



REVIEW ARTICLE

Overview of important methods used for causality assessment of adverse drug events in pharmacovigilance

Pushpraj Prafulla Gawai ^{a,*}

^a Senior Aggregate Reports Writer-Drug Safety, Sector-2, Airoli, Thane, New Mumbai 400708, India.

ARTICLE INFO

ABSTRACT



Received 23 September 2020;
Revised 08 November 2020;
Accepted 24 November 2020.

Keywords:

Adverse drug events, pharmacovigilance, Naranjo algorithm, WHO-UMC causality assessment, and French imputability

Introduction: The method of assessing causality between adverse events and suspect drugs is the most challenging task in pharmacovigilance. It requires attentive consideration of both the adverse events and suspect drugs, patient-related factors, and co-suspect drugs and other medical conditions of the patient.

Objectives: This review aimed to look for different methods available or reported for causality assessment and give a brief comparison between the methods.

Methods: Many pieces of literature were reviewed to present a summary of commonly used important methods for causality assessment.

Results: Though different methods were developed to assess causality, no single method has been proved to produce an accurate or authentic ascertainable evaluation of the causal relationship.

Conclusions: Hence, causality assessment has become an important step in evaluating drug safety. Due to a lack of uniformity, reliability, and rationality, no single method can be accepted as a standard one across the world.

An official publication of Global Pharmacovigilance Society.

Introduction

In the 1970s and 1980s, with the development of drug safety and the standardized processing of individual case safety reports (ICSRs) of adverse drug reactions (ADRs), the big question was raised for the causality between a treatment drug and adverse events (Miremont-Salame *et al.*, 2016). In pharmacovigilance, causality assessment is a method of finding the relationship between drugs administered and reported adverse drug reactions (Gawai *et al.*, 2020). Causality is the assessment of the relationship between a suspect drug and an adverse drug reaction. It is the most valuable step of drug safety, contributes to a better

assessment of the integrated risk-benefit analysis of suspect drugs (Macedo *et al.*, 2005).

Numerous methods have been available and two to three are used in daily pharmacovigilance activities. Many analysts reported different criteria such as time lag between drugs intake and occurrence of AEs, screening for non-drug-related causes, confirmation of the events by *in vivo* or *in vitro* testing, absence of other competing causes like other drugs and ongoing disease, dechallenge and rechallenge, clinical and pathological characteristics of the events, etc. to define ADRs in different categories (Gawai *et al.*, 2020; Danan *et al.*, 1993). The causality assessment includes of evaluation of the probability that the adverse reaction occurs due to a specific drug (Macedo *et al.*, 2005).



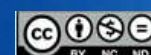
* Corresponding Author

Pushpraj Prafulla Gawai
E-mail: pushprajgawai@gmail.com
Contact: +919561217140

* Copyright: 2582-7235 // © 2020 The Author(s).

Published by Global Pharmacovigilance Society.

This is an open-access article under the [CC BY-NC-ND license](https://creativecommons.org/licenses/by-nc-nd/4.0/).



Available online 1 December 2020

Most of the drugs used for the therapeutic purpose are associated with unavoidable risks of adverse drug events that differ from minor to severe AEs (Curtin *et al.*, 2011). The causality assessment methods developed by the WHO-UMC and the Naranjo scale are the most accepted and routinely used methods of causality assessment in pharmacovigilance (Naidu *et al.*, 2013).

The WHO-UMC causality assessment

WHO-UMC causality assessment criteria are most commonly used in assessing the causality of adverse events in pharmacovigilance. These scales represent a suitable and practical approach for assessing the probability that a given reaction can be an input of a specific drug. The WHO-UMC system is used as a practical tool for the assessment of safety case reports (Rehan *et al.*, 2009). The clinical-

pharmacological aspects of the drug can be assessed by comparing the patient history and the quality of the case safety report. The different causality types are given in Table 1.

The WHO-UMC causality method involves the following criteria described in Table 2.

- The time between the drug administration and the occurrence of an adverse event.
- Absence of other causes like concomitant medications and current disease.
- Response to drug withdrawal or drug dose reduction (dechallenge).
- Response to drug administration after dechallenge (rechallenge).

Table 1: Types of causality as per WHO-UMC scale.

