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A Review on Perplexities of Causality Assessment Tools in Adverse Drug Reaction Monitoring

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ABSTRACT

Medical care has changed over the last hundred years and the availability of various treatment options and better patient knowledge led to patient-oriented medicine with more concern toward patient references. Causality assessment is crucial to assess the role of the drug in event causation. Adverse drug reactions can cause serious consequences even death. Causality assessment tools (CATs) are framed to prevent associated events and to produce transparent and reliable results. Among vast number of CATs, the WHO-UMC algorithm aids simple methodology. In 1974 the concept of a “trigger” (or clue) to identify adverse events in the medical record, maybe a valid method for safety and quality improvement work in-home healthcare. Specific CATs like ALDEN, the M & V System, RUCAM, MONARCSi etc are generated to enhance the results and earlier detection of ADRs. The ADR monitoring program for safety of medicinal products must be supported by health care professionals.

INTRODUCTION

Medical care has changed over the last hundred years and the availability of various treatment options and better patient knowledge led to patient-oriented medicine with more concern towards patient references[1]. In 21st century the main objective of healthcare systems overall the world is to assure the quality, continuous efforts, and policies were framed to improve the system. Due to serious unexpected effects and incidents, health care quality was improved in earlier times.[2].

Adverse drug reactions (ADRs) are a universal affair and require major responsibility. ADRs affect both children and adults with different intensities and magnitude. Despite the effect on human costs, ADRs cause a major impact on the system and also stretched health care systems. Therefore, post-marketing surveillance of drugs in the market is important [3].

In hospitalized patients about 10-20%, at least one ADR has been reported. WHO initiated Pharmacovigilance or ADR monitoring as a joint effort from more than 70 countries, piled out from the thalidomide tragedy. Many countries cultivated the policy of pharmacovigilance after the thalidomide tragedy for early detection and prevention of drug-related events [4].

The calculated drug-related effects on inpatients are about 5-6% and the Adverse Drug Events (ADEs) have been estimated to USD 2284–5640 per patient (2000 values). The costs caused by ADRs are largely unknown and also the indirect costs are not included[5]. Drug-related morbidity and mortality (DRM) are highly extensive and cause excess baggage to patients and health care systems[6]. The occurrences of ADR are primarily of gender or advanced age, and also in case of inappropriate prescriptions or drug-drug interactions [7].In developing countries, Public Health Programmes are conducted by agencies and health workers with a wide variety of skills and expertise. Patients do not usually have direct contact with a physician as would be usual with PHPs in developed countries. Consequently, without good guidance and training programs for health-care workers, patients in developing countries could be exposed to higher risks of medication error and/or preventable ADRs. These risks could be related to disease, population characteristics, medicine, health-care, or the health-care system[9].

In India, state and central governments associate with researchers and agencies to be equipped with tools to improvise the healthcare quality due to the expeditious and

intensification of both chronic and acute diseases. Regardless of the number of studies and focus that were given to ADRs they still represent a clinically significant problem[10].

CAUSALITY ASSESSMENT

Adverse Drug Reaction (ADR) can be defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or modification of physiological function'[11]. In the current situation of the healthcare system, the detection and reporting of ADR are very important which can be achieved by the pharmacovigilance system. Pharmacovigilance is the science of the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problem. The crucial step involved in the Pharmacovigilance process after detection is assessment, which can be achieved by causality assessment [12].

Drug monitoring is important in the detection of lack of efficacy, detection and prevention of counterfeit and substandard products in clinical practice. The ADR monitoring program for safety of medicinal products must be supported by health care professionals. Health care professionals should bear in mind that when reporting an ADR that ADR reports are, for the most part, only suspected associations that a drug has caused a particular adverse event. Reporting an ADR does not imply a causal association between the drug and the adverse reaction. However, in a doubtful case, it is better to report than not to report [13]. Every drug therapy is deep-rooted with risks of ADRs and is modulated by factors including dose and frequency of administration, genotype, and pharmacokinetic characteristics of special populations, such as pediatric and geriatric patients and those with hepatic or renal impairment. ADRs (major) can be buffeting both the healthcare and economy[14].

All drugs are capable of producing adverse effects and whenever a drug is given risk is taken. The weight of therapeutic benefits is compared along with the significant risks associated with drug use[15]. Causality assessment refers to the assessment of relationship between drug treatment and occurrence of an adverse event. It is an important regimen of medical practice. When drugs are identified delinquent to use that can prevent the user from serious ill effects or further damages caused. In current scenario, finding this culprit drugs are important as pharma market is flooded with variety of drugs which are used by fellow human beings and are more likely to cause adverse effects rather than the actual effects. Safety of drugs should be the primary concern but to maintain the efficacy such norms are usually ignored. To

safeguard the patients the methods and tools of causality assessment are used[16]. Causality assessment of ADRs practices progressed in 1970s and 1980s along with pharmacovigilance[17].

