Introduction

Pharmacoepidemiology, the application of epidemiological methods and data to evaluate the use and effects of therapeutics, finds itself at a crucial moment. For a long time, pharmacoepidemiology studies have served an important role in evaluating the safety of therapeutic agents as used in the population. Now, therapeutic risk management initiatives across the world have started to change the way the benefits and risks of therapeutic agents are evaluated and improved. Risk management addresses: systematic and planned estimation and evaluation of risk, determination of acceptable level of risk, communication of risk, implementation of interventions to minimize risk, and evaluation of the effectiveness of these activities. Most of these activities are not new. What is probably the largest change – and it is an important one – is the systematic, planned and integrated implementation thereof. As therapeutic safety risk management principles are applied, pharmacoepidemiology studies will grow both in number and in relative importance. Professionals working in this area are increasingly expected to provide both the population-based evidence through pharmacoepidemiological studies, as well as the public health perspective to propose, plan and evaluate these activities.

As we enter a period of heightened interest in pharmacoepidemiology, it is a good time to look back at the development of our field. When I was asked by the Esteve Foundation to provide a list of the 20–25 papers that have shaped the discipline of pharmacoepidemiology, I wanted to include a range of examples that have made an impact on the field because of the relevance of the topic, the method employed, the pioneering role, or the controversy they generated. I chose to include not only my personal choice, but also one that could represent, at least in some way, the views of other professionals in the field. The idea was not so much a systematic criteria-driven selection process, but a more personal reflection. I asked a number of colleagues, most

of them long-time researchers, and current or past Officers of the International Society for Pharmacoepidemiology, ISPE, to think back about reading studies that impacted our work as pharmacoepidemiologists. Many responded to the call, and their help is much appreciated. A selection of the proposed references are reprinted in this book. However, upon the request of a number of colleagues to whom I mentioned this work, I have included the complete list of the not reprinted references at the end of this Introduction.

The publications are ordered chronologically by date of publication, and they cluster around several areas. Studies focused on drug exposure and specific safety endpoints comprise the largest group (articles III-V, X-XII, XVI, XVIII-XXI, XXIII-XXVII). This group includes landmark studies such as the association of maternal diethylstilbestrol use and adenocarcinoma of the vagina. Also topics that created controversy, and through different research approaches and intense discussion at conferences and expert meetings drove forward the field through the development of new analyses, novel data collection methods, and identification of specific confounding and selection biases. The research topics cover areas such as thromboembolic disease and oral contraceptives, aspirin use and myocardial infarction, psychotropic agent use and hip fractures, drug-related blood dyscrasia, and liver injury, or appetite-suppressant drugs and cardiac-valve regurgitation. Personally coming into the field at the time of the controversy surrounding the use of fenoterol and asthma deaths, it was interesting to note that this was one of the most mentioned areas by colleagues, of different geographical areas and year of graduation. Many of my colleagues highlighted the vast amount of pharmacoepidemiological research and methodology developed around the evaluation of non-steroidal anti-inflammatory agents (NSAIDs). These topics have been evaluated by different investigator teams, in various populations, through different data-collection methods and designs, and serve as good examples of research areas that are revisited over time. I hope that this type of overview helps the reader to learn about the challenges in our field, and how useful it is to have various approaches complement each other in providing evidence. As in any scientific discipline we learn as much from what we know at the end of a study as from what we just learned that we do not know.

The second group of publications revolves around thought-provoking reviews (II, VII) and methods development, such as confounding and effect-modification (VI), the use of propensity scores (VIII), the case-crossover (XV) and the case-time-control (XXII) designs. These publications speak to the complexity of evaluations attempting to take into account multiple potential biases, and the importance of time in the definitions of exposure-relevant windows. Data collection has triggered much discussion over time. Timely results are key in this area of public health. The challenge of recruiting patients

into cohorts, obtaining valid exposure information from cases and controls selected from the same population and the availability of routinely collected health care data led to the extensive use of the latter for many studies. Two of the publications in this selection (XIII, XIV) are a sample of the controversy and discussions surrounding this data collection method in the late '80s, discussions which are still ongoing. Over the last decade, we still talk about "database" studies and "primary collection" studies. Readers may wish to focus on the source of data and data collection methods as they review the studies in this selection. Most studies rely at some point or other on both data collection methods. Cases in hospital-based case-control studies are often identified through computerized discharge listings, and primary record review is a requirement for a well-validated study using population databases. Maybe over time the focus will move towards combining the best of each approach to answer the question. The topic of NSAIDs and gastrointestinal bleeding is one that comes to mind as an example of an area in which studies using both data collection methods revealed concordant results once the real underlying issues were resolved: case validation, cases and controls selected from the same base population, appropriate control of confounding and ascertainment of exposure (agent, dose, duration).

The full list of publications reflects that epidemiologists identify cornerstone principles across many areas: clinical trials, pharmacology, classical epidemiology and last but not least single-case observations. For a field of professionals focused on populations, complex designs and statistical analyses it is relevant that the most mentioned publication was the first one in this selection, that of a single case report (I), the 1961 letter to the Lancet by McBride about cases of congenital malformations among thalidomide-exposed pregnancies. Due to the period during which proposals were requested, an important, and now recurring controversy, is not reflected in the list of publications: the value of observational and randomized research. This has been a core issue to the evaluation of the cardiovascular effects of hormonal replacement therapy and NSAIDs and COX-2 selective agents. Based on findings of randomized and observational studies in these areas, many in the scientific community have concluded that observational studies should be discarded, while disregarding limitations of randomized studies such as poor external generalisability, or the use of intention to treat analysis for non pre-specified safety endpoints. A more constructive approach should be more productive for the safety of patients, such as the continuous improvement of the design and overall quality of observational studies, or the development of hybrid study designs using the best principles of randomized and observational research. Quoting also from one of the referenced papers (Walker & Stampfer, 1996), "We should not denigrate the observational nature of the data. Most of

what we learn, and will continue to learn, about adverse drug effects comes from observational studies."

No doubt the future will bring new controversies and challenges, which will drive new methodological developments.

I hope that you enjoy this selection.

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Other mentioned publications

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