Identifying Causality

for Design of an Effective Pharmacovigilance Database Model

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The aim of this research project is –

1. **To clearly define the methods by which SAFETY (causality of adverse reactions) is attributed to a drug**

   This is important for understanding the information or data that must be gathered by a database if it is to provide a strong signal when adverse reactions occur.

2. **To clearly define the methods by which EFFICACY (causality of desired reactions) can be attributed to a drug**

   This may involve assessing the change in incidence of the target illness.

3. **To design a database entity relationship model for gathering and storing the data**

   An ER model must be carefully designed to all the required information for its sole purpose of signalling drug safety and efficacy, whilst maintaining –

   a) Simplicity

   b) User authentication

   c) Accessibility (for every country)

1. Methods for Assessing Causality

The total number of methods for establishing causality between a drug and its effects is 34 methods based on the results of a systematic review. These methods are called Causality Assessment Tools (CATS). "The principles and methods of causality assessment or causality assessment tool (CAT) help clinicians to identify the culprit drugs."

Ref : Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: A systematic review. Drug Saf. 2008;31:21–37. [PubMed] [Google Scholar] [Ref list]

However, all of these methods can be reduced to 4 cardinal principles **-**

> *"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."*
>
> **1. Temporal Relationship**
>
> **2. Biological plausibility**
>
> **3. Dechallenge**
>
> **4. Rechallenge**

“When dechallenge or rechallenge has occurred in the past, it is called positive prechallenge or negative prechallenge.”

Main Ref : "Causality or Relatedness Assessment in Adverse Drug Reaction and Its Relevance in Dermatology"

2. Difficulties in Attributing Causality

Difficulties in causality assessment arise from

1. Incomplete information of ADR,
2. polypharmacy – when the user took multiple drugs,
3. variable clinical responses,
4. poor understanding of biological plausibility – not understanding the mechanism – previous studies not clear about the effects of the drug,
5. other alternative causes – same symptoms can be attributed to other causes, and
6. lack of training to clinicians.

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.

Long latency of many adverse reactions is a problem since the reaction does not manifest straight away.

> *"When drug reaction is acute or a number of drugs are very few, clinical judgment is possible, whereas when adverse reactions 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."*

3. Causality Assessment Method Used by WHO at the Upsala Monitoring Centre

The WHO–UMC scale which is based on the knowledge of clinical pharmacology is widely used in individual case assessment.[4] The WHO–UMC is shown in Table 1 below.

Basic criteria for causality of these methods are knowledge about pharmacology and previous information of ADR, association of AE (time, place, etc.) and a drug, biological plausibility and exclusion of other causes.

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

1. Abnormal test
2. Temporal association
3. No other drugs
4. No other diseases / no diseases with these symptoms
5. Recovery following withdrawal
6. Plausible biological mechanism
7. Recognised effect of the drug
8. Symptoms resume after rechallenge

Ref : *The Use of the WHO-UMC System for Standardised Case Causality Assessment.* [Last accessed on 2017 Jun 25]. Available from: https://www.who-umc. org/media/2768/standardised-case-causality-assessment.pdf . Last updated on 2017 Jun 06.

4. Criteria commonly used across the globe to determine causality

Some of the commonly available criteria used across the globe are Naranjo's algorithm,[i] Kramer algorithm,[ii] Jones algorithm,[iii] Karch algorithm,[iv] Bégaud algorithm,[v] Adverse Drug Reactions Advisory Committee guidelines,[vi]

Refs :

i. 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;30:239–45. [PubMed] [Google Scholar]

ii. 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;242:623–32. [PubMed] [Google Scholar]

iii. Jones JK. Adverse drug reactions in the community health setting: Approaches to recognizing, counseling, and reporting. *Fam Community Health.* 1982;5:58–67. [PubMed] [Google Scholar]

iv. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. *Clin Pharmacol Ther.* 1977;21:247–54. [PubMed] [Google Scholar]

v. Bégaud B, Evreux JC, Jouglard J, Lagier G. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. *Therapie.* 1985;40:111–8. [PubMed] [Google Scholar]

vi. Mashford ML. The Australian method of drug-event assessment. Special workshop – Regulatory. *Drug Inf J.* 1984;18:271–3. [PubMed] [Google Scholar]

5. Naranjo's Algorithm

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

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: ≥9 = definite ADR, 5–8 = probable ADR, 1–4 = possible ADR, and 0 = doubtful ADR.

6. Bayesian Assessment

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.*

Ref :

Hutchinson TA. Computerized Bayesian ADE assessment. *Drug Inf J.* 1991;25:235–4. [Google Scholar]

Lanctôt KL, Naranjo CA. Computer-assisted evaluation of adverse events using a Bayesian approach. J Clin Pharmacol. 1994;34:142–7. [PubMed] [Google Scholar]