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PHARMACOVIGILANCE

Causality assessment in pharmacovigilance: The French method and its successive updates

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Summary The methods for causality assessment of adverse drug reactions were developed in the 1970s and 1980s, alongside the development of pharmacovigilance. The French method is one of the earlier of these, following on from the pioneering works by Irey and Karch and Lasagna. Initially published in 1978, it was updated in 1985, and again in 2011. The main alterations to the original method are presented in tables annexed to this paper. The successive versions improved the presentation, provided more formalised definitions of the criteria for assessing causality, while at the same time ensuring the method remained easy to use. Causality assessment enables the causal link between a drug and the occurrence of an adverse reaction to be formalised and explained. It contributes to diagnosis, and to determining the action to be taken in case of an adverse drug reaction. It can contribute to the quality and the relevance of the data stored in pharmacovigilance databases.

Abbreviations

ADRs	adverse drug reactions
B	bibliographic score
C	chronological score
CRI working group	causality assessment working group (*Cercle de réflexion sur l'imputabilité*)

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CRPV	Regional center of pharmacovigilance
I	intrinsic causality score
MAP	weighted assessment method (*méthode appréciative pondérée*)
NI	informativeness score (*niveau d'informativité*)
S	semiological score
SPC	summary of product characteristics

Introduction

As early as the 1970s and 1980s, with the development of pharmacovigilance and the systematic recording of case reports of adverse drug reactions (ADRs), the question of the evaluation of the causal relationship between a drug treatment and the occurrence of an adverse reaction was raised.

Numerous methods for causality assessment of ADRs were developed over this period, in North America, in Europe, in Japan, in Australia, etc. [1—9].

The method developed in France by a working group (Dangoumau, Evreux and Jouglard) within the French association of pharmacovigilance centres (CRPVs) was published in the journal *Thérapie* in 1978 [3], immediately after the pioneering works by Nelson Irey (1976) [1] and Karch and Lasagna (1977) [2]. The French method was updated in 1985 [10], officialised, and made compulsory for pharmacovigilance centres and pharmaceutical companies for the reporting of cases occurring in France [11]. A second update was published in 2011 by the *Cercle de réflexion sur l'imputabilité* (CRI working group) [12,13], and a validation has been recently published [14].

Numerous other causality assessment methods have been published, but few have been actually used. In 1983, Lagier et al. proposed the weighted assessment method *(méthode appréciative pondérée* [MAP]) that yields results in the form of probabilities [15], and Loupi et al. published a method for the evaluation of the teratogenic effects of drugs [16]. Internationally, more than thirty causality assessment methods applied to adverse drug reactions have been published, some of which are successive, improved versions of earlier proposals [1—10,12—26].

These different methods are based either on expert opinion, or on algorithmic approaches (''classic'' causality assessment methods), or on probabilistic approaches derived from Bayes' conditional probability theorem [19].

In the algorithmic methods, a given number of criteria are assessed successively, and the evaluations are combined by way of a decisional tree, a combination table, the summing of scores, or using a mathematical model, to arrive at a score in the form of a number (1, 2, 3, etc.), or a qualifier (highly unlikely, doubtful, probable, etc.), to reflect the potential causal link between a given drug and a given adverse event. The logistic causality assessment method is a somewhat similar procedure, but the results of the evaluation are expressed as a probability, respecting basic probability rules [20,21]. Most causality assessment methods used in pharmacovigilance are ''general'', that is to say they are applicable whatever the nature of the adverse event, the drug or the setting in which it is used. A few specific methods have been proposed, for instance concerning liver injuries [22], Stevens-Johnson syndrome and toxic epidermal necrolysis [23], or the adverse effects of vaccines [24].

Causality assessment in pharmacovigilance has had a mixed reception depending on the period and the country, and popularity has generally declined over time [25]. Fewer than 10 methods are still in current use in 2015. The French causality assessment method is among these, along with the method published by Naranjo [6] and the World Health Organization method [26], since it has been continuously used, from the first publication in 1978, by pharmacovigilance centres in France.

The aim of the present article, on the basis of the French method for causality assessment of ADRs and its main evolutions in the successive versions of 1978 [3], 1985 [10] and 2011 [12], is to set out the advantages, the limitations and the prospects of causality assessment in pharmacovigilance.

Definition, principles and criteria of the French method for causality assessment of ADRs

Causality assessment can be defined as an estimation of the putative causal relationship between a drug treatment and the occurrence of an adverse event, for a given person at a given time. The procedure is thus fairly close to that of a medical diagnosis, and different from risk evaluation of adverse drug reactions, and from the estimation of causality in the population *via* pharmacoepidemiological studies.

The French method is algorithmic, and is based on the evaluation of eight criteria divided into three groups: chronology, semiology, and bibliographic data.

Seven criteria enable the establishment of a chronological score (C) and a semiological score (S), which, once combined, yield the ''intrinsic'' causality score (I), which is allocated on the sole basis of the case of adverse reaction considered.

The chronological score comprises the following three criteria:

- time to onset from the start of drug administration to the occurrence of the adverse event (challenge);
- outcome of the adverse event, in particular following drug discontinuation (dechallenge);
- recurrence or not of the event in case of drug re-administration (rechallenge).

The semiological score is based on four criteria:

- whether or not there is any other potential non-drug-related cause for the occurrence of the event;
- the existence of a clinical or biological pattern of the adverse reaction that is ''characteristic'' of the suspected drug;
- the existence of one or more factors likely to favour the adverse reaction (previous history, drug interactions);
- results from specific, reliable tests in favour of the role of the drug in the adverse reaction.

The eighth criterion, which is the known potential of the drug to generate an adverse reaction, is used to derive an ''extrinsic'' or bibliographic score (B) for the reaction from a categorisation of the scientific literature available for the drug/adverse reaction association.