Updating the French Method for the Causality Assessment of Adverse Drug Reactions

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An updated method improved the assessment of adverse drug reaction in routine pharmacovigilance

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Abstract

Objective: Updating a logistic causality assessment method to improve its agreement with consensual expert judgment (CEJ).

Study Design and Setting: A random sample of 53 drug-event pairs from a pharmacovigilance database were evaluated independently by CEJ and by a group of experts in pharmacovigilance using the logistic method. Causes of disagreement between both approaches were analyzed, and changes in the assessment of some criteria of the logistic method were proposed and tested in models. The model giving results closest to the CEJ was retained and compared with the initial version on another set of drug-event pairs.

Results: Finally, only the criterion ''*Search for nondrug cause*'' was changed into ''*Search for other causes*.'' The assessment *not investigated*, *possible other cause* decreased the probability of drug causation instead of being neutral, whereas the assessment *not applicable*, *not required* remained neutral. This new version presents much improved specificity (0.56 vs. 0.33), relatively good sensitivity (0.96), and positive and negative predictive values (0.92 and 0.71).

Conclusion: The updated logistic method presented here improves the initial version that had poor specificity and tended to overestimate drug causation. This new version presents satisfactory characteristics to be used in routine pharmacovigilance.

Keywords: Pharmacovigilance; Adverse drug reaction; Causality assessment method; Probability; Algorithm; Logistic models

1. Introduction

More than 30 different methods have been proposed to assess the possible causal link between a drug treatment and the occurrence of an adverse event in a given patient [1]. They can roughly be divided into three main categories: expert judgment, operational algorithms, and probabilistic approaches [1−3]. Each has advantages and limitations. Expert judgment, or global introspection, relies on clinical experience and knowledge to assess the likelihood of a drug causing an adverse event. It mimics the clinical diagnosis process but is per se subjective and may suffer from poor intra- and inter-rater reproducibility [4−7]. Algorithms, which consist of assessing successive causality criteria combined by means of scores or a decision tree, have been developed to standardize causality assessment reasoning. The final result is expressed as an *x* degree score. Although this approach is easy to use and tends to minimize the inter- and intraobserver variability, the final assessment depends highly on the relative weighting of each criterion, which is often fixed more or less arbitrarily by the author(s) of the method [8,9]. Probabilistic approaches are derived mainly from the Bayes' theorem that converts a prior probability into a posterior probability for drug causation by means of likelihood ratios formalizing the relevant characteristics of the case studied. This presents an indisputable advantage by providing a formal causal assessment and results directly in the form of a probability [10]. However, Bayesian methods are rather difficult to use in routine practice as they require precisely quantified information to

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What is new?

- A logistic causality assessment method predicting the probability of drug causation on the basis of seven causality criteria statistically weighted with reference to consensual expert judgement has previously been developed. However, its specificity was poor and it tended to overestimate the probability of drug causation.

What this adds to what was known:

- An updated method calibrated on a larger sample of drug-event pairs with new definitions of certain criteria is now proposed, as well as a computerized version for faster and more straightforward assessment.

What is the implication, what should change now?

- Its relatively good sensitivity, specificity, and positive predictive capacity make this method worthy of use in routine pharmacovigilance.

derive probability distributions for each parameter studied, even if, in some cases, assumptions can be made [8,11].

Despite the range of strategies available, there is no unique operational tool providing an indisputable gold standard for drug causation assessment [1,12]. However, an assessment made by several senior experts interacting on a consensual basis, for example, by using the Delphi method [13], is generally considered as a reference [14,15], even if this is relatively fastidious to set up.

Recently, a new probabilistic approach was published [16]. It predicts a probability of drug causation by assessing seven criteria statistically weighted by consensual expert judgment (CEJ) by using a multilinear regression model. These assessments are combined by means of the logistic function that directly provides a probability for drug causation reproducing CEJ (Fig. 1).

