided solely by pre-approval or peri-approval clinical trials. The methodological advances made during the last three decades are unprecedented. The challenge is now to avoid focusing excessively on the method to the detriment of pharmacological and public health objectives.

KEYWORDS

Drugs; Pharmacoepidemiology; Drug risk; Clinical evaluation; Adverse drug reactions; Evidence-based medicine

Abbreviations

ATC: anatomical therapeutic chemical

BDCSP: Boston drug collaborative surveillance program

CPRD: clinical practice research datalink

DDD: defined daily dose

DURG: Drug utilization research group

GHC: Group health cooperative

GPRD: general practice research database

HMO: Health maintenance organization

IAAAS: International agranulocytosis and aplastic anemia study

IPPHS: International primary pulmonary hypertension study

ISPE: International society of pharmacoepidemiology

MRC: Medical research council

SCCS: self-controlled case series

WHO: World health organization

History can be defined as the account of what happened in the life of a people, country, institution, etc. usually with an analysis and explanation [1]. Based on this definition, writing the history of pharmacoepidemiology is far from easy, particularly because nobody knows the date and the nature of what could be considered as the first attempt to describe and analyze the way a medicine is used in a given population or the effects, beneficial or not, it may induce in it. If we consider the trademark of pharmacoepidemiology; i.e. the large scale and observational¹ study of drug-population interactions, (effects, practices or behavior) [2,3], there were probably dozens of examples in the long-ago past. An example in point is the multicenter observational study (73 sites, 63 of which from the “German Empire”) that compared in ... 1895, and in conditions of actual practice, the relative safety of various drugs used in general anesthesia [4]. After analyzing 52 677 cases of narcosis, the authors computed fatal outcome rates of 31/31 083 for chloroform (i.e. one per thousand), 6/15 712 (i.e. 0.38 per of thousand) for ether and 0/2148 for the association of ether with chloroform. One always could debate whether this pioneering study should be named large-scale clinical research or pharmacoepidemiology. In any event, since not providing confidence intervals and even less any attempt to control probable selection and confounding biases, this work would certainly not be considered for publication according to today’s standards, even though it was more original and contributive than many “modern” and methodologically appealing projects in the field.

It is therefore realistic to limit the scope of this paper to the recent decades with special attention to the genesis of the word *pharmacoepidemiology*. Moreover, owing to the subjective and therefore debatable character of the choices such a review imposes, the result will be *a history of pharmacoepidemiology* rather than *the history of pharmacoepidemiology*.

Pharmacoepidemiology before being named so

One can split the time course of the evaluation of medicines roughly into three eras.

The first one was the time (approximately until the middle of the twentieth century) when medicines were assessed or judged on the basis of personal experience with quite limited and often

¹ i.e. not interfering in any way with the natural course of events.

biased series of patients and without any structured post-marketing surveillance. Consequently, any market launch was a great leap in the unknown, some of these drugs being real blockbusters used by millions of individuals without any preclinical or clinical evaluation worthy of the name. In hindsight, one can only be surprised by the relative low number of sanitary crashes (lack of effectiveness or, above all, noxious consequences) identified during this long period; without any doubt a falsely reassuring consequence of the blindness or inexistence of surveillance systems. A shining example is aspirin, which was only “tested” by Heinrich Dreier on two frogs and “clinically assessed” by the discoverer Felix Hoffmann on his rheumatic father and some of his relatives [5]. An unsurpassed but successful challenge for a drug intensively used by millions of people as soon as it was marketed.

The second era took the opposing view and intended to wring the neck of subjectivity and biased assessments. It is indisputable that the comparative experiment with random allocation of exposure, i.e. the basic principle of any clinical trial, is the sole design which completely protects against confounding and consequently allows researcher to conclude firmly that the difference in outcomes observed between compared groups result from the assigned exposures. Making the patient and/or observer blind to the nature of exposure was a step further by minimizing the influence of subjectivity and placebo effects. *De facto*, the double-blind randomized comparative trial rapidly became the gold-standard for the scientific and regulatory evaluation of medicines after the Second War, and step by step, the unique source of *Truth*. Even if probably theorized far before (e.g. citation from Petrarch in 1364 in footnote²), the first successful example of a randomized evaluation was the James Lind’s brilliant demonstration of the efficacy of lemon juice in the prevention of sailors’ scurvy [6]. However, the first modern evaluation of a medicine was clearly the Medical research council (MRC, United Kingdom) trial in 1948 that proved the efficacy of streptomycin in pulmonary tuberculosis [7]. Cynically, one may note that in these pioneering times, the effect sizes of tested drugs were large enough to reach statistical significance with samples that were quite small: 55 patients versus 52 in the case of the MRC trial.