Causality term	Causality term Assessment criteria
Certain	'Event or abnormal laboratory tests, with a temporal relationship to drug intake' 'Cannot be explained by disease or other drugs' 'Positive De-challenge required' 'Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)' 'Re-challenge positive'
Probable / Likely	'Event or abnormal laboratory tests, with a temporal relationship to drug intake' 'Unlikely to be attributed to disease or other drugs' 'Response to withdrawal clinically reasonable' 'Re-challenge not required'
Possible	'Event or abnormal laboratory tests, with a temporal relationship to drug intake' 'Could also be explained by disease or other drugs' 'Information on drug withdrawal may be lacking or unclear'
Unlikely	'Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)' 'Disease or other drugs provide plausible explanations'
Conditional / Unclassified	'Event or abnormal laboratory tests' 'More data for proper assessment needed', or 'Additional data under examination and waiting for data'
Unassessable / Unclassifiable	'Report suggesting an adverse reaction' 'Cannot be judged because the information is insufficient or contradictory data' 'Data cannot be supplemented or verified'

Table 2: The WHO- UMC causality assessment method includes the following 4 criteria

Causality type	Time relationship	Other drugs/disease ruled out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

The extent of causality is based on a number of the above mention criteria. Causality is 'certain' when all the above 4 criteria are met. Causality is 'probable' when criteria 1, 2, and 3 are met. When only criterion 1 is met, the event is categorized as 'possible' and it is 'unlikely' when criteria 1 and 2 are not met. The term Unclassified/ Conditional is used when more safety-related data is needed and such data is being sought or is already under examination like laboratory data. Finally, when all the information in a report is insufficient or contradictory and cannot be reliable or verified, the causality is 'Unclassifiable'.

Naranjo algorithm causality assessment scale

The Naranjo Algorithm uses simple 10 questions to assess causality between an untoward adverse event and a suspect treatment drug by assigning probability scores. It assesses the causality in different clinical conditions using the types and definitions like 'definite', 'probable', 'possible', and 'doubtful'. The adverse reaction is assigned to a probability type based on the final score obtained after assessing 10 questions. If a total obtained score is ≥ 9 then the type is 'definite', 'probable' if the score is in-between 5-8, 'possible' if the score is in-between 1-4, and 'doubtful' when the score is ≤ 0 . The score calculated from this (Dangoumau *et al.*, 1978; Begaud *et al.*, 1985). This method is used for the alert system, which independently considers each drug taken by a patient together with any data on record. When an alert is established, the data are reviewed in the context of the national data bank. The main advantage of this unique method is the use of a common adverse drug reaction assessment system by all those

algorithm after the assessment is often used in reviews to crosscheck the validity of the author's conclusions with ADR (Naranjo *et al.*, 1981). Naranjo scale is always compared with the WHO-UMC scale to standardized causality assessment for adverse drug events.

French imputability causality assessment Scale

This method was first published by Dangoumau *et al* in 1978 and was revised by Begaud *et al.*, in 1985. It is the only causality assessment method that distinguishes between intrinsic and extrinsic accountability. French imputability is denoted with intrinsic imputability score - chronological criterion (C), intrinsic imputability score - semiologic criterion (S), extrinsic imputability score (B), and Intrinsic imputability score (I). C and S scores are assessed with details present within the reported information, these together determine the Intrinsic accountability which is represented by imputability score (I). B score is assessed using the current scientific literature available at the time and this determines the extrinsic accountability. France, both private and public sectors use the same method of imputability chosen for maximum sensitivity, at some cost to specificity

involved in the pharmacovigilance program. The types used for criteria, like "compatible", "suggestive" or "inconclusive", have never been completely defined, leading to incomplete reproducibility. The method of expert judgment is based on the decisive factor on which algorithms are based, nevertheless in an imprecise manner.

Table 3: Naranjo algorithm causality assessment scale

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction reappear when a placebo was given?	-1	+1	0	
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total score: ≤ 0 =Doubtful, 1-4 Possible, 5-8 Probable, ≥ 9 Definite				

Table 4: Criteria defining the chronological accountability of a drug

Time of occurrence of the event	Evolution of the event after stopping treatment (dechallenge)	Influence of a possible re-exposure to the drug (rechallenge)
Very suggestive	Suggestive	Positive
Incompatible	Inconclusive	Not made or unknown
Compatible	Non-suggestive	Negative

Table 5: Definition of the chronological imputability score according to the 3 criteria

Intrinsic imputability score- chronological criterion (C).							
Time to the appearance of event Evolution when the drug is curtailed	Highly suggestive			Compatibility		Incompatibility	
Suggestive	C3	C3	C1	C3	C2	C1	C0
Inconclusive	C3	C2	C1	C3	C1	C1	C0
Non-suggestive	C1	C1	C1	C1	C1	C1	C0
Rechallenge	R+	R0	R-	R+	R0	R-	R0

R +: positive rechallenge, R0: not done rechallenge, R-: negative rechallenge; C3: probable chronology, C2: plausible chronology, C1: doubtful chronology, C0: incompatible chronology

Table 6: Definition of the semiological imputability score according to the 4 criteria

