**Module-6**

Causality assessment:

The Adverse drug reactions once collected, and case processing done, the relationship between the suspected drug and the adverse event will be done with the help of causality assessment.

This step is entirely related to the Physician.

The causality provides a degree of likelihood to the relationship between a drug and an adverse reaction.

**The data to be assessed while doing causal assessment:**

* The time taken to the onset of adverse reaction after the drug intake.
* Does the reaction occurred or worsened after the drug is reintroduced.
* Does the reaction subsided or recovering after the drug is stopped.
* Has the patient previously exposed to the drug (in case of allergic reaction).
* Is the reaction occurring with respective to long term use of medication.
* Any other Alternative explanation like medical conditions, laboratory data which can explain the adverse reaction.
* Any other co suspect medications which can explain the adverse reaction.
* Is there a compatible biological or patho-physiological association between the suspected medicinal product and the adverse reaction.

For causality assessment, the terminology to understand:

Adverse event, adverse drug reaction, de-challenge, re-challenge, concomitant medications, suspect medications.

Adverse event and Adverse drug reaction already explained in the previous modules.

Dechallenge: Adverse reaction resolved or resolving after the drug is stopped or withdrawn.

Re-challenge: Adverse reaction restarted after reintroduction of the drug.

Re-challenge is not ethical.

How does the scale help:

* Is the relationship between medicine and event and how close it is.
* Was the adverse event caused by the suspected drug.

There are different types of causality assessment scales.

* WHO-UMC (World health organization-Upsala monitoring center) causality assessment scale.
* Naranjo ADR probability scale.
* Kramer scale
* European ABO system
* Karch & Lasangas Scale
* Bayesian network
* Yale Algorithm
* Spanish Imputation system

The most acceptable causality scale is WHO-UMC scale.

Most commonly used scale in USA is Naranjo ADR probability scale.

WHO-UMC causality 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 recognized pharmacological phenomenon) * Rechallenge satisfactory, if necessary |
| Probable / 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 / 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 |

Naranjo Causality scale:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Question | yes | no | Do not know | score |
| 1. Are there previous conclusive reports on this reaction? | +1 | 0 | 0 |  |
| 2. Did the adverse event appear after the suspected drug was administered? | +2 | -1 | 0 |  |
| 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 | 0 | 0 |  |
| 4. Did the adverse event appear when the drug was readministered? | +2 | -1 | 0 |  |
| 5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction? | -1 | +2 | 0 |  |
| 6. Did the reaction reappear when a placebo was given? | -1 | +1 | 0 |  |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 | 0 | 0 |  |
| 8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased? | +1 | 0 | 0 |  |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 | 0 | 0 |  |
| 10. Was the adverse event confirmed by any objective evidence? | +1 | 0 | 0 |  |

|  |  |
| --- | --- |
| Total Score | ADR Probability Classification |
| 9 | Highly Probable |
| 5–8 | Probable |
| 1-4 | Possible |
| 0 | Doubtful |

Both the causality scales are freely available online.

To decide whether the case is serious or not, the event should have

A few exercises for the causal assessment-based on WHO causal assessment.

1. A 40-year-old man with known history of diabetes and hypertension came with complaints of myalgia and after recent introduction of simvastatin for high cholesterol levels. The patient had used simvastatin for two months. The patient is on metformin and glimepiride for diabetes and telmisartan for hypertension. The simvastatin is stopped, and myalgia is slowly resolving.
2. What is the suspect drug?
3. What is the event?
4. What are concomitants in this scenario?
5. Is dechallenge positive?
6. How will you assess the causality in this case?
7. There is no past medical history mentioned and xxxxx patient received anastrozole at an unknown date for an unknown indication and the patient developed arthralgia and joint stiffness on an unknown date. No information available with outcome of the events.
8. What is the suspect drug?
9. Do we have timelines between event onset and therapy started date?
10. How will you assess the causality with the available data?
11. A 45-year-old patient recently diagnosed with high cholesterol levels and prescribed Atorvastatin. After few months the patient had got some infection and blood parameters showed leucopenia. The patient was treated symptomatically, and Atorvastatin is stopped. The event leucopenia started normalizing. Then the Atorvastatin reintroduced for high cholesterol levels, the patient again developed leucopenia. Suspecting the Atorvastatin, it was stopped completely and other hypolipidemic drug was prescribed.
12. How can you assess the WHO causality in this scenario
13. Does this case have Rechallenge positive.
14. What is the event in this case?

The cases designed only theoretically and based on the cases I came across during my clinical practice.

Further there will be exit examination for physicians while doing this module.