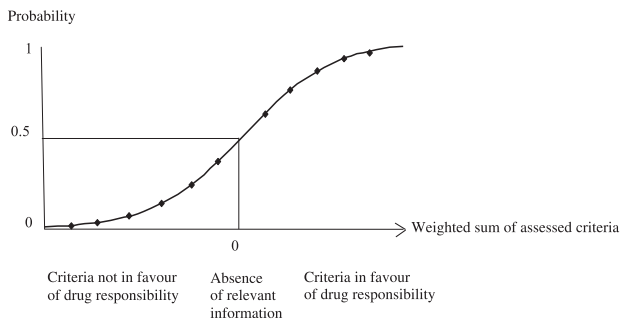

Fig. 1. Logistic method to obtain the probability of drug causation from the assessment of seven causality criteria weighted by a consensual expert judgment.

Since its publication in 2006 [16], the method has undergone a validation phase conducted to alter some criteria assessments and their weighting (Table 1). To take into account the fact that similar drug-event associations may have been reported or published, which is so-called *extrinsic* plausibility in the pharmacovigilance parlance, the assessments *positive/not available* or *unknown/negative* have been changed to *labeled reaction/not well known previously published only once* or *twice/not available/not previously reported*, respectively. A category *not applicable* has been added to the criteria "*Search for non–drug-related causes*" to take into account diseases or symptoms without known cause, for example, multiple sclerosis, for which there is no etiological investigation.

This logistic method offers several indisputable advantages. In particular, 1) such as the Bayesian approach, it respects the probability theory stating that absence of any relevant information, either through lack of information or conclusive arguments for or against the drug's responsibility, should lead to a neutral estimate, that is, a probability of 0.5 or an odds of 1 [8]; 2) it gives a precise estimate of drug causation, formalized as a probability on a continuous scale from 0 to 1; 3) it preserves the straightforward character of algorithms and is reinforced by a computerized version that directly converts criteria assessment into a probability [17]. However, a recent study comparing the logistic method to CEJ showed that, although results given by the logistic method were overall satisfactory, the method suffered from low specificity (0.42) and tended to overestimate drug responsibility [18]. The objective of the present article was to maintain the advantages of the previous version while improving the agreement with CEJ by re-evaluating the causality assessment criteria and their weightings.

2. Methods

A random sample of 53 drug-event pairs was used for the final analysis. Of the 50 drug-event pairs initially selected from spontaneous reports to the regional Pharmacovigilance Center of Bordeaux, one was excluded because it was considered ambiguous and difficult to assess by the experts. Four drug-event pairs were added to obtain a better representation of situations weakly represented in the initial sample and a better stability of weighting of the logistic method. These situations concern *positive rechallenge* and *investigations ruling out the main nondrug causes*, for which two drug-event pairs sampled from the pharmacovigilance database were added for each of these situations. For each case, available information was summarized using a standardized form, including characteristics of the patient, the suspected drug(s) with dates of beginning and end of the treatment, type of event, date of event onset, relevant biological and clinical data, other current medicines, and the time course of the event. The drug-event pairs were then assessed separately by two groups of experts.

Table 1. Distribution of criteria of causality assessment with the corresponding statistical weights for the initial logistic method

Criteria	Statistical weights
Time to onset	
Incompatible	−4 (stop)
Not suggestive	−1.2
Unknown or not available	0
Compatible	+0.1
Highly suggestive	+0.6
Dechallenge	
Against the role of the drug	−0.5
Not conclusive or not available	0
Suggestive	+0.5
Rechallenge	
Negative	−0.3
Not attempted or not conclusive	0
Positive	+0.3
Search for non–drug-related causes	
Nondrug cause highly probable	−2.2
Not investigated and/or another possible nondrug cause	0
Not applicable	0
Nondrug cause ruled out	+0.9
Risk factor(s) for drug reaction	
Ruled out or absent	0
Well validated and present	+0.5
Reaction at site of application or validated laboratory test in favor of a drug causation	
Unrelated or not available	0
Present and/or positive	+0.4
Previous reports of similar drug-event association and/or symptoms evocative of a drug causation	
Reaction not previously reported	−0.3
Not available	0
Not well known, previously published only once or twice	+0.3
Labeled reaction	+0.4