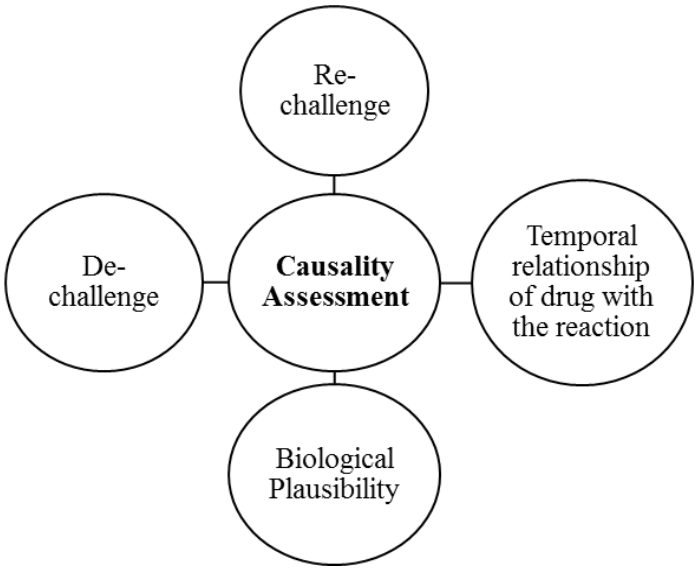

Figure No. 1: The major principles of causality assessment methods and tools

When de-challenge or re-challenge has occurred in the past, it is called positive pre-challenge or negative pre-challenge [18].

In pharmacovigilance, most of the illicit drug use effects are considered as Adverse drug reactions (ADR). When illeffects /unexpected effects due to drug consumption are seen, patients and healthcare professionals are asked to report, but in most cases, these effects are not particular for each drug and a drug rechallenge rarely occurs. To surmount these difficulties, the health care system has created innovative ideas and established causality assessment methods. Causality methods assess the risk-benefit evaluation of drugs in market thus it is an important tool in the pharmacovigilance system [19].

Causality assessment methods are majorly classified into three broad categories;

- Expert judgemental /Global introspection
- Probabilistic methods/Bayesian approaches
- Algorithms

No causality assessment methods are universally accepted due to the results of problems of reproducibility and validity. Each method is done accordingly with its criteria of causality evaluation [20].

GLOBAL INTROSPECTION

Global introspection is relatively one of the oldest and most popular causality assessment methods. The researcher/assessor evaluates every possible match with administered drugs and observed adverse events. The researcher observes and takes mental notes of the events. On the basis of considerable existing evidence, then the assessor decides the relatedness of drug action[21]. Here the assessments are solely based on expert knowledge and practice in the field, there is no standardized tool to conclude the causality[22].

Arizona Y et al. conducted a study to analyze and compare the judgments of five senior experts using global introspection about drug causation on a random set of putative adverse drug reactions and he concluded experts express marked disagreements when assessing drug causality independently and the overall agreement between experts was poor indicating global introspection as an unreliable method of causality assessment[23].

PROBABILISTIC METHODS (BAYESIAN APPROACHES)

A new and different approach of causality assessment, Bayesian Adverse Reaction Diagnostic Instrument (BARDI) was proposed based on the principle of Bayes theorem. The main objective of BARDI is to calculate the posterior odds that caused by a specific drug. This is the probability that a drug causes an adverse event given all the background and case information, divided by the probability that it did not cause the event given the same information. There is no particular limit to the factors that can be added while assessing thus the mathematics is complex[24]. The main contributing factor for the development of prototype computer programs such as MacBARBI-Q&A for the diagnosis of ADRs based on statistical methods is due to the earlier established computerized diagnostic systems for causality assessment. The main advantages of this modern method are the shortcoming of unaided clinical diagnosis has been recognized. Algorithms are pre-set questionnaires, as the method of assessment is vast and time-consuming. Humans cannot multitask in some situations, thus the chance of errors are high. So computerizing these techniques of assessment may help in decreasing the complexity and increase in acceptability [25]. Paradiso-Hardy F L et al. evaluated the extent to which ticlopidine causes hematological dyscrasias

using the Bayesian Adverse Diagnostic Instrument (BARDI), 91 cases are reviewed during the study. The author states, there is uncertainty associated with the BARDI[26].

