Abstract
Causality assessment essentially means finding a causal association or relationship between a drug and a drug reaction. Identifying the culprit drug or drugs can be lifesaving or helpful in preventing the further damage caused by the drug to our body systems. In dermatology practice, when it comes to cutaneous adverse drug reaction, this is much more important and relevant because many aetiologies can produce a similar cutaneous manifestation. There are multiple criteria or algorithms available as of now for establishing a causal relationship in cases of adverse drug reaction (ADR), indicating that none of them is specific or complete. Most of these causality assessment tools (CATs) use four cardinal principles of diagnosis of ADR such as temporal relationship of drug with the drug reaction, biological plausibility of the drug causing a reaction, dechallenge, and rechallenge. The present study reviews some of the established or commonly used CATs and its implications or relevance to dermatology in clinical practice.

Key Words: Causality assessment, causality assessment tool, cutaneous adverse drug reaction

Introduction
Causality assessment essentially means finding a causal association or relationship between a drug and a drug reaction. It is an evaluation of the likelihood that a particular treatment is the cause of an observed adverse event (AE).[1] This is an important and challenging part of pharmacovigilance, in which attempts are made to find out the exact drug responsible for causing drug reaction. This is important in clinical practice as more and more drugs are flooding the market and are used by our patients and more likely to cause side effects besides its effects. In the pursuit of efficacy, safety of these drugs is usually ignored. As the safety of the patients is more important than efficacy, identifying the culprit drugs becomes much more essential. The principles and methods of causality assessment or causality assessment tool (CAT) help clinicians to identify the culprit drugs. There are multiple criteria or algorithms available as of now for establishing a causal relationship in cases of adverse drug reaction (ADR), indicating that none of them is specific or complete. The present study reviews some of the established or commonly used CATs and its implications or relevance to dermatology in clinical practice.

Need for Causality Assessment in Dermatology
Causality assessment is important in every discipline of medical practice. Identifying the culprit drug or drugs can be lifesaving or helpful in preventing the further damage caused by the drug to our body systems. In dermatology practice, this is much more important and relevant because many aetiologies can produce a similar cutaneous manifestation. Many a time, multiple drugs are taken by the patient and it is difficult to ascertain the exact drug responsible for causing a drug reaction.

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and when the underlying disease is capable of producing the same cutaneous manifestation as caused by the drug. Unfortunately, there are no specific diagnostic tests. Although histopathology can provide a clue for the diagnosis of drug reaction, it is not sufficient to point toward a particular drug. Tests such as intradermal tests or patch tests require further standardisation in terms of test formulation, timings of the test, etc., and are thus inadequate. However, identifying the exact drug is of paramount importance as it directly influences decision-making by a clinician either to continue or to withdraw the likely drugs. This can be very critical in some circumstances and thus establishing causality with near perfection is desirable. In such circumstances, we require the help of some time-tested CATs as outlined in this review.

Causality assessment can be undertaken by clinicians, pharmaceutical industry people, academicians, and regulatory authorities in different settings including clinical trials.[2]

**Principles of Causality Assessment**

All causality assessment methods or tools follow 4 cardinal principles of diagnosis of ADR: (i) temporal relationship of drug with the drug reaction, (ii) biological plausibility, (iii) dechallenge, and (iv) rechallenge. When dechallenge or rechallenge has occurred in the past, it is called positive prechallenge or negative prechallenge.[3]

A patient with diarrhoea is given metronidazole and develops a fixed-drug reaction (FDR) after 2 days of starting metronidazole. As the patient develops suspected drug reaction, metronidazole is stopped and the patient is put on antihistamines and topical corticosteroids. The patient recovers well after stopping the drug albeit with postinflammatory hyperpigmentation (successful dechallenge). After 3 months, the patient takes metronidazole on his own and presents to a dermatologist with the onset of FDR at the same site after 2 days of metronidazole intake, dermatologist will diagnose metronidazole as the cause for FDR with greater confidence (successful rechallenge). As FDR started after the drug was initiated, there is a clear-cut temporal correlation of the drug with the drug-related cutaneous manifestation. To the best of our knowledge about metronidazole, it is biologically plausible that metronidazole can cause FDR. Thus, abovementioned example considers all cardinal aspects of causality of ADR. Most of methods that are listed below are based on these cardinal principles that help clinicians to arrive at a particular conclusion with regard to the likelihood of a suspected drug causing a given drug reaction.