2.1. Evaluation of the probability of drug causation by CEJ

A panel of 26 experts (seven specialized in clinical pharmacology and 19 specialized clinicians) was set up to evaluate the causality assessment of the drug-event pairs. For each pair, a group of three experts (one senior pharmacovigilance expert and two clinicians) was selected. Clinicians were chosen according to their field of expertise either with regard to the type of event, for example, hepatologist for liver injuries, or the treated disease, for example, a hematologist reviewed a case of seizures in a patient treated with vincristine for acute lymphoblastic leukemia. Each of these three experts was asked to express separately their judgment on the responsibility of the suspected drug on a 100-mm visual analogic scale (VAS) directly converted into a probability of drug causation ranging from 0 to 1. When the three experts were in total agreement, that is, judgments differed by less than 5 mm on the VAS, the probability was kept. When the extreme judgments differed by 5 mm or more but by less than 25 mm, the arithmetic mean of the three scores was retained. When the difference between the three judgments was 25 mm or more, the drug-event pair and former expert judgment were reanalyzed on a consensual basis by a second group of four senior experts (two senior pharmacovigilance experts and two clinicians), independent of the first group. This final probability was then kept. Probabilities obtained by this expert group were used as the gold standard for drug causation.

2.2. Probabilities for drug causation provided by the logistic method

Another panel of four experts (one clinician and three specialized in clinical pharmacology) was set up to assess drug causation for each drug-event pair and to evaluate the seven assessment criteria of the logistic method (Table 1): 1) time to onset, 2) dechallenge (i.e., the effect of drug discontinuation), 3) rechallenge (i.e., the effect of drug reintroduction, if any), 4) search for non–drug-related causes, 5) risk factor(s) for drug reaction (e.g., a drug–disease or drug–drug interaction increasing the toxicity of a drug), 6) reaction at site of application, or validated laboratory test clearly in favor of the drug's responsibility, and 7) previous reports or publication of similar drug–event associations, and/or symptoms evocative of a drug causation (extrinsic plausibility).

Probabilities obtained from the logistic method were compared with those given by the CEJ. For a difference of 30% or more, the group of experts who had used the logistic method analyzed the sources of disagreement between the two approaches. On this basis, changes concerning the assessment of some criteria in the logistic method were proposed.

2.3. Weighting of the logistic method

As previously described [16], the weights derived from the assessment of the seven criteria of the logistic method, symbolized by $X_1, X_2, \ldots, X_7$, are converted into a probability P of drug causation by the logistic function:

$$P = \frac{1}{1 + \exp\left[-\left(\alpha + \sum_{i=1}^{7} \beta_i X_i \right) \right]} \quad (1)$$

The intercept α was fixed at 0 to obtain a probability of drug causation of 0.5 when no criterion was assessable or discriminant ($\sum \beta_i x_i = 0$). The weights β_i producing the best fit between the probability P obtained from the CEJ and the assessment of criteria given by the pharmacovigilance expert group were deduced from the 53 drug-event pairs by using a multilinear regression model:

$$\ln\left(\frac{P}{1-P}\right) = \text{logit}(P) = b_1 X_1 + b_2 X_2 + \ldots b_7 X_7 \quad (2)$$

For each criterion, the nondiscriminant option was used as the reference (e.g., not attempted, not available) with

a weight set at 0. The values of β were obtained with the least squares method. Each change proposed in the assessment of criteria in the logistic method was tested in a model, and all corresponding models were compared. The one giving results closest to the CEJ was finally retained. For each model, the adjusted coefficient of determination, R^2, was used to assess and compare the adjustment ability of the different models. The intraclass correlation coefficient was used to measure the concordance between the probabilities given by the new version of the logistic method and by the CEJ. All statistical analyses were done with SAS statistical software (release 8.1; SAS Institute, Cary, NC).

2.4. Validation of the logistic method

The initial and the new versions of the logistic method were compared on a random sample of 59 drug-event pairs from notifications to the French pharmacovigilance system. For each drug-event pair, a group of three senior experts gave a consensual probability of drug causation by using both versions of the logistic method. Sensitivity, specificity, and positive and negative predictive values of the initial and new versions of the logistic method were computed with reference to the CEJ obtained from another group of three experts. Probabilities lower than 0.50 were considered as not being in favor of drug responsibility and probabilities of 0.50 or more as being in favor of it.

3. Results

3.1. Proposed changes concerning criteria assessment of the logistic method

The analysis of disagreements between the initial version of the logistic method and the CEJ for the drug-event pairs with a difference of probability of 30% or more (8 of 53, i.e., 15%) suggested possible improvements concerning three criteria: "*Time to onset*," "*Search for non−drug-related causes*," and "*Previous information on the drug-event association*."

