Causality Assessment

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Some Thoughts on Causality

- Causality or relatedness assessment
  - Determination of whether there is a reasonable possibility that the product is causally related to the adverse event. Causality assessment includes, for example, evaluation of temporal relationships, dechallenge/rechallenge information, association with (or lack of association with) underlying disease, presence (or absence) of a more likely cause, and biologic plausibility.
- Causality assessment is not required for spontaneous (unsolicited) reports that are serious and unexpected

WHY?

- Because they are presumed to be possibly related

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CIOMS on Causality

- “It should be emphasized that manufacturers should not separate out those spontaneous reports they receive into those that seem to themselves to be causally related to drug exposure and those they consider not causally related. A physician in making a spontaneous report to a manufacturer is indicating that the observed event may be due to the drug, i.e. the physician suspects that the event is a reaction.” (CIOMS I)

- As a practical matter, many companies do causality assessments on spontaneous reports as part of their signal analysis mechanisms.

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Causality on Individual Cases

- For regulatory reporting of individual cases
  - "… all spontaneous reports of serious unlabelled reactions made by medical professionals should be considered as CIOMS [i.e., expedited] reports. However, submission of such a report does not necessarily constitute an acceptance of causality by a manufacturer." (CIOMS I)
  - "For spontaneous reports, the applicant should assume that an adverse experience or fatal outcome was suspected to be due to the suspect drug or biological product (implied causality)." (FDA Guidance, 2001)

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How FDA Reviews Safety

Reviewer Guidance

Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2005
Good Review Practices

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072974.pdf

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FDA on Causality

- "For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g., stroke, pulmonary embolism).

- "Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with long - term follow-up, are usually needed to assess causality in such instances."

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Caveats

- It is important to distinguish the processes done by the FDA reviewer from the causality analyses of drug-related events often provided by investigators and sponsors.
- The analyses of drug-related AEs presented by applicants are usually based on assessments made by investigators at the time of an event, are highly dependent on information about the side effect profile of the drug available at the time of the study (e.g., what is in the investigator's brochure), and are not informed by awareness of the entire safety database. These analyses are generally not expected to provide much useful information in assessing causality.

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Caveats - 2

- Assessment of the drug-relatedness of an AE is different for frequent vs rare events.
  - For frequent ones, comparing the incidence of AEs in the study drug group to that in the placebo or other control group is done.
  - For rare events, the expected rate in a clinical trial database would be zero. Thus, if even a few cases (sometimes even a single case) of a rare life-threatening event occurred when none was expected, that would represent a serious safety problem for a drug product.

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Causality Assessment

- Whether the drug is capable of causing a particular AE in the population is usually of greater interest than whether the drug caused the event in each patient who reported the event.

Causality Assessment of Common AEs

- It is usually not necessary or helpful to consider each case individually. Rather, all reported cases can be considered potentially drug-related, and causality is assessed by comparing the rates of reports in patients treated with test drug and in control groups. If an event is clearly more frequent with test drug than the control, it can be attributed to treatment with the test drug.

Causality Assessment of Uncommon SAEs - 1

- Causality judgments are much more difficult for uncommon (e.g., < 1/1000) SAEs where there are no useful comparisons to control groups. The reviewer therefore must form a judgment as to the plausibility of drug-relatedness for the individual cases. Consider:
  - Was the patient in fact exposed to drug and did the AE occur after drug exposure?
  - Did the patient have a clinical experience that meets the criteria for the adverse event of interest?
  - Is there a reasonably compelling alternative explanation for the event?
  - Is the AE of a type commonly associated with drug exposure, such as hematologic, hepatic, renal, dermatologic or pro-arrhythmic events?

Causality Assessment of Uncommon SAEs - 2

- If there is no compelling alternative explanation, a comparison of the observed rate of the event in the database with a best estimate about the background rate should be done.
  - For aplastic anemia, with a background rate of perhaps 1 per million person years, finding even one case suggests a causal relationship.

- Evaluation of any other appropriate information:
  - Whether the drug is a member of a class of drugs known to be causally associated with the event of interest
  - Presence of other AEs in the database that may be associated with the event of interest (e.g., finding transaminitis in other cases in the database strengthens the signal generated by a single case of hepatic failure)
  - Positive re-challenge with the drug.

