at
pharmacovigilance
do for you!
relationship assessment is a better concept

CAUSALITY ASSESSMENT
Outline

- Background
- Data requirements
- Relationship / causality assessment
- TEST
Background

I’m not going to say much
Causality assessment

Two questions

- How close is the relationship between medicine and event?
  - relationship

- Was the event caused by the medicine?
  - causality
Causality assessment

Two approaches

- Individual case safety reports (ICSRs)
  - Single reports of suspected reactions
  - (spontaneous reporting)

- Epidemiological
  - Large numbers of reports of events
  - Includes CEM
Causality Assessment

Two definitions

- **Adverse reaction**: “a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man”

- **Adverse event**: *any* new clinical experience that occurs after commencing a medicine, not necessarily a response to a medicine, and is recorded without judgement on its causality.
Understanding events & reactions

Events = reactions + incidents

(incidents are those events thought not to be reactions –‘non-reactions’)

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Data requirements

I’ll say a little bit more
What data are needed?

- All medicines near the time of the event
  - dates
  - doses
  - indications
- The event description
  - date of onset
  - duration to onset
  - event dictionary term
What data are needed?

- **Results** of dechallenge & rechallenge
- Outcome of the event
- Patient medical history
  - past diseases of importance eg hepatitis
  - other current diseases (co-morbidities) eg
    - tuberculosis
    - diabetes
Two more definitions

- **Dechallenge:** the outcome of the event after withdrawal of the medicine
  - resolved, resolving, resolved with sequelae, not resolved, worse, death, unknown

- **Rechallenge:** following dechallenge and recovery from the event, the medicines are tried again, one at a time, under the same conditions as before and the outcome is recorded
  - recurrence, no recurrence, unknown, (no rechallenge)
Where are the data? (CEM)

- Medicine details: follow-up Q Section C
  - ARV medicines
  - Other medicines
- Event details: follow-up Q Section E
- Dechallenge & rechallenge: follow-up Q
  - dechallenge Section C
  - rechallenge Section E
- Event outcome: follow-up Q Section E
- Medical history
  - Baseline E
  - Treatment initiation C
  - Any new diseases

Handbook pages 99-101
The data elements and more

- We use all the information available on the report, and
- Our pharmacological knowledge, and
- Our knowledge of previous reports received, and
- Our search of the WHO database (VigiSearch) and
- Our knowledge of any literature reports
Assessment of relationship and causality

I’m going to say quite a bit
Assessment of each event 1

- Initially, what we are really doing is assessing the strength of the relationship between the drug and the event.
- We can seldom say without any doubt that a specific drug caused a specific reaction.
- We work with imperfect data and our conclusions are those of probability.
Assessment of each event 2

Relationship assessment is an essential discipline. *It ensures:*

- careful review of report details
- standardised assessment
- an in-depth understanding of the data
- standardised data for later evaluation
- the ability to sort reports by quality

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Relationship categories

1. CERTAIN

- Event with plausible time relationship
- No other explanation - disease or drugs
- Event definitive - specific problem
- Positive dechallenge
- Response to withdrawal plausible
- Key feature: Positive rechallenge
Relationship categories

2. PROBABLE

- Event with plausible time relationship to drug intake
- No other explanation
- Response to withdrawal (dechallenge) clinically reasonable
- No rechallenge, or result unknown
- **Key feature:** Positive dechallenge
3. POSSIBLE

- Event with plausible time relationship to drug intake
- Could also be explained by disease or other medicines
- Information on drug withdrawal lacking or unclear

**Key feature:** other explanations for the event are possible
Relationship categories

4. UNLIKELY

- Event with a duration to onset that makes a relationship improbable
- Diseases or other drugs provide plausible explanations
- Event does not improve after dechallenge
- **Key feature:** several factors indicate strongly that the event is not a reaction
Relationship categories

5. UNCLASSIFIED (conditional)

- An adverse event has occurred, but there is insufficient data for adequate assessment and
- Additional data is awaited or under examination
- Nature of event makes it impossible to attribute causality (needs epidemiological studies)
- **Key feature:** Can’t assess with the information available
Relationship categories