**Difficulties or Challenges in Developing Causality Assessment Methods**

However, when a patient of a suspected viral infection of upper respiratory tract develops a maculopapular rash after 2 days of antibiotic use, it is difficult to know whether the rash is due to viral infection or due to a drug as both of them are temporally related and are plausible to cause a rash. Dechallenge of both of them can result in successful resolution of the rash while rechallenge is difficult to perform ethically. For such practical reasons, we require some other methods for establishing causality. Thus, difficulties in causality assessment are incomplete information of ADR, polypharmacy, variable clinical responses, poor understanding of biological plausibility, other alternative causes, and lack of training to clinicians. Some of these factors such as variable clinical responses and biological plausibility are genetically or immunologically determined and thus not much can be done about them. Identifying causality in polypharmacy is a tricky situation as dechallenge–rechallenge analysis is not possible or permitted for every individual drug that is a part of polypharmacy. Furthermore, there are no objective immunological tests in allergic drug reactions as drug is an incomplete antigen or hapten. Due to these factors, most of the causality assessment methods mentioned below are not full-proof.

**Methods of Causality Assessment**

Causality assessment methods are broadly classified into clinical judgment or global introspection, algorithms, and probabilistic methods. The total number of methods as included in the above classification is 34 methods based on the results of a systematic review.[6] Needless to say, all these methods require inputs or information by a clinician and thus they are useless unless a clinician gives his/her opinion on a given case.

**Clinical Judgment/Global Introspection**

As far as a clinician is concerned, clinical judgment obviously is helpful in identifying the relationship likelihood in actual clinical practice. Knowledge and experience of the clinician plays a very important role in performing global introspection. Dermatologists are at an advantage because many ADRs encountered in dermatology practice are seen on the skin surface and dermatologists are familiar with the pattern of various cutaneous drug reactions. Some of the drugs such as dapsone, phenytoin sodium, and carbamazepine are so notorious to produce some of severe cutaneous adverse drug reaction (CADR) in dermatology practice that dermatologists by their prior experience and knowledge are unlikely to miss the ADR and most of the times causality assessment in individual cases can be very accurate. Sharing of the information about the suspected case of drug reaction with colleagues or experts
through e-mail or WhatsApp or with the help of newer tools of communication has helped clinicians in general and dermatologists in particular to improve their clinical acumen or judgment. This has added to the likelihood of establishing a causal relationship in actual clinical practice.

One of the limiting factors in clinic-based causality assessment in dermatology practice is long latency of many CADRs. Examples of CADR with long or unknown latency include lichenoid drug reaction, psoriasiform drug reaction, and drug-induced pigmentation. In such a scenario, an improvement in suspected drug manifestation after drug withdrawal is difficult to evaluate as they may resolve after a long period or may not resolve at all. Thus, in dermatology practice, when drug reaction is acute or a number of drugs are very few, clinical judgment is possible, whereas when CADRs are slow to develop and when a number of drugs are more and underlying disease can produce a similar manifestation, clinical judgment or global introspection has limits. Furthermore, there are individual variations in causality assessment because of differences in knowledge and experience of clinicians. To impart some degree of uniformity, two methods have been suggested. These are Swedish method and World Health Organisation–Uppsala Monitoring centre (WHO–UMC) scale, which are clinic-based or clinical judgment-based CAT. Of these, the WHO–UMC scale which is based on the knowledge of clinical pharmacology is widely used in individual case assessment.