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Plausibility of Uncommon SAEs

- Be cautious about dismissing uncommon, SAEs *that don't seem plausibly drug-related.*
- Examples of SAEs that do not seem plausibly related to the drug but were found to be:
  - Tendon rupture associated with the quinolone antibiotics
  - Heart valve lesions associated with fenfluramine
  - Retroperitoneal fibrosis with Sansert
  - Pulmonary hypertension with Aminorex (a European weight loss drug), and various other drugs
  - Suicidal ideation with interferons, Accutane
  - Intussusception with rotovirus vaccine
  - Pulmonary fibrosis with amiodarone

Bottom Line

- Keep an open mind & be humble about causality when doing your daily PV work.

Why Assess Causality

- It is legally required by FDA, EMA & most other HAs for all SAEs for some expedited reporting (alert reports)
- It is needed to determine whether the AE should be considered in the signaling review & benefit/risk determination and whether it should be listed in the labeling (Package Insert, SmPC, etc.)
- Warn patients, investigators, HCPs

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Drug Related AEs

- For AEs that seem drug related additional analyses should be done:
  - Explorations for dose dependency.
  - Time to onset.
  - Adaptation & tolerance to certain AEs (e.g. nausea, somnolence).
  - Drug-demographic, -disease and -drug interactions.
  - Analysis of the AE by severity.

Before Assessing Causality

- Be sure coding is consistent & correct & the case information is as complete as possible
- Be clear on what causality you are looking at:
  - "Regulatory reporting causality" (No grey zone)
    - In clinical trial expedited reporting the classification is simple:
      - No: absolutely, positively unrelated
      - Yes: possibly, probably, remotely, unlikely…
  - "Medical causality" (Looks at the grey zone)
    - Attempts to judge & quantify likelihood of causal association for use in signaling & labeling
  - "Legal causality"

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Ways to Determine Causality

- Methods used to determine causality:
  - Global introspection (clinical judgment)
    - Having smart, experienced medical people (usually MDs) make a judgment
  - Algorithms
    - Use of a formal, defined mechanism or decision tree to come to a conclusion
      - Imputability (France), Roussel-Uclaf (France), Venulet (Switzerland), Karsh-Lasagna (US), WHO (Sweden), Naranjo (Canada)
  - Probablistic, Baysian analysis & other "statistical methods"
    - Generally require more data than is available or data that is "introspective" – not yet practical.

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Basic Criteria for Causality

- Pharmacology and previous knowledge of ADRs
- Association (time & place) of AE and drug
- Plausibility (medical/biological)
- Likelihood or exclusion of other causes

- Analyze everything in the report & note what data are NOT in the report

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Naranjo Causality Scale - 1

1. Are there previous conclusive reports on this reaction?

   Yes (+1) No (0) Do not know or not done (0)

2. Did the adverse event appear after the suspected drug was given?

   Yes (+2) No (-1) Do not know or not done (0)

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

   Yes (+1) No (0) Do not know or not done (0)

4. Did the adverse reaction appear when the drug was readministered?

   Yes (+2) No (-1) Do not know or not done (0)

5. Are there alternative causes that could have caused the reaction?

   Yes (-1) No (+2) Do not know or not done (0)

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Naranjo Causality Scale - 2

6. Did the reaction reappear when a placebo was given?

Yes (-1) No (+1) Do not know or not done (0)

7. Was the drug detected in any body fluid in toxic concentrations?

Yes (+1) No (0) Do not know or not done (0)

8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?

Yes (+1) No (0) Do not know or not done (0)

9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

Yes (+1) No (0) Do not know or not done (0)

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Naranjo Scoring

> 9 = definite ADR

5-8 = probable ADR

1-4 = possible ADR

0 = doubtful ADR

Naranjo et.al. Clin Pharmacol Ther. 1981 Aug;30(2):239-45

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WHO Methodology

- Certain
  - Good timing, no other cause, withdrawal response plausible, rechallenge, “definitive”
- Probable
  - Good timing, other cause unlikely, withdrawal
- Possible
  - Good timing, other causes possible
- Unlikely
  - Poor timing, other causes more likely
- Unassessable
  - Insufficient or contradictory information

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Algorithms Compared - 1

- Six assessors (2 pharmacists, 2 MDs and 2 nurses), assessed 200 ADR reports for causality using the Naranjo and Venulet algorithms. Agreement between assessors using the same algorithms was examined, and agreement between the algorithms for the same assessor was also measured.