Responses associated with the criterion "*Time to onset*" were not thought to be sufficiently discriminant. Therefore, it was suggested that the assessment *compatible* be divided into *compatible* and *suggestive*. For the criterion "*Search for non−drug-related causes*," the assessment *not investigated* and/or *another possible nondrug cause* was thought to be ambiguous and not to cover all possible situations. In the initial version, its weight was conservatively set at 0, the absence of information not being thought to modify the probability of drug causation. This criterion was changed to "*Search for another cause*" to consider other drugs taken by the patient and more suspect than the drug studied. For the etiological diagnosis, it was proposed to change the assessment *not investigated* and/or *another possible nondrug cause*, the weight of which was 0 in the initial method, to etiological diagnosis *required* and *not investigated* and/or *another possible cause*. This assessment was tested both with the weight newly computed by multilinear regression and with a weight set at 0. The assessment *not applicable* of the initial method was changed to *not required* and/or *not applicable* with an associated weight kept at 0. For the criterion "*Previous information on the drug-event association*," it was proposed to add the category *pharmacological effect* for better assessment of events related to the mechanism of drug action, that is, hemorrhage with anticoagulants, anticholinergic effect for first-generation antihistaminic drugs.

3.2. Comparison of the different models

A total of eight models presented in Table 2 were tested. The addition of the *suggestive* assessment (models 1−4) for the criterion "*Time to onset*" produced incoherent results with weights higher for *suggestive* than for *compatible* (models 1 and 3), or positive for *incompatible* (models 2 and 4). Therefore, this assessment was not retained in the final model.

The weights produced by models 1, 3, 5, and 7 for the assessment *search for other cause required and not investigated* and/or *possible other cause* were negative for all the models tested, and were comprised between those corresponding to *other cause highly probable* and *not required* and/or *not applicable investigations*. This was expected, that is, that another possible cause decreased the probability of drug causation but less than if another cause was highly probable. These modifications were retained in the final model.

The weight associated with the assessment *pharmacological effect* gave incoherent results in model 8. Only models 5 and 7 gave consistent weights for all causality assessment criteria. Both models, which only differed by including or excluding the category *pharmacological effect*, gave quite similar weights (differing about 0.01−0.02) and thus produced very close probabilities. Model 5 giving a slightly better fit (adjusted R^2 0.686 vs. 0.678) was retained for the final version (Table 3). Model 5 weighted without the bibliographical criteria is also presented in Table 3.

3.3. Comparison of new version of logistic method to initial one

In both versions, the weights associated with the criteria were very similar for six assessments: highly suggestive delay, suggestive dechallenge, positive rechallenge, another cause highly probable, not previously reported adverse drug reaction, and labeled reactions. For criteria not in favor of drug responsibility, the weights were overall more negative in the updated than in the initial method: *not suggestive time to onset* −0.5 vs. −1.2, *dechallenge against the role of drug* −1.3 vs. −0.5, *negative rechallenge* −1 vs. −0.3,

Table 2. Weighting of the criteria obtained from the multilinear regression on logit (*P*) from the 53 drug-event sample for the eight models tested