ALGORITHMS

A standardized causality assessment tool is the need of the hour, due to the vast number of ADR cases reported. Framing a systematic and structured method of causality assessment can produce reliable and reproducible results. The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC), and the Naranjo Probability Scale is the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology. The above scales are structured, transparent, consistent, and easy to apply assessment methods [27].

Table No. 1: List of other published algorithms or decision aids

ALGORITHMS/DECISION AIDS	YEAR
KARCH ALGORITHM	1977
NARANJO ALGORITHM	1981
JONES ALGORITHM	1982
ADRAC GUIDELINES	1984
YALE ALGORITHM	1984
BEGAUD ALGORITHM	1985

During the 70s and 80s, the algorithms were formulated and developed to assess causality which consists of yes/no questions. Algorithms are structurally specific and designed primarily for causality assessment. Causality assessment algorithms must have a better between and within rater agreement than global introspection methods. Thus algorithms are a better method of causality assessment predictors that reduce the conflicts among different opinions of an expert panel and can classify the uncertainty in a semiquantitative way[29].

Sangha Ratna Bajracharya et al. are done a retrospective descriptive study which included 35 reported cases of ADRs in the Drug Information Unit (DIU) in a hospital. He assessed the ADR using the Naranjo scale, categorized ADRs into possible, probable (majority) and found the Naranjo scale to be an effective causality assessment tool[30].

The World Health Organisation (WHO) defines Pharmacovigilance as science related to the detection, assessment, understanding and prevention of adverse reactions towards a medicinal product or any other medicine-related problems in human beings. The main aim of establishing pharmacovigilance is to monitor and compute earlier reported ADRs and to reduce both mortality and morbidity rates[31]. The WHO 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' [32]. The main function of pharmacovigilance is the early detection and assessment of signals. Late signal detection can cause serious ill effects [33].

In 1974 the concept of a "trigger" (or clue) to identify adverse events in the medical record was introduced by Jick. To identify only adverse medication events in 1999 the use of triggers with manual record reviews was initially developed by the Institute for Healthcare Improvement (IHI)[34].

The trigger can be of many types including laboratory trigger, medical trigger, and clinician trigger. IHI formulated the method to ease manual patient case chart review by developing a Global Trigger Tool (GTT). GTT consists of 19 triggers to monitor the adverse events rates that can be mimicked in the hospital setting, without or with e-records[35]**.** Marléne Lindblad et al. conducted a study to develop a trigger tool (TT) for the identification of both AEs and no-harm incidents affecting adult patients admitted to home healthcare in Sweden and to describe the methodology used for this development. The study showed that adapted triggers with definitions and decision support, developed to identify AEs and no-harm incidents that affect patients admitted to home healthcare, maybe a valid method for safety and quality improvement work in home healthcare[36].

COMPARISON OF ALGORITHMS

Fabiana Rossi Varallo (2017) et al. studied the comparison between ten causality assessment algorithms and their data suggested that WHO-UMC algorithm is the most consistent for causal imputation of hospital ADR that affected patients admitted to an internal medicine unit of a medium complexity hospital. The tool is used during post-marketing surveillance which helps in finding the relatedness of adverse events and better reproducibility between judges opinions [37].Beniwal R (2019) et al conducted a cross-sectional hospital-based study. A total of 200 consecutive patients with Cutaneous adverse drug reactions (CADRs) were evaluated

using WHO-Uppsala Monitoring Centre (UMC) and Naranjo scale and he concluded the WHO-UMC method is easier to apply and produced reliable and reproducible results [38].Renuka P Munshi (2014) et al. found WHO-UMC is easier and less time consuming than the Naranjo scale[39].MacedoAF (2006) et al. did a study based on expert panel assessed causality of adverse reports by using the WHO global introspection (GI) and also the same reports using 15 published algorithms. 500 ADRs were studied and he concluded that Algorithms do not replace GI and are not definite alternatives in the individual causality assessment of suspected ADRs[40]. Ravi Goyal (2019) et al compared the three methods of causality assessment of adverse drug reactions to antihypertensive drugs using WHO-UMC, Naranjo's algorithm, and VCAT method. This study showed excellent agreement between Versatile Causality Assessment Tool (VCAT) method and WHO-UMC method, indicating that VCAT method is a better-standardized tool of causal assessment [41].