6. UNASSESSABLE (unclassifiable)

- A report with an event
- Cannot be judged because of insufficient or contradictory information
- Report cannot be supplemented or verified
- **Key feature:** Data elements concerning the event are inadequate and will not be available
The process of assessment 1

**Apply a standard event term**

- Apply a standard term that fits the clinical details
  - For ICSR reports use a reaction dictionary (WHOART / MedDRA) - VigiFlow
    - For use with Individual Case Safety Reports (spontaneous reports)
    - Suspected adverse reaction
  - For event monitoring use the event dictionary - accessible in CemFlow
    - For use with a CEM programme (event monitoring)
    - If a suitable term cannot be found, use free text
The process of assessment 2
Establishing the relationship

Objective evaluation (ICSRs & CEM)

- Dates of use of all medicine(s)
- Date of onset of event
- Response to dechallenge
- Response to rechallenge
- Outcome
- Disease being treated
- Other diseases
The process of assessment 3
Establishing causality

Subjective evaluation (ICSRs & CEM)

- Is a reaction plausible?
- Consider
  - indication for use
  - background or past disease
  - pharmacology
  - prior knowledge of similar reports with the suspect drug or related drugs
- Is there a possible mechanism?
The process of assessment 4

Establishing causality

Epidemiological evaluation (CEM)

- All the subjective evaluations above
- Compare patients with the event of interest with those without the event
  - Search for non-random results
    - age
    - gender
    - dose
    - duration to onset (life table analysis)
- Other statistical analyses of the data
- Disregard events with a relationship of 4, 5 or 6
The process of assessment 5
The end process

- Discuss and consult
- Establish an opinion on causality
- Publish
- Be prepared to revise your decision
Causality Assessment

Two questions

- How close is the relationship between medicine and event?
  - relationship

- Was the event caused by the medicine?
  - *What could have caused the event?*
  - causality
Ha Ha!!
What relationship? 1

An event with:

- a plausible time to onset
- no dechallenge information
- other medicines could have caused the event

- Relationship = ........................................
What relationship? 2

An event with:

- a plausible time to onset
- no other obvious causes of the event
- positive dechallenge & rechallenge

- Relationship = ............................................
What relationship? 3

An event with:

- a plausible time to onset
- no other obvious causes of the event
- event resolved on dechallenge
- a rechallenge was undertaken, but the result is not known

- Relationship = ...........................................
What relationship? 4

An event with:

- unknown duration to onset
- positive dechallenge
- rechallenge not stated
- no other obvious cause

- Relationship = .................................................
What relationship? 5

An event with:

- a plausible time to onset
- no other obvious cause
- event outcome ‘death’
- cause of death was a known reaction to the medicine

- Relationship = .................................................
What relationship? 6

An event with:

- a plausible time to onset
- no other obvious causes of the event
- a dechallenge was undertaken, but the event did not resolve

- Relationship = .................................................
The process of assessment 6

The very end process

Check your logic

- You should not have causality 1
  - if there has been no rechallenge, or the outcome of rechallenge is unknown

- You should not have causality 2
  - if there has been no dechallenge or the result of dechallenge is unknown or,
  - if the outcome is unknown or,
  - if there are other possible causes

- You cannot have an event if it started before the medicine!!
The very, very, end (maybe)

Thank you
Practice 1

- Male aged 34
- On tenofovir, stavudine, efavirenz from Feb 2003
- Events
  - July 2003 had MI – onset 5 months
  - Dyslipidaemia – onset time unknown
- Treatment changed (dechallenge)
- Outcome:
  - Recovery after angioplasty
  - No information on lipids
- Relationship = 


Practice 2

- Male aged 45
- receiving HAART for 6 years
  - 2 regimens including ritonavir & lopinavir
- Event:
  - penile ulcers
  - onset unknown, but after starting ART
  - biopsy – herpes? – unresponsive to treatment
- Treatment stopped July 2007
- Outcome: resolved completely in 1 month
- Relationship = ........................................
Practice 3

