Opportunities and challenges of adverse drug reaction surveillance in electronic patient records

Adverse drug reaction surveillance

The purpose of adverse drug reaction (ADR) surveillance is to highlight emerging evidence in support of causal associations between medicines and adverse events. The systems for ADR surveillance have been successively developed since the thalidomide disaster of the 1960s[1]. They complement clinical trials prior to drug approval by covering larger and more diverse patient populations. Unlike carefully regulated trials, they reflect actual clinical practice, which may differ in terms of demographics, doses, indications for treatment, and co-medications.

The main mode of operation of ADR surveillance is exploratory. The capability to detect the unexpected requires a wide scope in terms of the types of patterns and medical conditions considered. Some severe diseases including agranulocytosis and Stevens-Johnson syndrome are known to often be drug-induced and deserve special attention. At the same time, a comprehensive surveillance system must allow for the detection of issues that do not match the pattern of previous crises. In this context, the massive number of drugs and symptoms of potential interest and the need to maintain an adequate sensitivity without generating unnecessary false alarms are the key challenges of pharmacovigilance.

Over the past forty years, individual case safety reports, otherwise known as spontaneous reports, have remained the primary basis for raising hypotheses of unexpected ADRs. The strengths and limitations of case reports are well-described. They draw on the experience and expertise of the reporting health professional in identifying the abnormal and in soliciting the necessary information for a solid safety assessment[2]. They are particularly suitable for adverse events with low background frequency (globally or for the patient at hand, such as myocardial infarction in a young, otherwise healthy person) or with clinical features that suggest an association between the medical condition and drug intake, such as a distinct time-to-onset or a clear link to the known pharmacology[3]. The interpretation of summary statistics requires care; collections of ADR reports do not provide information on the number of patients exposed so incidence rates cannot be obtained. Moreover, the degree of under-reporting is unknown but can be expected to vary. Finally, reports are not necessarily independent, but can include duplicate entries referring to the same incident as well as more subtle clusters of reports, such as those submitted by the same health professional. Thus, while ADR reporting rates have proven useful for early hypothesis generation, they require careful clinical consideration and must not be quoted out of context[4].

Electronic patient records

Large collections of electronic patient records are a common resource for confirmatory pharmacoepidemiological studies[5]. Over recent years, there has been an increased interest in using patient records also for the purpose of early ADR surveillance[6-10]. International initiatives in the area include the Observational Medical Outcomes Partnership, the FDA's Sentinel Initiative, and the European projects EU-ADR and PROTECT. Like case reports, patient records reflect the effects of medicines in actual clinical practice. One key advantage is that they provide information on the total number of patients exposed to a medicine so that recording rates of medical events can be compared across treatments (or to unexposed controls). In addition, recording rates post and prior to drug exposure can be contrasted against one another. For medical conditions with acute onset, this is a powerful approach to reduce the negative impact of time-constant confounders[9-10].

Information in patient records is collected primarily to manage the patient and for

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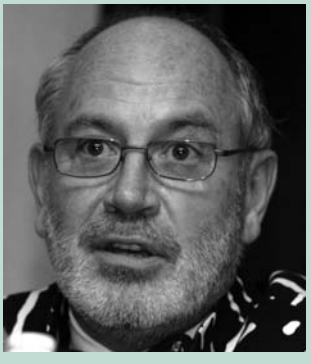

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administrative purposes. As a consequence, patient records may not contain all the information required to properly assess whether a medical event in a given patient record is likely to be causally related to the use of a medicine. On the other hand, potential adverse drug reactions can be identified based on excessive recording rates on the population level, either as compared to a set of controls or at characteristic points in time relative to drug prescription. This is an advantage for the detection of adverse events with high background incidence, with which the traditional systems struggle.

Screening methodology

Early detection of ADRs using patient records does require a trade-off between method customisation and their scope of application. Appropriate case definitions, comparator groups, and methods to control for confounding are fundamental to effective data analysis. For confirmatory studies, these choices can be carefully optimised for the pre-specified hypothesis of interest. Broad surveillance on the other hand requires a generic analytical framework that works well enough for a variety of drugs and ADRs, while being robust to data quality issues. Such surveillance would typically include a range of analytical approaches customised for various combinations of drugs and ADRs to be used in parallel rather than implementing case-by-case study designs for each potential pattern of interest.