Criteria	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Time to onset								
Incompatible	−5	−5	−5	−5	−5	−5	−5	−5
Not suggestive	−0.63554	*0.01259*	−0.6381	*0.00488*	−0.48647	*0.24363*	−0.4884	*0.23331*
Unknown or not available	0	0	0	0	0	0	0	0
Compatible	*0.57087*	0.45246	*0.56242*	0.44085	—	—	—	—
Suggestive	*0.48955*	0.67535	*0.47311*	0.65021	—	—	—	—
Compatible, suggestive	—	—	—	—	0.72218	0.74162	0.71277	0.72481
Highly suggestive	0.60458	1.00779	0.60239	1.00211	0.7919	1.13034	0.79298	1.12904
Dechallenge								
Against the role of the drug	−1.36961	−1.75233	−1.3559	−1.72996	−1.32394	−1.64243	−1.31408	−1.62199
Not conclusive or not available	0	0	0	0	0	0	0	0
Suggestive	0.44279	0.43951	0.4461	0.44436	0.45961	0.53995	0.45995	0.5398
Rechallenge								
Negative	−0.95299	−0.52391	−0.93703	−0.50324	−0.97045	−0.49039	−0.95744	−0.47195
Not attempted or not interpretable	0	0	0	0	0	0	0	0
Positive	0.36167	0.99238	0.36904	0.99927	0.19114	0.73489	0.20348	0.75156
Search for other causes								
Investigated and another cause highly probable	−2.82177	−1.58993	−2.8204	−1.59549	−2.74122	−1.67627	−2.73554	−1.67631
Required and not investigated and/or possible another cause	−1.08055	0	−1.07601	0	−1.04487	0	−1.03927	0
Not required and/or not applicable	0	0	0	0	0	0	0	0
Required and another causes ruled out	0.1295	0.5662	0.13834	0.57643	0.16723	0.60608	0.17542	0.61482
Risk factors for drug reaction								
Ruled out or absent	0	0	0	0	0	0	0	0
Well validated and present	1.18789	1.82598	1.15177	1.76933	1.18048	1.84683	1.14845	1.78394
Reaction at site of application or validated laboratory test								
Unrelated or not available	0	0	0	0	0	0	0	0
Present and/or positive	1.26869	1.56482	1.28253	1.58321	1.25352	1.57889	1.26508	1.59623
Previous reports on drug-event association or symptoms evocative of a drug causation								
Reaction not previously reported	−0.19144	−1.30487	−0.18437	−1.28771	−0.42331	−1.5077	−0.41957	−1.49085
Not available	0	0	0	0	0	0	0	0
Not well known or previously published once or twice	0.19275	*−0.4521*	0.19199	*−0.44924*	0.02686	*−0.78358*	0.02845	*−0.77311*
Known and labeled	0.57064	*−0.14966*	0.56069	*−0.15977*	0.36131	*−0.37803*	0.35212	*−0.38726*
Pharmacological effect	—	—	0.73361	0.0927	—	—	0.50335	*−0.12018*
Adjusted R^2	0.6694	0.5934	0.6611	0.5841	0.6863	0.6109	0.6784	0.6026

Results in italicized numbers correspond to illogical weights.

another cause highly probable −2.7 vs. −2.2, *another possible cause* −1 vs. 0, *reaction not previously reported* −0.4 vs. −0.3. The intraclass correlation coefficient between probabilities given by the new logistic method and the CEJ was 0.85 (vs. 0.86 for the initial logistic method [16]). The distribution of probabilities obtained with all possible combinations of criteria for the initial and updated methods was presented in Appendix at www.jclinepi.com. All probability values from 0 to 1 were produced with the new version of the method, unlike the initial one.

Comparison of the two versions on another set of 59 drug-event pairs randomly sampled from spontaneous notifications showed that the new version had a slightly decreased sensitivity (0.96 vs. 1) and negative predictive value (0.71 vs. 1) but a much better specificity (0.56 vs. 0.33) (Table 4).

Table 3. Distribution of causality assessment criteria with the corresponding statistical weights calculated, with and without the bibliographical criteria, for the final model

Criteria	No (%)	Statistical weights with bibliographical criteria	Statistical weights without the bibliographical criteria
Time to onset			
Incompatible	0 (0)	−5 (stop)	−5 (stop)
Not suggestive	1 (1.9)	−0.48647	−0.6171
Unknown or unavailable	4 (7.5)	0	0
Compatible	43 (81.1)	+0.72218	+0.81659
Highly suggestive	5 (9.4)	+0.79190	+1.00473
Dechallenge			
Against the role of the drug	3 (5.7)	−1.32394	−1.00847
Not conclusive or not available	19 (35.8)	0	0
Suggestive	31 (58.5)	+0.45961	+0.6171
Rechallenge			
Negative	2 (3.8)	−0.97045	−0.92025
Not attempted or not interpretable	48 (90.6)	0	0
Positive	3 (5.6)	+0.19114	+0.24583
Search for other causes			
Required and another cause highly probable	1 (1.9)	−2.74122	−3.25893
Required and not investigated and/or possible another cause	26 (49.1)	−1.04487	−1.06196
Not required and/or not applicable	20 (37.7)	0	0
Required and another causes ruled out	6 (11.3)	+0.16723	+0.15443
Risk factor(s) for drug reaction			
Ruled out or absent	50 (94.4)	0	0
Well validated and present	3 (5.7)	+1.18048	+1.3424
Reaction at site of application, or relevant and reliable laboratory test strongly in favor of a drug causation			
Unrelated or not available	48 (90.6)	0	0
Present and/or positive	5 (9.4)	+1.25352	+1.34133
Previous report of similar drug/event associations and symptoms evocative of a drug causation			
Reaction not previously reported and type B reaction	5 (9.4)	−0.42331	—
Not available	1 (1.9)	0	—
Not well known or previously published once or twice	9 (17.0)	+0.02686	—
Well known and labeled reaction	38 (71.7)	+0.36131	—