- Pregnant woman age 24
- LFTs normal
- lamivudine, zidovudine, nelfinavir at 16 w
- Event - jaundice leading to liver failure
  - onset after 13 weeks
  - outcome: recovered after liver transplant
- Post op: efavirenz, emtricitabine, tenofovir
  - well at 12 months
- Relationship = ........................................................................
Data Requirements for Reports

James¹, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
1 James
1. James

PATIENT IDENTITY
Data Requirements for Reports

James¹, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
2. while
2. while
Data Requirements for Reports

James\(^1\), while\(^2\) sleeping\(^3\) on a bank\(^4\) was flattened\(^5\) by a Sherman\(^6\) tank\(^7\). The ground was soft\(^8\), the tank was large\(^9\) and James was buried\(^10\), free of charge\(^11\).
3. sleeping
3. sleeping

DISEASE
Data Requirements for Reports

James₁, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
4. Bank
(where?)
4. bank

ADDRESS
Data Requirements for Reports

James\(^1\), while\(^2\) sleeping\(^3\) on a bank\(^4\)
was flattened\(^5\) by a Sherman\(^6\) tank\(^7\).
The ground was soft\(^8\), the tank was large\(^9\)
and James was buried\(^10\), free of charge\(^11\).
5. flattened
5. flattened

ADVERSE REACTION
Data Requirements for Reports

James¹, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
6. Sherman

Sherman 75-mm

The Sherman 75-mm was the most common tank used by the Anglo-American Allies in Europe. By D-Day the Sherman was becoming obsolete. Compared to the German Panther and Tiger tanks, it had a high, vulnerable profile and weak armour, and its 75-mm gun was incapable of penetrating the frontal armour of either of these German tanks. It became common for Sherman crews to attach additional armour and sandbags onto their tanks.

Combat-loaded, the Sherman medium tank weighed about 34 tons. It was manufactured under these designations: M4, M4A1, M4A2, M4A3, M4A4, M4A6. The designations depended on the tank's engines and on whether they had a rounded, cast hulls or flat-sided, welded hulls. Close to 50,000 Shermans were built in 1942-46.
6. Sherman

PROPRIETARY NAME
Data Requirements for Reports

James, while sleeping on a bank was flattened by a Sherman tank. The ground was soft, the tank was large and James was buried, free of charge.
7. tank

The Sherman 75-mm was the most common tank used by the Anglo-American Allies in Europe. By D-Day the Sherman was becoming obsolete. Compared to the German Panther and Tiger tanks, it had a high, vulnerable profile and weak armour, and its 75-mm gun was incapable of penetrating the frontal armour of either of these German tanks. It became common for Sherman crews to attach additional armour and sandbags onto their tanks.

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The designations depended on the tanks’ engines and on whether they had rounded, cast hulls or flat-sided, welded hulls. Close to 50,000 Shermans were built in 1942-46.
7. tank

GENERIC NAME
Data Requirements for Reports

James¹, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
8. soft
8. soft

PREDISPOSING FACTORS
Data Requirements for Reports

James¹, while² sleeping³ on a bank⁴ was flattened⁵ by a Sherman⁶ tank⁷. The ground was soft⁸, the tank was large⁹ and James was buried¹⁰, free of charge¹¹.
9. large
9. large

DOSE
Data Requirements for Reports

James\(^1\), while\(^2\) sleeping\(^3\) on a bank\(^4\) was flattened\(^5\) by a Sherman\(^6\) tank\(^7\).
The ground was soft\(^8\), the tank was large\(^9\) and James was buried\(^{10}\), free of charge\(^{11}\).
10. buried
10. buried

DIRECT OUTCOME
Data Requirements for Reports

James\(^1\), while\(^2\) sleeping\(^3\) on a bank\(^4\) was flattened\(^5\) by a Sherman\(^6\) tank\(^7\).
The ground was soft\(^8\), the tank was large\(^9\) and James was buried\(^{10}\), free of charge\(^{11}\).
11. free of charge
11. free of charge

INDIRECT OUTCOME