Intrinsic imputability score - semiologic criterion (S)						
semiology (clinical or para-clinical) : Other explanation not attributable to the drug :	Evocative of the role of drug (and/or highly suggestive factor)			Other semiologic possibilities		
Absent (after appropriate workup)	S3	S3	S1	S3	S2	S1
Possible (present or not sought)	S3	S2	S1	S3	S1	S1
Specific test	L+	L0	L-	L+	L0	L-

L +: positive laboratory test, L0: laboratory test not done, L-: negative laboratory test; S3: plausible semiology, S2: plausible semiology, S1: doubtful semiology

Table 7: Definition of the extrinsic imputability score

Extrinsic imputability score (B)			
B0 effect never published in inter-national reference documents, even after the exhaustive bibliographic search	B1 effect not described in international reference works	B2 not well-known effect published once or twice only, different semiology or a similar drug	B3 well-known effect described in the VIDAL dictionary or reference works

Table 8: Association of chronological C and semiological S criteria in imputability score I

Chronology / Semiology	Intrinsic imputability score (I)		
	S1 doubtful	S2 plausible	S3 probable
C0 excluded		I0 excluded	
C1 doubtful		I1 doubtful	I2 plausible
C2 plausible	I1	I2	I3
C3 probable		I3 probable	I4 very probable
I4: very likely imputability, I3: likely imputability, I2: plausible imputability, I1: doubtful imputability, I0: incompatible imputability			

Intrinsic imputability gives the time and effect relationship between treatment drug and an adverse effect occurrence, on 3 chronological criteria (Tables 4 and 5) and 4 semiological criteria (Tables 6). Some charts allow these criteria to be associated with an intrinsic imputability score (Table 7). Extrinsic accountability looks for similar cases in the literature. It is based on bibliographic criteria (Table 8).

Kramer causality assessment scale

This algorithm is used in the assessment of a single clinical event and its signs and symptoms appear after administration of a single treatment drug (Kramer *et al.*, 1979). Each drug causality is assessed separately with this method if multiple suspect drugs are involved. The major benefit is its transparency in causality assessment. Kramer algorithm scale is depending on six decision tables with a scoring system incorporated into each axis. An already Assessment of adverse events is either evaluated by a single person or by a group of experts.

Swedish method of causality assessment

Swedish method of causality assessment used by the Swedish regulatory agency is based on expert group judgments. In most of the cases, the doctors identify the causal relationship by assessing seven different-different factors: (i) the time sequence of event occurrence (ii) already known information on the drug and class of drugs (iii) dose relationship with event (iv) response pattern to the drug from previous knowledge of drug (v) dechallenge, and rechallenge (vi) alternative candidates like medical history and ongoing medical conditions (vii) concomitant medication. Adverse drug reactions are categorized as 'probable' or 'possible' and 'non-assessable' or 'unlikely' after assessment of causality (Wiholm *et al.*, 1984).

given score like +1, 0, or -1 is assigned for the weight of evidence on each axis. Analysis of adverse events from in large clinical trials can be analyzed separately. Cases are assigned to probability categories based on a total obtained score that ranges from -7 to +7 from each axis.

Expert Judgement or Global Introspection

Almost 80 % of adverse events are suspected or identified by either doctor or clinical investigator (Hoskins *et al.*, 1992). This is based on expert judgment or global introspection and this is a process in which an individual expert gives judgment about possible causality of events with the drug by considering all available relevant data related to a suspected adverse event (Arimone *et al.*, 2005), evaluate their significance and assigns weights to decide the probability of the association of suspect the drug with the unwanted event (Hoskins *et al.*, 1992).

Probabilistic or Bayesian methods

The Bayesian method makes use of particular discoveries in a safety case to transform a before a posterior probability of drug causality (Hutchinson *et al.*, 1991). A probability ratio (like report-specific data, such as time sequence or re-challenge/dechallenge that helps to differentiate between causes of events) is further differentiated into different parts. Each part is used to a specific group of case information, and the final result is calculated by multiplying out the various terms to obtain a posterior probability of drug causality (Benichou *et al.*, 1992). This method can be used to assess many causes at the same time. In this method, there is no limit to the information of report details that can be assessed at the same time. It can be performed with a spreadsheet on either paper or electronically. This method provides immediate mathematical and realistic results as soon as new evidence of the suspected ADR is resulted (Hutchinson *et al.*, 1991). It is considered the most logical method for the assessment of causality (Ennis *et al.*, 1988).