- Conclusions: Comparability between assessors was found to be `fair' or less for the ADR causality assessment methods. The most consistent results were produced by the Naranjo algorithm and the least consistent by the Venulet algorithm.

Algorithms Compared - 2

- The high level of disagreement in the results produced using the assessment scales in this study question the robustness of causality assessments

An Investigation of Disagreement in Causality Assessment of Adverse Drug Reactions. Davies et al. Pharmaceutical Medicine, Volume 25, Number 1, 1 February 2011 , pp. 17-24(8)

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Comparisons

- Another older study of global introspection vs algorithms showed a concordance of only 45% for certain, 61% for possible and 17% for unrelated

- Conclusion: No method is shown to be better. Most use some form of global introspection

Causality

- Common classifications to assess causality
  - Definitely related
  - Probably related
  - Possibly related
  - Unlikely/Remotely related
  - Definitely not related
- Or, preferably it is simplified:
  - Related
  - Not related
- Each company should decide which system they will use or a combination of both
- For SUSAR reporting, the answer must be either related or not related

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Difficulties in Assessing AE Causality

- Incomplete information
  - Reporter may see only one of a particular AE whereas the sponsor or HA may see many from other sources & drugs
- Multiple drugs taken (polypharmacy)
- Variability of clinical responses
- Underlying illness mimics AE
- Intercurrent illness
- Different medical training or viewpoint

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Clues to Causality: CIOMS III - 1

- Positive dechallenge, rechallenge
- Occurrence in a study designed to investigate the AE
- Statistically significant differences in clinical trials
- Recognized consequences of overdosage with drug
- Pharmacokinetic evidence for interaction
- Seen in animal studies
- Increase in frequency vs placebo
- Known mechanism
- Recognized class effect
- Consistency among cases of presenting symptoms
- Consistency of time to onset among reported cases
- Definitive cases

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Clues to Causality: CIOMS III - 2

- Similar properties to drugs with this AE
- Similar AEs already recognized for this drug
- Time to onset is plausible
- Identifiable subgroup at risk
- High frequency of reports
- Biological plausibility
- When AE occurs, usually drug-related (e.g. Stevens Johnson)
- Lack of confounding factors
- Amount & duration of drug exposure is appropriate
- Drug affects same body system in some other way
- Reporters feel AE due to drug

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Clues to Causality: CIOMS III - 3

- Low background incidence
- Cases are clear-cut & easily evaluated
- Data are objective rather than subjective
- Lack of obvious alternative explanations
- Comeds unlikely to play a role
- Reported to occur in children
- High status credible reporters
- Although there is no other corroborative evidence, there is no contrary evidence

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Key Criteria for Causality - 1

- Product indication; duration of medication use
- Temporal relationship of ADR
  - Appearance of ADR = *"challenge"*
  - Disappearance of ADR = positive *"dechallenge"*
  - Reappearance of ADR = positive *"rechallenge"*
- Previous exposure = *"prechallenge"* (previous exposure to suspect drug)
  - Positive prechallenge = ADR occurred in past when patient exposed to drug
  - Negative prechallenge = ADR did not occur in past when patient exposed to drug

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Key Criteria for Causality - 2

- Patient's drug and medicine history
  - ADR occurred without exposure to suspect drug; AE did not occur in past
- Concomitant medications (indication, dosage)
- Preexisting or concomitant conditions, diseases
- Plausible or biologic or pharmacologic explanation

Examples: Definitely Related

- Dizziness ¾ hour after ingestion of an oral antihypertensive drug with no concomitant drugs
  - AE stops on stopping drug (positive dechallenge) & restarts when taken again (positive re-challenge)
- Injection site reaction 30 seconds after a subcutaneous injection
- A large tablet gets stuck in the pharynx (obstruction) while swallowing it & it has to be removed in the ER

Examples: Probably Related

- Thrombocytopenia after taking an oncology drug
- Diarrhea after ampicillin
- Vaginal candidiasis after an antibiotic for bronchitis

Examples: Possibly Related

- Abnormal liver function tests after taking an antihistamine
- Headache
- Dyspepsia after a tablet or capsule

Examples: Unlikely Related

- Cancer of the colon diagnosed after 3 doses of an antibiotic
- Myocardial infarction 3 weeks after taking a drug that has a terminal half life of 10 minutes
- Auto accident but…
  - Did the drug cause dizziness which caused the accident?

