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REVIEW ARTICLE ON CAUSALITY ASSESSMENT IN PHARMACOVIGILANCE

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ABSTRACT

Adverse drug reactions (ADRs) are a major cause of morbidity, hospital admission, and even death. Hence it is essential to recognize ADRs and to establish a causal relationship between the drug and the adverse event. An adequate causality classification of ADRs, especially in institutions providing high complexity assistance, may contribute to their early recognition, prevention of recurrence and optimization of drug therapy, thus improving the quality of patient care. There are some available tools with applicability for this classification, as algorithms, probabilistic approaches and global introspection methods. The World Health Organization-Uppsala Monitoring Center (WHO-UMC) system has been considered one of the most adequate method for establishing causal relationship in hospitalized patients.

KEYWORDS: Adverse drug reactions, causality assessment, pharmacovigilance.

INTRODUCTION

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug related problem.[1] These adverse drug reactions (ADRs) not only add to the suffering of patients but also increase morbidity and mortality along with a financial burden on society.[2] The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts.[3] In the last decade, there has been an increase in reporting of adverse events.[4] However, establishment of a causal relationship between the drug and the adverse event is a challenge and carries utmost importance in the current scenario of emerging adverse events.[4] In current medical practice in emerging countries,

many health-care professionals (HCP) are still unaware of adverse drug reactions (ADR) reporting process or importance of causality assessment. A major cause of morbidity increased hospital admissions has been directly linked to ADRs.[4]

The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Center (WHO-UMC) and the Naranjo probability scale are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology.[4]

METHODS OF CAUSALITY ASSESSMENT

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s).[5] Causality assessment of ADRs may be undertaken by clinicians, academics, the pharmaceutical industry and regulators, and in different settings, including clinical trials.[5] We describe here three broad categories of various methods of causality assessment: expert judgment/global introspection, algorithms and probabilistic methods (Bayesian approaches).[6] Expert judgments are individual assessments based on previous knowledge and experience in the field using no standardized tool to arrive at conclusions regarding causality. Algorithms are sets of specific questions with associated scores for calculating the likelihood of a cause-effect relationship. Bayesian approaches use specific findings in a case to transform the prior estimate of probability into a posterior estimate of probability of drug causation. The prior probability is calculated from epidemiological information and the posterior probability combines this background information with the evidence in the individual case to come up with an estimate of causation. As a result of Problems of reproducibility and validity, no single method is universally accepted. Reproducibility ensures an identical result, regardless of who the user is, and when he uses it. Validity means the ability of the method to distinguish between cases where the drug is responsible and cases where it is not.[7]

EXPERT JUDGEMENT/GLOBAL INTROSPECTION

In expert judgment or global introspection, an expert expresses a judgment about possible drug causation after having taken into account all the available and relevant information on the considered case.[8] The World Health Organization-Uppsala Monitoring Center (WHOUMC) system is a global introspection method, used for causality assessment, based on expert judgment, though delimited by specific criteria.[9]

World Health Organization (WHO) – Uppsala Monitoring Centre (UMC) causality assessment criteria

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.[10] The various causality categories are listed in Table 1.

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with plausible time 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 laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

ALGORITHMS

An algorithm is a problem-specific flow chart with step-by-step instruction on how to arrive at an answer.[11] Few algorithmic methods are

Kramer *et al.* method[12]

This algorithm applies to a single clinical manifestation occurring after administration of a single suspect drug. In cases where multiple drugs are involved, each is assessed separately. One of the advantages of this algorithm is its transparency. However, certain levels of expertise, experience andtime are required to use this method effectively.

Naranjo et al. method (Naranjo scale)[13]

It is used to assess causality in a variety of clinical situations using the conventional categories and definitions of „definite", „probable", „possible" and „doubtful". It consists of ten questions (Table 2) that are answered as „yes", „no", „unknown (don"t know)". The event is assigned to a probability category based on the total score. A total score of ≥ 9 is „definite", „probable" is 5–8, „possible" 1–4 and „doubtful" ≤ 0. This scale is intended to assess the likelihood of an ADR associated with only one drug, not for adverse drug events resulting from interactions between two drugs. The Naranjo scale does not address the main points that are necessary in causality evaluation of potential drug interactions.

Questions	Yes	No	Don't know
Presence of previous conclusive report on adverse reaction.	+1	0	0
Did adverse event appear subsequent to administration of suspected drug?	+2	-1	0
Did adverse event improve on drug discontinuation or on administration of specific antagonist?	+1	0	0
Did the adverse event reappear when the drug was re-administered?	+2	-1	0
Are there any alternative causes other than the suspected drug that could have caused the reaction on their own?	-1	+2	0
Did the adverse event reappear when a placebo was administered?	-1	+1	0
Was the incriminated drug detected in toxic concentrations in blood (fluids)?	+1	0	0
Did the adverse event worsen on increasing the dose or decreased in severity with lower doses?	+1	0	0
Past history of any similar reaction to the same or similar drugs.	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score 0– Doubtful 1–4 Possible, 5–8 Probable, ≥9 Definite			

Drug Interaction Probability Scale (DIPS)[14]

It was proposed by Horn et al. Drug Interaction Probability Scale (DIPS) is used to evaluate drug interaction cases. The DIPS uses ten questions that are answered „yes" or „no" to yield a

score estimating the likelihood of drug interaction. The questions concern the pharmacological properties of the drug, the possible role of other drugs and specific patient information. The method was developed to assist users in the assessment of drug-interaction-induced adverse outcomes and also to serve as a guide for the further study of potential drug interactions. Only requirement is the adequate knowledge of either the drugs involved and/or the basic mechanisms of interaction.