SPECIFIC TOOLS

a) The Algorithm for Drug Causality for Epidermal Necrolysis (ALDEN) is used for SJS/TEN causality assessment[42].

b) RUCAM (RousselUclaf Causality Assessment Method) or its previous synonym CIOMS (Council for International Organizations of Medical Sciences) is a well-established tool in common use to quantitatively assess causality in cases of suspected drug-induced liver injury (DILI) and herb induced liver injury (HILI) [43].

c) The M & V System of assessment of causality in drug-induced liver injury was developed by Drs. V.A.J. Maria and R.M.M. Victorino (Faculty of Medicine, Lisbon, Portugal) in an attempt to improve upon the RUCAM system, by the addition of other clinical elements and by simplifying and changing the relative weight of elements in the assessment of causality[44].

d) The MONARCSi exploratory causality decision support tool is a novel drug-event pair causality assessment method that combines selected parts of Naranjo's original score with aggregate feature weights determined by safety professionals and a logistic function[45].

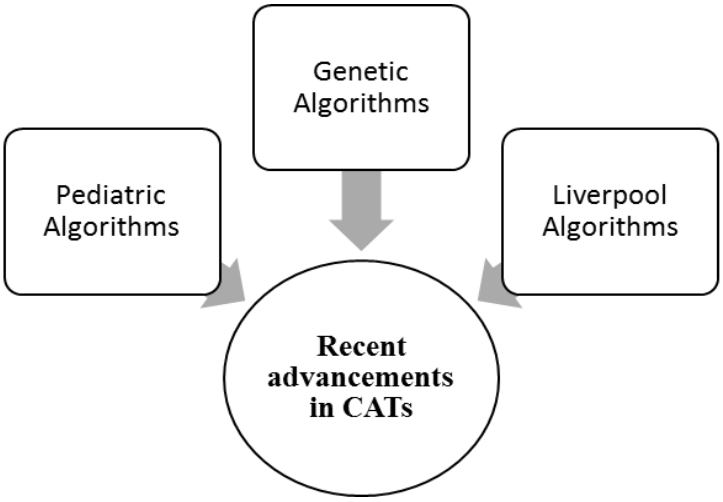

Figure No. 2: Recent advancement in causality assessment tools (CATs) [46].

LIMITATIONS

Causality assessment methods should be universally accepted, no gold standard of causality assessment tools are available thus they suffer a major drawback to verify and invalidate the causality. Thus by the globalization of drug monitoring helps in wider acceptance of one method as it would help to understand better how and why a particular assessment was reached[47]. No method of causality assessment is considered to be complete or reproducible. Only some methods take account of the actual relatedness and occurrence of an event. The different classification and methods of algorithms do produce wide disagreement and confusion thus decreasing its reliability[48]. Naidu RP et al briefed the limitations of causality assessment to the difficulty in reaching the same results with the given same information. He also points out this causality assessment forces the assessor to explain the method of obtaining results, the assessor is also obliged to complete the assessment with any theory or assessment. The assessor should also balance the effect of suspected ADRs against the probability of an alternative drug caused it[49].

DISCUSSION

Methodological challenges should be offered after surveilling the adverse effects of drugs. Potential ADRs should be considered by physicians for differential diagnosis. Ineffective medicines are no longer indicated and medicines should be deprescribed. For every minor ailment, physicians should not prescribe medications, which enhances the chance of developing ADRs or it can be due to the effect of other co-prescribed medications. When

expected clinical outcomes are not attained the best way is to avoid the administration of new multiple drugs. Drugs are one of medicine's most important therapeutic tools and are constantly proliferating. It is no surprise that the surveillance of their adverse effects should offer methodological challenges[50].

When a healthcare professional concentrates on pinpointing adverse effects of drugs that can prevent future risks to the patient. Pharmacists should provide patients with health education and counseling. Whenever there is a benefit of drug therapy and the possibility of risks is also high, providing therapy with minimal risk with the least cost should be the fundamental criteria [51].

CONCLUSION

Healthcare professions are mainly dealing with health disciplines, but clinical prevention and population health services are also elemental. Thus admixing these practices along with academics or educational curricula by continuous education and training programmes helps in seeking the goal[52].In clinical practice, enhancement of public health and strategies for examining and monitoring drug safety is imperative. So establishment and practice of pharmacovigilance in systematic manner are important. The nature of reporting ADRs by both healthcare professionals and patients should be encouraged[53]. Deprescribing of drugs should be followed when drugs are no longer indicated or ineffective. Clinicians should assess ADRs as part of every differential diagnosis [54]. Pharmacists are custodians of drugs and especially clinical pharmacists can play a vital role in preventing the ADRs and optimal management of ADR events.

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