One step further in the quest of the truth was the introduction of evidence-based medicine, meta-analyses and systematic reviews. In 1985 after Prof. Alvan R Feinstein, among others, pointed out the limitations and pitfalls of clinical judgment and desacralized the “art of medicine” [8]. Five

² « If a hundred or a thousand men of the same age, same temperament and habits, together with the same surroundings, were attacked at the same time by the same disease, that if one half followed the prescriptions of the doctors, and that the other half took no medicine but relied on Nature’s instincts, I have no doubt as to which half would escape. »

years later, Archibald Cochrane stated that many practices assumed to be effective were not supported by the results of controlled trials [9]. This led to the foundation of the Cochrane Collaboration in 1993 as a response to Cochrane's call for up-to-date systematic reviews. The Cochrane reviews, later complemented by meta-analyses in turn became the gold standard for rational prescription, the opposable Bible. In less than fifty years, the paradigm of evaluation had been completely reversed.

Paradoxically, the fully justified preeminence of the experimental design and evidence-based medicine as references for medical judgment became their main limitation. The basic fact that the target of medicines is the population and not some hundreds of patients included in a trial has been forgotten. The quest for strictness and evidence ended up convincing opinion leaders and regulators that a well-conducted experiment inside an aquarium suffices to know the ocean. The premises of pharmacoepidemiology ensued in good part from this logical frustration.

Pharmacoepidemiology: a new paradigm

The third era, markedly overlapping with the previous one, began with the awareness that the most important part of the evaluation should be made in the real world of prescription and use of medicines. What we today call pharmacoepidemiology, resulted from three progressively recognized facts:

- 1) Clinical trials are conducted on a limited number of patients, over a usually short duration, and in extremely standardized conditions. Consequently, they cannot predict what actually happens when the drug is used massively, seldom as recommended, by millions of individuals all different with respect to their characteristics. This nowadays generally well-recognized reality has been extensively discussed elsewhere [10].

- 2) Drugs do not induce only beneficial and therapeutic effects. In 1961, the thalidomide disaster [11] demonstrated that it would be criminal to continue to launch drugs massively without establishing programmes aiming to detect early signals of the onset of adverse reactions. This disaster paved the way for structured pharmacovigilance under the auspices of the World health organization (WHO). Immediately, this incentive gave rise to many local initiatives and fruitful methodological research. The continuous surveillance of drug adverse effects was set up at the

national level in a dozen of countries with a highly regarded organization in France based on a network of what is now 31 regional centres [12,13]. In that sense, pharmacovigilance, contributed immensely to structuring pharmacoepidemiology.

3) Despite being marketed with theoretically precise indications and surrounded by international recommendations, it was and is obvious that drugs are used in quite different ways from a country to another, both quantitatively (prevalence of use) and qualitatively (characteristics of patients, indications, duration of treatment, co-medications, etc.). It is also indisputable that these differences can totally alter the benefit-risk balance of most of drugs, without mentioning the economical consequences. *De facto*, researchers and health insurance systems (an example being the Health maintenance organizations, HMO, in the USA) started to set up drug utilization studies. As recommended during a WHO European symposium in 1969, a common classification system for drugs was developed (the anatomical therapeutic chemical or ATC coding) and, overall, a standardized measure, the defined daily dose or DDD was adopted as a comparative unit of drug use [14]. They were the routine tool of the very active Drug utilization research group or DURG. Even if the published DDD levels were derived from sales statistics and not from field studies, they clearly showed that what was expected and what is observed were worlds apart.

The three objectives of pharmacoepidemiology became clear: to study the effectiveness, safety and utilization of drugs in the real-world of practice.

Origin of the word pharmacoepidemiology

The term was first coined in 1984 in England [15], and it would indeed be inelegant not to quote *in extenso* the words of one of the fathers of pharmacoepidemiology: Prof. David H Lawson: “*The centre for medicines research held an one-day meeting ... That meeting led to another which took the form of a four-day residential seminar in Minster Lowell. Its main conclusion was that drug surveillance requires no less than a recognition and fostering of a new discipline: pharmacoepidemiology. This discipline already exists in embryo in Britain and United States but is rarely acknowledged as such. The name seems lengthy but is needed for a proper definition of the*

two essential disciplines: pharmacology defining both beneficial as well as adverse drug effects and epidemiology studying the response of the population to these effects.” To be fair, one should pay tribute to another pioneer: Jan Venulet [16] who ten years before had used the term “*pharmaceutical epidemiology*” in a visionary article [17].

