

Use of Measures of Disproportionality in Pharmacovigilance

Three Dutch Examples

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Abstract

Spontaneous reporting systems for suspected adverse drug reactions (ADRs) remain a cornerstone of pharmacovigilance. In The Netherlands 'the Netherlands Pharmacovigilance Foundation Lareb' maintains such a system. A primary aim in pharmacovigilance is the timely detection of either new ADRs or a change of the frequency of ADRs that are already known to be associated with the drugs involved, i.e. signal detection. Adequate signal detection solely based on the human intellect (case by case analysis or qualitative signal detection) is becoming time consuming given the increasingly large number of data, as well as less effective, especially in more complex associations such as drug-drug interactions, syndromes and when various covariates are involved. In quantitative signal detection measures that express the extent in which combinations of drug(s) and clinical event(s) are disproportionately present in the database of reported suspected ADRs are used to reveal associations of interest. Although the rationale and the methodology of the various quantitative approaches differ, they all share the characteristic that they express to what extent the number of observed cases differs from the number of expected cases.

In this paper three Dutch examples are described in which a measure of disproportionality is used in quantitative signal detection in pharmacovigilance: (i) the association between antidepressant drugs and the occurrence of non-puerperal lactation as an example of an association between a single drug and a single event; (ii) the onset or worsening of congestive heart failure associated with the combined use of nonsteroidal anti-inflammatory drugs and diuretics as an example of an association between two drugs and a single event (drug-drug interaction); and (iii) the (co)-occurrence of fever, urticaria and arthralgia and the use of terbinafine as an example of an association between a single drug and multiple events (syndrome).

We conclude that the use of quantitative measures in addition to qualitative analysis is a step forward in signal detection in pharmacovigilance. More research is necessary into the performance of these approaches, especially its predictive value, its robustness as well as into further extensions of the methodology.

After marketing of a drug, close monitoring for unexpected adverse drug reactions (ADRs) remains necessary due to the limited size of pre-marketing trials, the selection of the patients involved and the limited duration of the trials.^[1] A primary aim in pharmacovigilance is the timely detection of either new ADRs or a change of the frequency of ADRs that are already known to be associated with the drugs involved, i.e. signal detection. The WHO Uppsala Monitoring Centre (UMC) defines a signal as: 'reported information on a possible causal relationship between an adverse event and a drug, of which the relationship is unknown or incompletely documented previously'.^[2] Despite its inherent limitations, spontaneous reporting systems (SRSs) for suspected ADRs still play a major role in signal detection and exist in many countries which in their turn are part of international systems such as the databases of the UMC and the European Agency for the Evaluation of Medicinal Products (EMA).

Classically, signal detection is based upon the review by trained assessors of every incoming reported combination between a drug and a clinical event, i.e. the suspected ADR: case-by-case analysis or qualitative signal detection. Adequate signal detection solely based on the human intellect is becoming time consuming given the increasingly large amount of data, as well as less effective especially in more complex associations such as drug-drug interactions, syndromes and when various covariates are involved. Quantitative methods may be of value in addition to qualitative signal detection. In quantitative signal detection, combinations of drug(s) and clinical event(s) that are disproportionately present in the database of reported suspected ADRs, may reveal an important signal.^[3] Subsequently these highlighted combinations must be interpreted by the critical human mind and often be further evaluated using analytic study designs. In contrast to hypothesis testing studies where quantitative estimates are used to express the strength of an association, in spontaneous reporting systems these are primarily used for selection of potential signals.