### Algorithmic Methods

Algorithms are simple and mostly questionnaire-based CAT in which scores are assigned to answers of its questions and the given ADR is categorised into categories such as definite, probable, possible, or unlikely. Some of the commonly available criteria used across the globe are Naranjo’s algorithm, Kramer algorithm, Jones algorithm, Karch algorithm, Bégaud algorithm, Adverse Drug Reactions Advisory Committee guidelines, etc. Many of them are also modified. Algorithms are inflexible and have been designed to reduce intra-rater and inter-rater variability to make this CAT more reproducible and valid. The discussion about many of these algorithms is outside the scope of this article, details of Naranjo’s scale or algorithm are given in Table 2.

When questions in the above questionnaire are answered by a clinician, a score is obtained. Based on this score, ADR is categorised into the following four categories: $\geq 9$ = definite ADR, $5–8$ = probable ADR, $1–4$ = possible ADR, and $0$ = doubtful ADR.

### Bayesian Methods or Probabilistic Methods

Bayesian methods follow different and complex statistical approach for finding the cause of a drug reaction. It includes Bayesian Adverse Reaction Diagnostic Instrument (BARDI). BARDI considers prior probability of the drug in question as obtained by prior epidemiologic studies (prior probability or prior knowledge) combining it with the likelihood ratio as obtained by a given case information (current case information provided by a clinician). In short, it calculates so-called posterior probability or posterior odds of the drug causing a given drug reaction. Prior odds factor is the ratio of expected drug attributable risk to the background risk of a certain AE. The likelihood ratio is calculated for history, timing of the AE with regard to drug, characteristics of the event, dechallenge referring to signs and symptoms after drug withdrawal, and rechallenge.

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### Table 1: World Health Organisation-Uppsala Monitoring Centre causality assessment scale

| 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 or likely | Event or laboratory test abnormality, with reasonable 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 reasonable 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 or 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 |
Bayesian methods use Bayesian spreadsheets which are complex and cumbersome for a clinician as it involves complex statistical calculation. These are now converted to easy computer-aided programs such as Mac-BARDI Q and A.\[13\] In dermatology, this program is well developed for sulfonamide-related exanthematous drug reactions and anticonvulsant-induced hypersensitivity reactions.

Thus, given our limitation about understanding the knowledge of CADR and drugs and lack of objective diagnostic tests for the diagnosis of CADR, CATs as outlined above should be used in clinical practice accepting their pros and cons. There is no substitute for clinical observations and experience of the clinicians when it comes to identify the cause of drug reaction. Safety-conscious physicians can help in reducing mortality and morbidity associated with ADRs using their clinical acumen assisted by some CATs.

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 2: Naranjo’s algorithm or scale**

| Question                                                                 | Yes | No | Don’t know or not done |
|--------------------------------------------------------------------------|-----|----|------------------------|
| Are there previous conclusive reports on this reaction?                  | +1  | 0  | 0                      |
| Did the adverse event appear after the suspected drug was given?         | +2  | −1 | 0                      |
| Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? | +1  | 0  | 0                      |
| Did the adverse reaction appear when the drug was readministered?        | +2  | −1 | 0                      |
| Are there alternative causes that could have caused the reaction?        | −1  | +2 | 0                      |
| Did the reaction reappear when a placebo was given?                     | −1  | +1 | 0                      |
| Was the drug detected in any body fluid in toxic concentrations?         | +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                      |

**What is new?**

While dermatologists have been doing causality assessment based on their individual knowledge and wisdom, the current article has reviewed some of the lesser used causality assessment tools like Naranjo’s scale and WHO-UMC causality assessment tools. These algorithms are clinic-based tools offering some objectivity and lesser inter-individual variations. Some of methods like Bayesian Adverse Reaction Diagnostic Instrument (BARDI) uses complex statistical methods requiring clinical inputs from a clinician and prior epidemiologic information of suspected offending drug. These causality assessment tools will help in better reporting of CADR by a dermatologist for effective pharmacovigilance approach to a drug reaction.

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