The deed was done. The first annual and international meeting specifically devoted to pharmacoepidemiology was held in 1985 in Minneapolis (USA), followed by four others with a growing up number of attendees. In 1989, the group became the International society of pharmacoepidemiology (ISPE) with annual meetings (nowadays with mid-year meetings) scheduled alternately in the USA and in Europe, and later including the rest of the world.

Pharmacoepidemiology: thirty years of methodological creativity

Almost twenty years before the officialization of the ISPE, visionary researchers started to set up large surveillance programmes. The most famous and historically important was the Boston drug collaborative surveillance program (BDCSP) established in 1966 (five years after the thalidomide drama) in Boston (USA) by Prof. Hershel Jick. It was the first group to conduct large-scale epidemiologic research to quantify the risk of adverse reactions of drugs prescribed in the framework of actual practice. The BDCSP utilized in-hospital monitoring and played a major role in the development of pharmacoepidemiologic methods. It adopted systematic computer recording in 1970 and can therefore be considered as the father of modern research databases [18]. The scope of the BDCSP included therapeutic effects and one should be recalled that one of the contributions of the BDCSP was nothing less than the ability of aspirin to prevent cardiovascular events. Interestingly, this major therapeutic advance was published in the British Medical Journal in 1976 under the format of a modest letter to the editor [19]. The experience of the BDCSP inspired another historical reference, the Group health cooperative of puget sound (GHC) located in Seattle (USA), which has been systematically recording hospital discharge diagnoses and prescriptions on computers since 1972 [20].

In the late 80s, computers started to become rather common in general practice, notably in the United Kingdom where the VAMP Health group designed software to help general practitioners to file their patients’ records. A joint effort between the VAMP and the BDCSP group led to the

dream of any researcher: the first large database fed by data extracted from the routine activity of thousands of practitioners. The general practice research database (GPRD) was born and remains one of the rare examples of a tool specifically conceived for pharmacoepidemiologic research. In 2012, the GPRD became the clinical practice research datalink (CPRD) with larger ambitions and different stakeholders.

Another historical corner stone in the development of pharmacoepidemiology was the drug epidemiology unit funded in 1975 by Dennis Slone and Samuel Shapiro at the Boston University school of medicine. It was named the Slone epidemiology center after the Dennis Slone's death in 1982. The Slone developed many fruitful initiatives like the pregnancy health interaction survey, the Slone survey and a case-control surveillance programme for studying risk factors associated with certain diseases [21]. The best example is the International agranulocytosis and aplastic anemia study (IAAAS) which was probably the first large-scale international study of this type. It provided incidence rates and geographical differences for these two diseases with numerous spin-offs for pharmacovigilance. Its results have been valorized by numerous scientific articles and one entire book [22]. In Europe, the International primary pulmonary hypertension study (IPPHS) was another example of an international disease-centered study. It greatly improved the knowledge about this rare but serious disease, its incidence and risk factors. Overall, it contributed to the banishment of amphetamine-like appetite suppressants from the European market [23].

Analyzing in details populations as large as millions of individuals and deriving robust results from observation was an unprecedented challenge. De facto, an often-forgotten fact is the contribution of pharmacoepidemiology to the development of new methods and approaches nowadays widely utilized in other fields of epidemiology and public health. Among dozens of examples, one can cite the disproportionality analyses of large databases for signal generation, the self-controlled case series (SCCS) [24], the case-population-approach [25] and, more recently, the matching and adjustment by using propensity scores or high-dimensional propensity scores [26,27]. Pharmacoepidemiologic studies were also the starting point for scrutinizing numerous types of biases such as confusion and interpretation types, some of them which had never been conceptualized before like prescription channeling, confounding by indication, depletion of susceptibles [28], and immortal time bias [29].

Conclusion

Pharmacoepidemiology introduced a new paradigm, the notion of *real-world evidence* and is now the third, but not the least, pillar of drug evaluation after the preclinical and clinical phases. Its contribution to pharmacology, public health and methodological development in statistics and epidemiology is immense and the future remains an open avenue, notably with the new territories of big data and social networks. As for clinical trials and evidence-based medicine, the threat is that the fascination for the refinement of methods progressively comes to occupy the center of the stage to the detriment of pharmacological and public health objectives.

Disclosure of interest

Author has no competing interest to declare.

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