Although the concept of quantitative signal detection originates from more than 30 years ago,^[3,4] its application and further development has been boosted in recent years mainly due to the general availability of powerful information technology. The use of a measure of disproportionality is currently being applied in various national spontaneous reporting centres as well as the UMC. Although the methodology of the various approaches differs, these all share the characteristic that they search the databases for disproportionality. In other words, does the number of observed cases differ from the number of expected cases? The statistical measures of disproportionality all express the extent to which the reported ADR event is associated with the suspected drug compared with the other drugs in the database. The occurrence of ADRs related to other drugs in the database is used as a proxy for the background incidence of ADRs. Several point estimates like the reporting odds ratio (ROR), proportional ADR reporting ratio (PRR) or Yule's Q, have been used, in combination with additional estimators of the precision of point estimates such as the Chi-square test, or the lower limits of the 95% confidence intervals of the point estimates.^[5-9] Furthermore, the probability of receiving a certain number of reports on a given combination, under the assumption that no relationship exists, can be calculated by means of the Poisson probability.^[10,11] Another approach is the use of Bayesian logic, specifying the relation between the prior and posterior probability before and after linking data fields, and of adding new data to the database. This approach is currently being used for example by the UMC in the Bayesian confidence propagation neural network (BCPNN) analysis.^[12-14] This relationship is expressed as the 'information component' (IC). Also the US Food and Drug Administration (FDA) is developing a Bayesian approach as an aid in signal detection.^[15]

The objective of this paper is to present three Dutch examples of the use of a measure of disproportionality in quantitative signal detection in pharmacovigilance: (i) the association between a single drug and a single event; (ii) the association

between two drugs and a single event (drug-drug interaction); and (iii) the association between a single drug and multiple events (syndrome).

1. Examples of Application of Measures of Disproportionality in Signal Detection

1.1 Setting

All the following examples originate from the spontaneous reporting system for suspected ADRs in the Netherlands Pharmacovigilance Foundation Lareb. The Netherlands Pharmacovigilance Foundation Lareb collects and analyses suspected ADRs reported by Dutch physicians and pharmacists on behalf of the Dutch Medicines Evaluation Board. A report may concern one or more clinical events and one or more suspected drugs. All reports are evaluated by trained assessors, coded and filed in a database. All ADRs are coded according to the WHO Adverse Reaction Terminology (WHO-ART). In this respect, possible ADRs are assigned to a so-called ‘preferred term’, which gives a detailed description of the clinical event. Preferred terms are linked to ‘high-level terms’, which provides a code for qualitatively similar conditions. As an example, the preferred terms ‘anxiety’ and ‘nervousness’ share the same high-level term ‘anxiety’. In this way clustering of ADRs for analysing purposes is possible. The suspected drugs as well as concomitantly used drugs are coded according to the WHO anatomical therapeutic chemical (ATC) classification, which also allows clustering on chemically and therapeutically related drugs.

1.2 The Basic Concept

In all analyses the basic concept is that of a case/non-case analysis. All reported clinical events of the outcome of interest are defined as cases. All reported other clinical events are defined as non-cases (controls). Next, the distribution of the exposure (drugs) categories of interest is compared among the cases and the non-cases and expressed in a quantitative relative estimate of disproportionality. We apply the ADR ROR. It is

defined as the ratio of the exposure odds among reported cases of a given suspected ADR to the exposure odds among reported non-cases (controls). The ADR ROR provides an estimate for the risk of developing a certain ADR for patients using the index drug relative to patients using reference drug(s). The ADR ROR is calculated as:

(a / c)
(b / d)

(see figure 1) and expressed as a point estimate with 95% confidence intervals (CI). ADR RORs can easily be adjusted for covariates (e.g. age and year of reporting) using logistic regression analysis.

The analysis can be applied to all reports in the database or to a rational subset.

1.3 Example of an Association Between a Single Drug and a Single Event

This example concerns the association between the use of antidepressant drugs and the occurrence of non-puerperal lactation. The full report has been described elsewhere.^[16]

For this study all reports concerning women with non-puerperal lactation were selected as cases; all remaining reports concerning women were included as controls. The relative frequency

		Reported suspected ADRs	
		Event of interest	Other events
Suspected medicine	Exposure of interest	a	b
	Other exposures	c	d

Fig. 1. Cross table methodology for calculation of reporting odds ratios. ADRs = adverse drug reactions.