Exploratory analysis demands a different frame of mind than confirmatory analysis. For the former, at the point of study specification, the main challenge is to select an analytical framework that provides enough power for a broad variety of pattern types, without pre-conceptions of what the exact patterns might be. Whereas confirmatory analysis requires most of its thought go into the process prior to performing the study, exploratory analysis is an iterative process of constant re-evaluation and interpretation, requiring considerable intellectual input beyond the point of study specification. While confirmatory analysis must be limited to one pre-specified view of data, the consideration of multiple perspectives is fundamental to effective exploratory analysis. The latter can highlight that fundamental assumptions have been violated or that there are unexpected aspects of data that alter the original inference. Open-ended screening for patterns related to the demographics, co-moribidities and co-medications of patients who are prescribed a given medicine, and then experience a certain adverse event, can be an important addition to temporal pattern

ADR reports	Electronic patient records
Information on the patient's experience at around the time of the suspected ADR	Information on extended parts of the underlying medical histories of patients
Includes patients exposed to at least one medicine	Includes exposed and unexposed patients
Includes patients who have experienced at least one adverse event	Includes patients with and without adverse events
Under-reporting	Under-recording
International coverage	Subsets of national populations
Information collected for the purpose of causality assessment	Information collected for the purpose of managing the patient
Data collection requires proactive participation from health professionals	Data collection in which health professionals do not need to recognise an adverse event as an adverse drug reaction
Hypothesis testing	**Exploratory analysis**
Ultimate aim: draw conclusion	Ultimate aim: highlight interesting patterns along with aspects of data that may alter the interpretation of other patterns in the same data set
Focus on a small set of research questions	Consideration of broad range of research questions of potential interest
Careful selection of study design for the research question(s) of specific interest	Generic study design applicable to a broad range of pattern types and robust to data quality issues

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discovery. The consideration of multiple time-periods in parallel is also effective[10]. **Figure 1** displays the pattern of temporal association of the occurrence of chest pain relative to nifedipine prescriptions in IMS UK Disease Analyzer data. The recording rate of chest pain is clearly elevated in the month after nifedipine prescription compared to during unexposed patient-time. However, as the graphical overview highlights, the increased recording occurs both before and after nifedipine prescription, which suggests that chest pain might be associated with the underlying disease rather than directly with nifedipine. Such pattern discovery is powerful in its own right, but also as a complement to confirmatory epidemiological studies.

Due to the broad scope of exploratory analysis, the highlighted patterns cannot be taken at face value, but generally require independent confirmation. One must be careful in how exploratory and confirmatory analyses are coordinated. Hypotheses raised in exploratory analysis cannot easily be tested within the same data (the basis for the test would have to be uncorrelated with the data for hypothesis generation – perhaps by studying another drug in the case of a suspected class effect). There is concern that the use of patient records for early ADR surveillance will limit their applicability for confirmatory studies. However, the problem is not the exploratory analysis in itself but the communication of highlighted patterns to a broader audience. Anyone informed of an issue identified in exploratory analysis will have reduced power in carrying out a confirmatory study on that topic in the same data set. For this reason, highlighted patterns should only be communicated after substantial efforts have failed to refute the relevance of the identified pattern. Such critical appraisal of initial findings[11] might be very effective on the basis that biases do tend to be more problematic than random variation in observational data. In fact, some patterns may be strong enough to withstand even a Bonferroni correction (see for example the temporal association between nifedipine and localised oedema in **Figure 2**). Modern methods for effective management of multiple comparisons[12] can be used to reserve the power of ADR surveillance for the severe and often drug-induced diseases, such as Stevens-Johnson syndrome, leaving patterns with milder adverse events tentative. The extent to which future patient time added to existing data sources can be used for validation should be also considered. Alternatively, as the infrastructure improves for combining data from various collections of patient records, the setting aside of data for validation may also be considered.

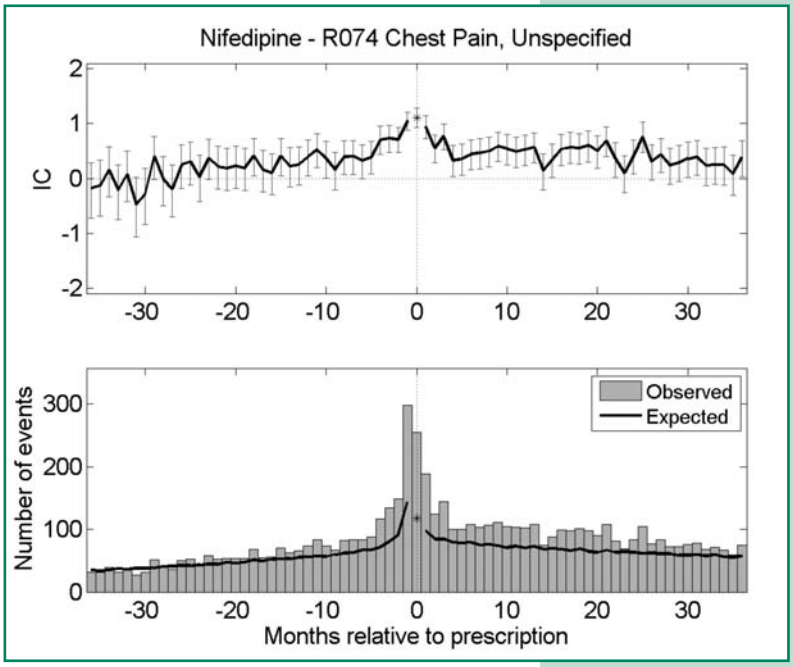

Figure 1. Graphical overview of the recording rate of chest pain in different time periods relative to nifedipine prescription in a collection of electronic patient records. The upper graph displays a smoothed version of the logarithm of the ratio of the observed to expected number of events (referred to as the Information Component, IC)[10].