4. Discussion

The updated logistic method presented here is an improvement on the initial version that had poor specificity and tended to overestimate drug causation [18]. The main cause of disagreement between the initial method [16] and the CEJ arose from the criteria "*Search for non–drug-related cause*." This criterion has consequently been changed in the new version in "*Search for another cause*." Unlike in the initial version, the causality analysis now considers whether investigations to search for another etiology are required or not; if required but not carried out or if another etiology remains possible, the probability of drug causation is decreased (weight of −1.04 instead of 0 in the previous version). This refers to events for which the investigation of alternative causes is critical (e.g., hepatitis, anemia) or to nonspecific events (e.g., headache). This assessment is also relevant when a putative alternative cause may suffice to explain the occurrence of the event (e.g., a meningeal syndrome in a patient with vasculitis treated for a cold by vasoconstrictive drug, both the vasculitis *and* the vasoconstrictive drug being possible causes of the meningeal syndrome), or when a drug is clearly more suspect for the event than the drug under assessment, owing to its temporal relationship with the event or the pharmacovigilance data concerning it. If investigations were not needed because they were not relevant (e.g., pruritus *sine materia* on the chest) or without added value

Table 4. Sensitivity, specificity, PPV, and NPV of the initial and new versions of the logistic method taking expert consensus as reference on a randomly sample of 59 drug-event pairs

Parameter	Initial version of the logistic method	New version of the logistic method
Sensitivity	1	0.96
Specificity	0.33	0.56
PPV	0.89	0.92
NPV	1	0.71

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

(e.g., anaphylactic shock during intravenous drug administration), the assessment *not required*, *not applicable* of neutral influence is retained.

The analysis of algorithms retrieved from the literature showed that most of them addressed the question of alternative etiological causes with a binary *yes/no* [14,19−24]. Even if a category *unknown* or *not done* [25−27] is made available, there is no opportunity to take into account the adequacy and completeness of investigations made. Not considering all possible options may be a source of misinterpretation and poor reproducibility. Unfortunately, routine pharmacovigilance is often more complex than situations planned in published algorithms. For example, at what point can other explanations for an adverse event be ruled out? How can one assess this criterion when some etiological investigations have been made but incompletely? In the present method, the weight assigned by the model when investigations to rule out a possible alternative cause were required but not completely performed decreases the probability of drug causation, but less than if an alternative cause was favored after complete investigations. Unlike previous algorithms, particular attention was paid to the case where etiological investigations had not been conducted:

- In the particular case of events that were almost always drug caused, for example, fixed drug eruption, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), if investigations were not made, the corresponding assessment is *other causes ruled out* with a weight of +0.17 to increase the probability of drug causation;
- If investigations were not made because no precise etiology is known for the event considered, for example, multiple sclerosis, the corresponding assessment would be *not applicable* with a weight of 0 so as not to influence the probability of drug causation;
- If investigations were not conducted because they were not relevant, for example, effect known to be often associated with a drug etiology (e.g., pruritus *sine materia* or urticaria) or related to the mechanism of drug action (e.g., hyponatremia with diuretics), the corresponding assessment would be *not required* and the weight of 0 would not modify the probability of drug causation;
- If investigations were not made although were required to rule out a plausible alternative etiology (e.g., liver injury), the corresponding assessment would be *possible another cause*, which has a weight of −1.04 that decreases the probability of drug causation.

The few algorithms such as those of Kramer et al. [26] and Maria and Victorino [28] that take into account a not relevant or incomplete exploration of possible alternative causes were assigned a score of 0, which does not influence the final score. Only the algorithm reported by Danan and Benichou [29], which is specific for liver injuries, was assigned a negative score when relevant investigations for excluding the most common alternative causes were not made.