PROBABILISTIC OR BAYESIAN APPROACHES

Bayesian approaches use specific findings in a case to transform the prior estimate of probability into a posterior estimate of probability of drug causation. The prior probability is calculated from epidemiological information and the posterior probability combines this background information with the evidence in the individual case to come up with an estimate of causation.[15]

Bayesian Adverse Reactions Diagnostic Instrument (BARDI)

Bayesian Adverse Reactions Diagnostic Instrument (BARDI) was developed to overcome the numerous limitations associated with expert judgments and algorithms.[16] This BARDI is used to calculate the odds in favor of a particular drug causing an adverse event compared with an alternative cause.

These odds are referred to as the posterior odds. The posterior odds factor is calculated by considering six assessment subsets: one deals with background epidemiologic or clinical trials information (the prior odds) and the other five deal with case specific information (the likelihood ratios). The prior odds (PrO)factor is the ratio of the expected drug-attributable risk and the background risk of a certain adverse event in a population sharing basic characteristics with the patient being considered (such as medical condition). The five likelihood ratios (LRs) deal with any information of differential diagnostic value under the categories of patient history (Hi); timing of the adverse event with respect to drug administration (Ti); characteristics of the adverse event (Ch); drug dechallenge (De), which refers to any signs, symptoms, or occurrences after drug withdrawal; and drug rechallenge (Re) or readministration of the suspected causal drug(s).

The product of these factors is the posterior odds (PsO)[11]

$$PsO = PrO \times LR(Hi) \times LR(Ti) \times LR(Ch) \times LR(De) \times LR(Re)$$

CONCLUSION

The different methods for establishing a causal relationship between a drug and an ADR was understood. There are a number of methods for establishing a causal relationship between a drug and an adverse drug reaction and each of these methods have different advantage and disadvantage. No single method can provide reliable measures of the relationship between a drug and ADR because of various disadvantages. So a single method cannot be accepted universally for establishing the causal relationship.

REFERENCES

1. Rehan HS, Chopra D, Kakkar A; Physician's guide to pharmacovigilance: Terminology and causality assessment. European Journal of Internal Medicine, 2009; 20: 3-8.
2. Lazarou J, Pomeranz BH, Corey PN; Incidence of adverse drug reactions in hospitalized patients. JAMA, 1998; 279: 1200–1205.
3. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond), Oct., 2016; 16(5): 481-485. doi: 10.7861/clinmedicine.16-5-481. PMID: 27697815; PMCID: PMC6297296.
4. Naidu RP. Causality assessment: A brief insight into practices in pharmaceutical industry. Perspect Clin Res., Oct, 2013; 4(4): 233-6. doi: 10.4103/2229-3485.120173. PMID: 24312892; PMCID: PMC3835968.
5. Smyth RL, Peak M, Turner MA, et al. ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods. Southampton (UK): NIHR Journals Library; 2014 Jun. (Programme Grants for Applied Research, No. 2.3.) Chapter 5, Causality assessment of adverse drug reactions. Available from: https://www.ncbi.nlm.nih.gov/books/NBK262740/
6. Taofikat BA, Savovi J, Ernst E; Methods for Causality Assessment of Adverse Drug Reactions A Systematic Review. Drug Safety, 2008; 31(1): 21-37.
7. Danan G, Benichou C; 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. Jclinepidemiol., 1993; 46(1): 132-142.
8. Arimone Y, Miremont-Salamé G, Haramburu F, Molimard M, Moore N, Fourrier-Réglat A, Bégaud B. Inter-expert agreement of seven criteria in causality assessment of adverse drug reactions. Br J Clin Pharmacol, Oct, 2007; 64(4): 482-8. doi: 10.1111/j.1365-2125.2007.02937.x. Epub 2007 Aug 15. PMID: 17711539; PMCID: PMC2048553.
9. Rezende de Menezes R, Graciano Silva MDD, Pinho Ribeiro AL, Martins Pinto Filho M, Martinho GH, Carvalho Ferreira LE, Parreiras Martins MA. Causality assessment of

adverse drug reactions by applying a global introspection method in a high complexity hospital. Explor Res Clin Soc Pharm., Sep. 2, 2021; 3: 100064. doi: 10.1016/j.rcsop.2021.100064. PMID: 35480605; PMCID: PMC9032013.

10. World Health Organization (WHO), Uppsala Monitoring Centre [Internet]. The use of the WHO-UMC system for standardized case causality assessment. Available from:http://www.who-umc.org/graphics/4409.pdf.
11. Lanctot KL, Naranjo CA; Computer-assisted evaluation of adverse events using a Bayesian approach. J. Clin Pharmacol., 1994; 34: 142-147.
12. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR; An algorithm for the operational assessment of adverse drug reactions: I. Background, description, and instructions for use. JAMA, 1979; 242: 623-632.
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA et al.; A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther., 1981; 30: 239-245.
14. Horn JR, Hansten PD, Chan LN; Proposal for a new tool to evaluate drug interaction cases. Ann Pharmacother., 2007; 41: 674-680.
15. Hutchinson TA; Computerized Bayesian ADE assessment. Drug Inf J., 1991; 25: 235-241.
16. Naranjo CA, Lanctot KL; A consultant‟s view on the role of Bayesian differential diagnosis in the safety assessment of pharmaceuticals. Drug Inf J., 1992; 26: 593-601.