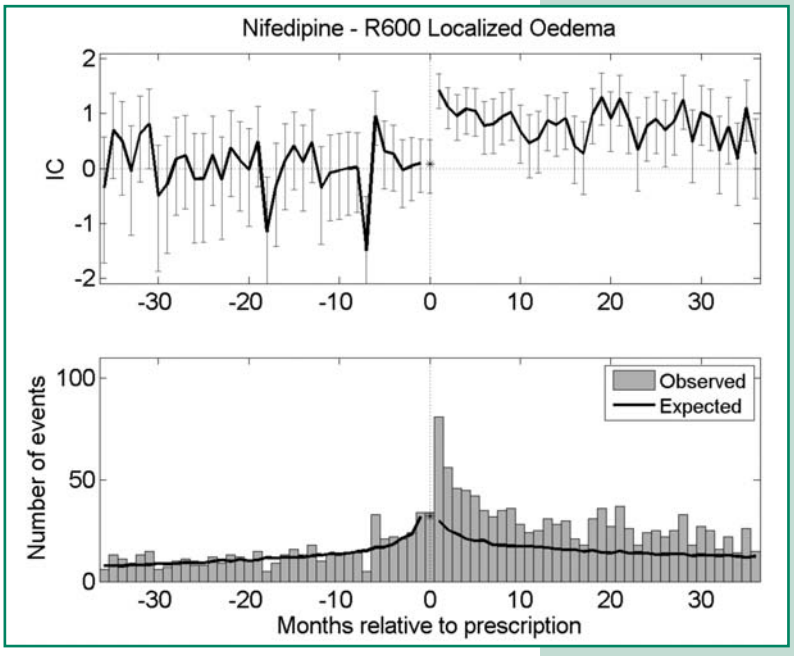

Figure 2. Graphical overview of the recording rate of localised oedema in different time periods relative to nifedipine prescription in a collection of electronic patient records. The upper graph displays a smoothed version of the logarithm of the ratio of the observed to expected number of events (referred to as the Information Component, IC)[10].

Challenges

Patient records do not reflect accurately every detail of a true medical history. There may for example be inadequate coverage of herbal products and other substances which do not require prescription. In a primary care/general practitioner-based system there may be limited information from in-patient care or specialist treatment. More subtly, in order for any medical diagnosis to be noted, it must be brought to the managing physician's attention and the physician must choose to record it. This may result in differentially missing data and bias. The correspondence between recording rates and true incidence rates will depend on the extent to which different medical diagnoses tend to be noted in the patient record when they do occur. For example, less severe disease is unlikely to be recorded unless there happens to be an appointment for other reasons at that time. This can be compensated for in the analysis by accounting for health-care usage. However such an approach does not provide a panacea as it will over-adjust in the case of disease severe enough to make the patient seek treatment. Again the use of different study designs in parallel is advisable, and can be viewed as a form of sensitivity analysis. Conflicting results have to be resolved based on more refined analysis and subjective clinical judgment.

The potential unreliability of recorded diagnoses is another challenge. Reimbursement rules and other regulation can affect coding practices. As always in the interpretation of structured medical information there is a challenge in ascertaining all observations of a given disease since symptoms may be coded in a wide range of different terms. A related issue is that the timing of a diagnosis does not necessarily reflect the occurrence of the disease, so that a medicine often prescribed before a specific diagnosis may in fact be used to alleviate its symptoms. It is essential to be aware of these potential pitfalls.

Causal inference under confounding by indication is inherently difficult in observational, non-randomised data. However, its identification as in **Figure 1**, goes some way towards avoiding inappropriate conclusions, which emphasises the importance of exploratory analysis also as an adjunct to confirmatory pharmacoepidemiology.

The future

There is great interest and ambition in utilising healthcare databases for early signal detection. While some progress has been made over the past few years, much work remains in terms of automating and optimising study designs for large-scale screening purposes, and in defining the areas of relative strengths of different analytical approaches and data sources. A fundamental challenge is to find the right balance between confirmatory and exploratory modes of operation that will allow for the detection of the unexpected without compromising the need to minimise the number of unnecessary false alarms that may distract from true safety signals.

An ideal system for ADR surveillance would combine the strengths of case reports with those of patient records. Case reports communicate real clinical concerns and provide the information required for proper causality assessment. A framework for tracing case reports to their corresponding patient records, would allow absolute reporting rates to be computed, and provide additional information on extended parts of the underlying medical history of the patient and other useful information. In combination, the two sources of information would allow for quantitative and clinical scrutiny in parallel and in the end better focused adverse drug reaction surveillance.

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