The addition of the category *pharmacological effect* was an appealing idea to increase the sensitivity and the discriminant value of the method when the event is likely to be related to a pharmacological property of the drug. However, it did not show any added value in the tested models and was not retained in the final version. That could be due to the colinearity between the assessments *investigation not required* and *pharmacological effect* because the "S*earch for other causes*" becomes unfounded whenever the event can be explained by a pharmacological property of the drug.

One strength of the proposed method is its weighting process, which is founded on actual case reports representative of pharmacovigilance practice. It was based on a larger sample of drug-event pairs than the initial version (53 vs. 30), thereby providing better representation of situations encountered in practice. Only the assessment *incompatible* delay was never encountered in the 53 drug-event pairs. A weight of −5 was arbitrary attributed to this quotation to obtain a final probability near to 0 (0.007) because an event onset preceding drug introduction is in itself sufficient to rule out the responsibility of the latter.

Since its publication in 2006, a computerized version of the method has been developed that directly provides a probability for drug causation after assessment of the seven criteria [17]. Therefore, there was no need to round the weighting coefficients to multiples of 0.5, as was the case in the initial version to facilitate manual computation. This use of actual, that is, not rounded, weights produces a continuous range of probabilities from 0 to 1, what was clearly not the case in the previous version.

An endless debate in the domain of drug causality concerns the role of literature and pharmacovigilance data, often called *extrinsic plausibility* [19], in the assessment process. In other words, if the six other criteria are equal, should a drug be more suspected if already known to have caused similar events? The final version of the logistic method was weighted and computerized with and without this extrinsic plausibility to address different issues encountered in pharmacovigilance. The first option mimics the diagnostic process and is preferable for advising physicians about continuing or not a drug treatment. The second option, that is, without extrinsic data, provides a probability based only on case information and may be of interest to identify signals in routine pharmacovigilance because this does not decrease the probability of drug causation on the pretence that such a drug-event association was never reported before.

The logistic method roughly uses the same criteria as other causality assessment algorithms [1,30]. Therefore, it theoretically suffers from the same difficulties in routine use to differentiate between the options offered for

assessing a given criterion. For example, in some instances, for the criterion ''*Time to onset*,'' it could be difficult to choose between the following options: *compatible* only describing general situations where the drug treatment was started before the onset of the first symptoms of the disease, *suggestive* being used when the delay appears to be consistent with the pharmacokinetic data of the drug and/or the physiopathology of the disease or symptom, and *highly suggestive* being restricted to the rare instances in which the time course is almost conclusive in itself such as seizures during an intravenous infusion. This could explain why the proposed distinction between *compatible* and *suggestive* delays was not retained in the final model. To limit such ambiguities that are putative sources of inter- and intrarater variability, the computerized version of the method proposes interactive assistance that is illustrated with examples.

An obvious limitation of the logistic method presented here is that its weighting is based on a relatively small sample, that is, 53 drug-event pairs, which does not represent all the possible combinations of criteria. This could be problematic when assessing situations that were not encountered in the sample. As in other studies using experts as a reference, the alternative would have been to increase the number of cases at the expense of a less indisputable reference. Indeed, the gold standard used was reliable thanks to the step-by-step consensual assessment of each case by a group of three senior experts who were able to refer to four other experts in case of disagreement. Such a validation process is not realistic for a markedly larger number of cases.

5. Conclusion

The new method preserves the advantages of the initial version: 1) by offering rational modeling of expert judgment thanks to the logistic function; 2) by weighting the different options offered by each criterion with a statistical approach based on a consensus of two groups of senior experts as reference; 3) by providing directly a probability for drug causation.

Reweighting of the method criteria on a larger sample of drug-event pairs representative of real pharmacovigilance practice produced a statistical weight for each causality assessment criteria. A major change in the new version is that the probability for drug causation is now decreased when the investigations to rule out the main alternative causes for the event were required but not completely performed. Its discriminant value is improved because all probability values from 0 to 1 can now be produced. The assessment process is made faster and more straightforward thanks to a computerized version of the method, which is a major help for its routine use. This updated method has relatively good sensitivity, specificity, and positive predictive value to be used in routine pharmacovigilance.

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Appendix

Supplementary material

Supplementary data related to this article can be found online at doi:http://dx.doi.org/10.1016/j.jclinepi.2012.04.015.

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