CONFERENCE PAPER

Drug Safety 2007; 30 (7): 611-613
0114-5916/07/0007-0611/$44.95/0

Epidemiological Context of Signalling

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Abstract

Epidemiology has become the conscience and soul of signal detection and interpretation from assuring insights into the strengths and limitations of the data source to articulating the disease natural history and its relationship to other diseases, outcomes and treatments. The epidemiologist has struggled to bring several issues into focus including the analysis and interpretation of surveillance data, the integration of signalling and causality criteria, the statistical issues of multiple comparisons and multiple looks at the data, whether one significant disproportion is a signal or whether it should persist over time before it is 'declared'. However, epidemiology, like signalling, has its proper place with its own strengths and limitations. This paper will attempt to bring everyone up to speed on the role of epidemiology in the context of signalling and how signalling fits into the broader context of epidemiology, how perceptions and biases may affect our application of these methods and why context and communication have become so important in this field.

"*Signs can often be misleading and it is important that we have a map to help us through that.*"

One role of epidemiology is to provide maps, to supply us with a context and a background that help to understand some of the signals that may arise.

1. Data Sources

Data mining takes place in data from various sources, each one of them with their own strengths and weaknesses. Understanding the strengths, weaknesses and limitations of the data sources that we use helps to make sense of the emerging signals.

Coded clinical terms, the backbone of signal detection, do not often follow the same structured approach as in making a diagnosis: criteria for a given code may vary by pharmaceutical company, reporter or scientist. Although using the same terminology, each pharmaceutical company drug safety department codes according to a different standard, which may distort aggregated results when records are pooled together across a number of different decision rules. One need only look at the wide variation found in studies of disease using different criteria most dramatically depicted in one example where the prevalence of dementia varied from 29.1% (Diagnostic and Statistical Manual of Mental Disorders [3rd Edition] criteria) down to 3.1% (International Classification of Diseases [10th Edition] criteria) when applied to the same population.[1]

2. Surveillance versus Research

A distinction should be drawn between surveillance and research. Surveillance is an ongoing process of watchful waiting usually supported by simpler analyses, and mostly used for hypothesis generation, rapid recognition and dissemination of potential issues. Research is a hypothesis testing, time limited and fairly structured process whose ultimate goal is to generalise its findings to a broader population. We need to be careful when we apply research tools to surveillance data.

3. Disease and Co-morbidity

The natural history of disease is the backbone of epidemiology and the basis of its contribution to the signalling process. More energy should be placed in understanding the target indication for which the drugs are used, comorbid and consequent illnesses, how those affected use health care services and what happens to their disease over time.

Chronic diseases rarely occur in isolation. In every-day practice, drugs are being used for a whole spectrum of people with specific chronic conditions, but almost always, they are highly predisposed to having another associated disease whether diagnosed or not. It is critical that we remember the role that comorbid disease has in patient compliance, outcome and risk as we tend to focus on a single exposure in our investigation of signals. It is also important to recognise the potential contribution of other medications, some of which may be natural remedies and other substances often not revealed to the physician.[2]

Finally, as part of the course of disease, most events reported as suspected to be drug-related have a background rate of occurrence in the general population, which may be very small or more pronounced, but in either case may bear on actual drug-related event rates. Insight can be gained from looking at research into the varying rates of adverse non-drug reactions.[3,4]

4. Reliability and Validity

Signal-detection methods aim at an unknown target. Under such conditions of uncertainty, establishing thresholds for screening algorithms depends mostly on the perspective of the stakeholder. For example, a regulatory agency cannot afford to miss any potential hazard, and the threshold is established to detect all signals at the cost of some false positives. On the corporate side, the aim is to rationalise the threshold so as not to overextend resources trying to understand false positives. In the absence of a gold standard, the aim is to make sure that at least if a mistake is made it is known which side the error is on (over- or underestimating).

5. Bias

Bias is a "systematic, non-random deviation of results from the truth, or processes leading to such deviation"[5] and there is a vast literature describing the various types of biases in research. There are a few critical ones to highlight, the most prominent of which is confounding bias, or a particular subtype called 'confounding by indication', where the disease is itself a risk factor for the event of interest. The intricacy resides in teasing out the effect of the drug from the effect or natural history of the disease. 'Channelling' is one other type of bias where some people are more likely to receive a drug because of a perceived characteristic, which may not be known to be associated with the risk of developing the event of interest, for example the severity of the disease or previous intolerance to other drugs. There is also protopathic bias where treatment is initiated for what may be early signs of another disease process; however, the drug itself may be implicated erroneously for leading to an outcome consistent with the eventual clinical disease. One may also hear of the 'innocent bystander' effect results from the detec-

tion of an apparent association of a drug with an adverse event that is in fact caused by a frequently co-prescribed therapy.

6. Association is not Causation

Statistical significance is not the truth; it is an approximation to it. Good signalling is not a matter of choosing between a Chi-square and an odds ratio, but a matter of learning from those statistics and making informed decisions to go ahead with further study or not.

The comparison and the control are key. The essence of epidemiology is 'compared with what?' Who is getting the therapy? Why are they getting it? And are they different from those taking the comparator therapies? Ultimately, epidemiology is providing the tools and context to help inform a critical scientific decision.

Acknowledgements

No sources of funding were used to assist in the preparation of this paper. The author has no conflicts of interest that are directly relevant to the content of this paper.

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