CAUSALITY SCALE

in

PHARMACOVIGILANCE

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Causality assessment in pharmacovigilance is a crucial process aimed at determining the likelihood that a particular drug is responsible for an adverse event. This assessment is essential for ensuring patient safety, optimizing therapeutic efficacy, and managing risks associated with drug therapy. Given the complexity and variability of drug reactions, standardized methods and scales have been developed to provide a systematic and consistent approach to causality assessment. These scales help in evaluating the temporal relationship, de-challenge and re-challenge effects, alternative causes, and other relevant factors to draw conclusions about the causality between drug intake and adverse events. Below, we explore some commonly used causality assessment scales in pharmacovigilance:

1) World Health Organization (WHO) Causality Assessment

This method classifies causality into categories such as certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable based on the evidence and criteria specific to each category.The WHO scale categorizes causality into the following categories:

- Certain: A clinical event with a plausible time relationship to drug intake, not explained by disease or other drugs, and a positive re-challenge (if applicable).
- Probable/Likely: A clinical event with a reasonable time relationship to drug intake, unlikely to be due to disease or other drugs, and a positive de-challenge response.
- Possible: A clinical event with a reasonable time relationship to drug intake, but could also be explained by disease or other drugs.
- Unlikely: A clinical event with a temporal relationship to drug intake that makes a causal relationship improbable.
- Conditional/Unclassified: A clinical event with insufficient information to make a proper assessment.
- Unassessable/Unclassifiable: A clinical event that cannot be judged due to insufficient or contradictory information.

2) Naranjo Scale

A widely used questionnaire-based method that assigns a numerical score to determine the probability of an adverse drug reaction, categorizing the relationship as definite, probable, possible, or doubtful. The Naranjo scale is a questionnaire designed to estimate the probability of adverse drug

reactions. It consists of 10 questions with answers of "Yes," "No," or "Do not know," and each answer has a different score. The total score categorizes the causality:

- Definite: Score > 9
- Probable: Score5-8
- Possible: Score1-4
- Doubtful: Score ≤ 0

3) European Medicines Agency (EMA) Algorithm

A structured approach that considers factorssuch as the temporal association, de-challenge/re- challenge information, and alternative explanations to classify the causality of adverse events. The EMA algorithm also provides a structured approach to causality assessment:

- Certain: Clinical event with a clear temporalassociation and no alternative explanations.
- Probable: Eventwith a reasonable time relationship and unlikely to be causedby other factors.
- Possible: Eventthat could be due to the drug or other factors.
- Unlikely: Event with a time relationship that makes causality improbable.
- Unassessable:Insufficient data to assess.

4) Kramer Algorithm

A detailed algorithm that incorporates multiple factors, including temporal relationship, dose- response relationship, and exclusion of other causes, to assess the causality of adverse drug reactions. The Krameralgorithm is a detailed, algorithmic method that considers various factors:

- Temporal relationship between drug intake and event
- De-challenge and re-challenge information
- Presence of alternative causes
- Drug levels and dose-response relationships

Key Steps in Causality Assessment

1. Data Collection: Gather comprehensive information about the adverse event, patient's medical history, and drug exposure.

2. Temporal Association: Determine the time relationship between drug administration and the onset of the adverse event.
3. De-challenge and Re-challenge: Assess if the event resolves upon discontinuation of the drug (de-challenge) and recurs upon re-administration (re-challenge).
4. Alternative Explanations: Evaluate other possible causes of the adverse event.
5. Consistency with KnownInformation: Compare the event with known pharmacological and toxicological profiles of the drug.

Conclusion

Each of these scales has its own strengths and limitations, and their application may vary depending on the specific clinical scenario and available information. Understanding and correctly applying these scales is fundamental for healthcare professionals involved in pharmacovigilance to ensure accurate and reliable assessments of drug safety. Therefore, causality assessment is an essential process in pharmacovigilance to ensure patient safety and effective risk management. Utilizing standardized scales like the WHO, Naranjo, EMA algorithm, and Kramer algorithmhelps to provideconsistent and reliableevaluations of adverse drug reactions.

Example 1: WHO Causality Assessment

Case: A 45-year-old woman develops a severe skin rash after taking a new antibiotic.

Assessment:

- Certain: The skin rash appears within 24 hours of taking the antibiotic, resolves completely upon discontinuation, and reappears when the antibiotic is re-administered. There are no other medications or medical conditions that could explain the rash.
- Probable/Likely: The rash appears within 24 hours and resolves upon discontinuation of the antibiotic, but there is no re-challenge, and the patient is taking no other medications.
- Possible: The rash appears within 24 hours, but the patient is also taking another medication known to cause skin rashes, and discontinuation of the antibiotic alone doesn't resolve the rash.

- Unlikely: The rash appears three weeks after starting the antibiotic, or there are other more plausible explanations (e.g., another new medication, or an underlying skin condition).
- Conditional/Unclassified: The rash appears, but there is insufficient information about the timing, resolution, or other medications.
- Unassessable/Unclassifiable: The information provided is contradictory or insufficient to make any assessment.

Example 2: Naranjo Scale

Case: A 60-year-old man experiences nausea and dizziness after starting a new blood pressure medication.