of exposure to antidepressant drugs (ATC N06A) versus other drugs as well as of exposure to serotonergic (ATC N06AB and clomipramine) antidepressants versus other antidepressants was compared and expressed as an ADR ROR. The analysis showed that 38 cases of non-puerperal lactation were reported, of which 15 were associated with the use of antidepressant drugs. In general, antidepressants were associated with a higher risk of non-puerperal lactation in comparison with other drugs (ROR 8.3; 95% CI 4.3 to 16.1). Serotonergic antidepressants were associated with a higher risk (ROR 12.7; 95% CI 6.4 to 25.4), whereas other antidepressants were not (ROR 1.6; 95% CI: 0.2 to 11.6) compared with the group of all other drugs. There is pharmacological evidence that this effect is mediated by an indirect inhibitory effect of serotonin on the dopaminergic transmission. This finding is in line with the occurrence of other antidopaminergic effects, such as extrapyramidal symptoms, in patients using serotonergic antidepressants.

1.4 Example of an Association Between Two Drugs and a Single Event (Drug-Drug Interaction)

This example concerns onset or worsening of congestive heart failure (CHF) associated with the combined use of nonsteroidal anti-inflammatory drugs (NSAIDs) and diuretics.^[17] All reports submitted to Lareb between January 1st 1990 and January 1st 1999 of patients older than 50 years were included in the analysis. A decrease in the efficacy of diuretics may express itself as the occurrence of oedema or other signs indicating the onset or worsening of CHF. The presence of one or more of the following WHO-ART preferred terms on the reports was therefore considered as a possible indication for this situation: 'oedema', 'oedema dependent', 'oedema generalised', 'oedema peripheral', 'cardiac failure', 'cardiac failure left', 'cardiac failure right', 'pulmonary oedema' and 'oedema legs'. Reports that mentioned one or more of the aforementioned ADRs were defined as cases. Non-cases were defined as all other reports.

All drugs used at the moment the suspected ADR occurred, as known from the patient's pharmacy dispensing history, were considered a possible cause of the ADR, i.e. not only the drug indicated by the reporter as being suspected. Exposure categories were the use of NSAIDs (ATC M01A), or diuretics (ATC C03) versus the use of neither of these drugs. For the analysis the following logistic model was used:

$$\log(\text{odds}) = \beta_0 + \beta_1 N + \beta_2 D + \beta_3 N \times D + \beta_{n-x} C_{n-x}$$

where N = NSAIDs, D = diuretics, C_{n-x} = different covariates, i.e. age, source, and reporting year.

A statistically significant value of the interaction term β_3 indicates an additional effect of concomitant use of diuretics and NSAIDs. Covariates used in the analysis were: type of health professional that reported the ADR (either pharmacist or physician), year of reporting, age and gender of the patient involved, the use of antidiabetic drugs (ATC A10), cardiac glycosides (ATC C01), antihypertensive drugs (ATC C02), peripheral vasodilating drugs (ATC C04), β -blocking agents (ATC C07), calcium channel blocking agents (ATC C08), and drugs acting on the renin-angiotensin-aldosterone system (ATC C09). The analysis showed that the use of diuretics or NSAIDs itself was not statistically significantly associated with an increased risk for onset or worsening of symptoms of CHF. However, the odds ratio of the statistical interaction term NSAIDs $\times$ diuretics, was statistically significantly elevated (adjusted ROR 2.0; 95% CI 1.1 to 3.7). This is an indication for an enhanced chance of cases being reported, associated with the combined use of both drugs, which is in line with previous findings.

1.5 Example of an Association Between a Single Drug and Multiple Events (Syndrome)

Since the introduction of the oral antifungal drug terbinafine, Lareb has received 294 reports of suspected adverse reactions to terbinafine. Eight reports concerned arthralgia. In four of these reports the reporting physician or pharmacist also mentioned the presence of skin reactions, includ-

ing two reports of urticaria. Two patients who reported arthralgia also had a fever. The reports are suggestive for a clustering of arthralgia, fever and urticaria.