Table 9. Questions for Drug Interaction Probability Scale

Sr. No	Question	Yes	No	NA
1	'Are there previous credible reports of this interaction in humans?'	+1	-1	0
2	'Is the observed interaction consistent with the known interactive properties of the precipitant drug?'	+1	-1	0
3	'Is the observed interaction consistent with the known interactive properties of the object drug?'	+1	-1	0
4	'Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?'	+1	-1	0
5	'Did the interaction remit upon de-challenge of the precipitant drug with no change in the object drug?'	+1	-1	0
6	'Did the interaction reappear when the precipitant drug was re-administered in the presence of continued use of the object drug?'	+1	-2	0
7	'Are there reasonable alternative causes for the event?'			
8	'Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?'	+2	-1	0
9	'Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?'	-1	+1	0
10	'Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?'	+1	0	0
Total Score		+1	0	0
Highly Probable: >8, Probable: 5- 8, Possible: 2- 4, Doubtful: <2				
"A NO answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation."				

Conclusions

Different methods have been used to assess the causality of adverse events but to date, no single method is universally used due to some disadvantages. The present article gives a brief overview of only important methods for causality assessment use in daily pharmacovigilance activities. This article will be useful for the drug safety physicians and industry personnel in causality assessment.

Acknowledgment

None

Conflict of Interest

The author declares that there is no conflict of interest.

References

- Arimone, Y., Bégaud, B., Miremont-Salamé, G., Fourrier-Réglat, A., Molimard, M., Moore, N., & Haramburu, F. (2006). A new method for assessing drug causation provided agreement with experts' judgment. *Journal of clinical epidemiology*, 59(3), 308–314.
- Bégaud, B., Evreux, J. C., Jouglard, J., & Lagier, G. (1985). Imputabilité des effets inattendus ou toxiques des médicaments. Actualisation de la méthode utilisée en France [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Thérapie*, 40(2), 111–118.
- Benichou, C., Danan, G. (1992). Causality assessment in the European pharmaceutical industry: presentation of the preliminary results of a new method. *Drug Information Journal*, 26(4), 589-592.
- Curtin, F., & Schulz, P. (2011). Assessing the benefit: risk ratio of a drug--randomized and naturalistic evidence. *Dialogues in clinical neuroscience*, 13(2), 183–190.
- Danan, G., & Benichou, C. (1993). Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *Journal of clinical epidemiology*, 46(11), 1323–1330.
- Dangoumau, J., Evreux, J. C., & Jouglard, J. (1978). Méthode d'imputabilité des effets indésirables des médicaments [Method for determination of undesirable effects of drugs]. *Thérapie*, 33(3), 373–381.
- Ennis, M., Ohmann, C., Lorenz, W., Zaczek, R., & Schöning, B. (1988). Prediction of risk for pseudoallergic reactions and histamine release in patients undergoing anaesthesia and surgery: a computer-aided model using

independence-Bayes. *Agents and actions*, 23(3-4), 366–369.

Gawai, P. P. (2020). Introduction and evaluation of Pharmacovigilance for beginners. *International Journal of Scientific Reports*, 6(10), 425-432.

Horn, J. R., Hansten, P. D., & Chan, L. N. (2007). Proposal for a new tool to evaluate drug interaction cases. *The Annals of pharmacotherapy*, 41(4), 674–680.

Hoskins, R. E., & Mannino, S. (1992). Causality assessment of adverse drug reactions using decision support and informatics tools. *Pharmacoepidemiology and Drug Safety*, 1(5), 235-249.

Hutchinson, T. A. (1991). Computerized Bayesian ADE assessment. *Drug Information Journal*, 25(2), 235-241.

Hutchinson, T., Dawid, A., Spiegelhalter, D. (1991). Computerized aids for probabilistic assessment of drug safety: A spreadsheet program. *Drug Information Journal*, 25(1), 29-39.

Kramer, M. S., Leventhal, J. M., Hutchinson, T. A., & Feinstein, A. R. (1979). An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use. *JAMA*, 242(7), 623–632.

Macedo, A. F., Marques, F. B., Ribeiro, C. F., & Teixeira, F. (2005). Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel. *Pharmacoepidemiology and drug safety*, 14(12), 885–890.

Miremont-Salamé, G., Théophile, H., Haramburu, F., & Bégaud, B. (2016). Causality assessment in pharmacovigilance: The French method and its successive updates. *Thérapie*, 71(2), 179–186.

Naidu R. P. (2013). Causality assessment: A brief insight into practices in pharmaceutical industry. *Perspectives in clinical research*, 4(4), 233–236.

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Janecek, E., Domecq, C., & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical pharmacology and therapeutics*, 30(2), 239–245.

Rehan, H. S., Chopra, D., & Kakkar, A. K. (2009). Physician's guide to pharmacovigilance: terminology and causality assessment. *European journal of internal medicine*, 20(1), 3–8.

Wiholm B. E. (1984). The Swedish drug-event assessment methods. Special workshop--regulatory. *Drug information journal*, 18(3-4), 267–269.