Cascade or Secondary AEs/Causality

- Patient takes a drug which produces anemia & has a myocardial infarct due to the anemia
  - Is the anemia considered an AE related to/caused by the drug?
- Patient takes a drug that produces dizziness causing the patient to fall and break her leg
  - Is leg fracture considered an AE related to/caused by the drug?
- No clear answer in all cases. It may be appropriate to mention this in the IB or product labeling for some AEs

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Relating the Two Classifications

Signaling Causality	Regulatory Causality
Definitely related	**Related**
Probably	**Related**
Possibly	**Related**
Unlikely/remotely	**Related**
Unrelated	Unrelated

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Examples - 1

- A 65 year old male, obese, smoker, hypertensive, type 2 diabetic (poorly controlled) with hypercholesterolemia starts a new drug and has an inferior wall myocardial infarction 8 days after starting.

- Related to the drug?

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But…

- His parents both smoke & have elevated cholesterol and are 98 years old alive & fairly well.
- He only took one dose and stopped because it gave him headaches. The terminal half life is 20 minutes.
- His 20 year old dog died the day before and this was very stressful.
- He worked in his garden for 5 hours the day of the attack.

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Example 2

- A pregnant woman takes a drug early in her pregnancy to prevent a miscarriage (spontaneous abortion).
- Fourteen years later her daughter develops cancer of the vagina.

- Related to the drug?

DES

- Diethylstilbestrol (DES) is an estrogen that prescribed DES to pregnant women to prevent miscarriages. As a result, an estimated 5-10 million pregnant women and the children born of these pregnancies were exposed to DES in the US. At the time, physicians thought DES was safe.
- In 1953, published research showed that DES did not prevent miscarriages or premature births. However, DES continued to be prescribed until 1971. In 1971 a study identified DES as a cause of a rare vaginal cancer in girls and young women who had been exposed to DES before birth (in utero).
- The news that DES could be harmful led to a national effort to find women prescribed DES while pregnant and notify them of the potential DES-related health problems. Physicians reviewed patients' medical records and notified women who had been prescribed DES. As a result of this effort, many women were made aware of the DES health risk known at that time, known as clear cell adenocarcinoma (CCA), a rare vaginal cancer. Women were encouraged to have their DES-exposed daughters screened regularly by a gynecologist because CCA was found in girls as young as 8 years old.

- http://www.cdc.gov/des/consumers/about/history.html

Example 3

- Can a drug can cause nausea and vomiting before exposure to it?

Cis-Platinum Anticipatory Vomiting

- “Anticipatory nausea and vomiting (ANV), also referred to as conditioned, learned or psychological nausea and vomiting, is widely believed to be a learned response to chemotherapy that 25% of patients develop by the fourth treatment cycle. It appears to link psychological, neurological and physiological systems. The risk of ANV tends to increase with the number of cycles received and the symptoms may persist long after the completion of chemotherapy [. ANV is difficult to control by pharmacological means, whereas behavioral therapies, most notably systematic desensitization, can be used to effectively treat it.”
- http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136579/ Support Care Cancer. 2011 October; 19(10): 1533–1538.
- http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page4

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Example 4

- A 75 year old female takes nitroglycerin for chest pain and gets dizzy, falls, breaks her hip, has surgery, recovers, develops pneumonia and dies 12 days later.
- Did the nitroglycerin cause:
  - Dizziness?
  - Fall?
  - Hip fracture?
  - Death?
- What would you put in the product labeling: AEs, warnings, precautions, geriatric use?

Example 5

- A new drug for weight loss is heavily promoted to teenagers. 10,000 women between the ages of 11 and 21 take the drug in the first 3 months of marketing.
- A case of mitral valve stenosis is reported from Paris.
  - Related to the drug?

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Example 5 continued

- A famous hip hop entertainer says on Facebook that she took it and lost 40 pounds but had a heart attack and is suing the company.
  - Related to the drug?

Example 5 continued

- 73 other cases of heart attacks and 14 of mitral stenosis are reported in the next 2 weeks?
  - Heart attacks related to the drug?
  - Mitral stenosis related to the drug?

Conclusion

- Causality assessment is very tricky!