Assessment:

- The adverse event appeared after the drug was administered: Yes (+2)
- The adverse reaction improved when the drug was discontinued or a specific antagonist was administered. Yes (+1)
- The adverse reaction appeared upon re-administration of the drug. Do not know (0)
- There are alternative causes (other than the drug) that could, on their own, have caused the reaction: No (+2)
- The reaction appeared when a place given: No (+1)
- The drug was detected in the blood (or other fluids) in concentrations known to be toxic. No (0)
- The reaction was more severe when the dose was increased or less severe when the dose was decreased: Do not know (0)
- The patient had a similar reaction to the same or similar drugs in any previous exposure: Yes (+1)
- The adverse event was confirmed by objective evidence: Yes (+1)

Total Score:8 (Probable)

Example 3: EuropeanMedicines Agency (EMA) Algorithm

Case: A 30-year-old woman develops liver enzyme abnormalities after starting an oral contraceptive.

Assessment:

- Certain: Liver enzyme levels were normal before starting the oral contraceptive, elevated significantly after starting the drug, returned

to normal upon discontinuation, and elevated again when re-challenged with the same contraceptive.

- Probable: Liver enzyme levels were normal before starting, elevated after starting, and returned to normal after stopping, but no re-challenge was performed. No other plausible cause was identified.
- Possible: Liver enzyme levels elevated after starting the contraceptive, but the patient also has a history of alcohol consumption, which could also explain the liver abnormalities.
- Unlikely: Liver enzyme levels elevated significantly two months after starting the contraceptive, and the patient also started another medication known to cause liver enzyme elevation at the same time.
- Unassessable: The patient reports elevated liver enzymes but has not provided information on other medications, alcohol consumption, or timing of the enzyme tests.

Example 4: Kramer Algorithm

Case: A 70-year-old man on a statin for cholesterol management reports muscle pain and weakness.

Assessment:

1. Temporal Relationship: The muscle pain started one week after starting the statin.
2. De-challenge: The muscle pain improved significantly upon discontinuation of the statin.
3. Re-challenge: The muscle pain returned upon restarting the statin.
4. Alternative Causes: No other new medications or underlying conditions that could explain the muscle pain.
5. Drug Levels and Dose-Response: Muscle pain correlates with high doses of the statin, and symptoms improve with a lower dose.

Conclusion: Based on the detailedassessment considering all these factors,the relationship between the statin and muscle pain can be classified as "Probable."

PRACTICING

Scenario 1: WHO Causality Assessment

Case: A 55-year-old man with a history of hypertension starts a new medication for blood pressure control. Two days after starting the medication, he develops a severe headache and nausea.

Questions:

1. Did the adverse event (headache and nausea) appear after the drug was administered?
2. Did the symptoms improve when the drug was discontinued?
3. Are there any other plausible causes(e.g., underlying conditions, other medications)?
4. Is there a clear temporal relationship between the drug intake and the onset of symptoms?

Scenario 2: NaranjoScale

Case: A 40-year-old woman is prescribed an antibiotic for a urinarytract infection. She develops a rash on her arms and legs three days after starting the antibiotic.

Questions:

1. Did the rash appear after the antibiotic was administered? (+2)
2. Did the rash improve when the antibiotic was discontinued? (+1)
3. Did the rash reappear when the antibiotic was re-administered? (+2)
4. Are there other potential causes for the rash? (-1)
5. Was the rash confirmed by objective evidence? (+1)
6. What is the total score, and how would you classify the causality?

Scenario 3: European Medicines Agency (EMA) Algorithm

Case: A 65-year-old woman starts a new medication for arthritis. After one month, she experiences significant weight gain and swelling in her legs.

Questions:

1. Is there a temporal association between the start of the medication and the onset of symptoms?

2. Did the symptoms improve after stopping the medication?
3. Are there any other factors that could explain the weight gain and swelling(e.g., dietary changes, other medications)?
4. How would you classify the causality (Certain, Probable, Possible, Unlikely, Unassessable)?

Scenario 4: Kramer Algorithm

Case: A 30-year-old man begins taking a new antidepressant. Two weeks later, he started experiencing severe insomnia and agitation.

Questions:

1. What is the temporal relationship between starting the antidepressant and the onset of insomnia and agitation?
2. Did the symptoms resolve upon discontinuation of the antidepressant?
3. Did the symptoms reappear when the antidepressant was restarted?
4. Are there any other potential causes for the insomnia and agitation?
5. Based on the Kramer algorithm, how would you classify the causality?

Scenario 5: WHO Causality Assessment

Case: A 70-year-old woman with diabetes is started on a new medication to control her blood sugar levels. After one week, she experiences severe hypoglycemia (low blood sugar).

Questions:

1. Is there a plausible time relationship between the medication and the hypoglycemia?
2. Did the hypoglycemia resolve upon discontinuation of the medication?
3. Are there any other potential causes for the hypoglycemia (e.g., diet changes, other medications)?
4. How would you classify the causality (Certain, Probable, Possible, Unlikely, Unassessable)?

Scenario 6: NaranjoScale

Case: A 50-year-old man is given a new pain medication for chronic back

pain. He develops gastrointestinal bleeding three days after starting the medication.

Questions:

1. Did the gastrointestinal bleedingappear after the pain medication was administered? (+2)
2. Did the bleeding improve when the medication was discontinued? (+1)
3. Did the bleeding reappear when the medication was re-administered? (+2)
4. Are there other possible causes for the bleeding (e.g., pre-existing gastrointestinal conditions, other medications)? (-1)
5. Was the gastrointestinal bleeding confirmed by objective evidence (e.g., endoscopy)? (+1)
6. What is the total score, and how would you classify the causality?