The objective of this study was to analyse the clustering of these symptoms statistically in order to determine whether there was a signal for a syndrome.^[18] All reports with a reporting date between March 1st 1992 and January 1st 1999 involving patients older than 10 years of age were included in the evaluation.

To study a possible relationship between fever, urticaria and arthralgia, the ADRs were considered being covariates and the presence of terbinafine as the suspected drug on the report form being the dependent variable. The extent to which the covariates are interrelated can also in this case be examined by using statistical 'interaction terms' in a logistic regression model. Since we were interested in expressing the presence of terbinafine as a function of arthralgia, fever and urticaria, cases were defined as reports on which terbinafine (oral administration) was mentioned as the suspected medication, non cases were defined as all other reports. ROR were calculated, which were adjusted for age and gender of the patients, source of the reports and year of reporting. Both urticaria (adjusted ROR 1.72; 95% CI 1.35 to 2.18) and arthralgia (adjusted ROR 3.14; 95% CI 1.52 to 6.47) were significantly associated with reports on terbinafine. The covariates being the best predictors of the dependent variable were urticaria (adjusted ROR 1.66; 95% CI 1.29 to 2.14) as well as the interaction terms arthralgia $\times$ fever (adjusted ROR 2.35; 95% CI 1.32 to 4.17) and arthralgia $\times$ urticaria (adjusted ROR 3.33; 95% CI 1.03 to 10.73). These results are suggestive of an association between the use of the antifungal agent terbinafine and the co-occurrence of arthralgia, fever and urticaria. These findings might point towards a shared mechanism of these symptoms, presumably an immunological reaction.

2. Discussion

In this paper we presented three examples of the use of quantitative measures in signal detection. These three examples show the applicability in three different situations: an association between a single drug and a single event, an association between two drugs and one event (drug-drug interaction), and an association between one drug and more events (syndrome). The concept can easily be extended to for example risk factors for a certain ADR and time trend analysis. The basic concept is using a quantitative measure to express disproportionality in (a subset of) the database of reported suspected ADRs. It has to be stressed that the use of such quantitative measures is primarily a filtering approach, sifting out the possible associations of interest, giving the human mind of the experienced assessor the opportunity to concentrate on the possibly interesting associations. This human interpretation is essential since various sources of bias may make casual associations appear as causal associations.^[19] Special attention has to be paid to the potential bias caused by differential (under)reporting.^[20]

Quantitative approaches are becoming increasingly important in signal detection in pharmacovigilance. This is not to say that they detract from case-by-case analyses, a method which has been an important tool in the analysis of spontaneous reporting systems for many years. Each method applied in pharmacovigilance (e.g. spontaneous reporting, prescription event monitoring or case control surveillance) follows a more or less individual approach to signal detection.^[1] This not only applies to the classical case-by-case analysis, in which each report is individually assessed as to whether or not the reported association represents a signal, but also to quantitative signal detection. Case reports or case series resulting from the former approach are highly sensitive in picking up qualitative signals. On the other hand, they are limited in their ability to provide quantitative information. Quantitative approaches in signal detection unify the qualitative and quantitative aspects of detection.

There has been some debate on which measure of disproportionality to use. In a recent comparison of the various measures their performance appeared to be roughly the same when applied to the dataset of the Netherlands Pharmacovigilance Foundation.^[21] Only in the case of less than four reports on an association, did the Bayesian analysis as applied by the UMC result in less signals than the more frequentistic measures such as the ROR and the PRR. It remains to be shown whether this reflects a lower sensitivity (i.e. less signals) or a higher specificity (i.e. less false positives). In other words, either the number of false positive signals increases for combinations of less than four reports for each of the frequentistic measures compared to the results of the Bayesian analysis, or the potential signals highlighted by the frequentistic measures are in fact true positives which the Bayesian analysis does not pick up at the same moment in time, although these might be highlighted later as more information accumulates.

In conclusion, the use of quantitative measures in addition to qualitative analysis is a step forward in signal detection in pharmacovigilance. More research is necessary into the performance of these approaches, especially its predictive value, its robustness as well as into further extensions of the methodology.

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