Causality assessment in case series

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Outline

- Causality
- Single case assessment
- Case series assessment:
  - strength
  - specificity
  - timing
  - dose
  - diversity
**Case series**

- For this presentation, defined as a group of patients with similar exposure (drug) and similar outcome (suspected ADR)

- How is case series review different from single case review?
Causality

- Deterministic causality
  - one cause, one effect
- Probabilistic causality
  - multiple causes (risk factors)
  - each increases the likelihood of the outcome
- Most ADRs have multiple possible causes
- Causality assessment is difficult!
- Example: fall while taking antipsychotic
Drugs and falls

• The risk of having a fall or recurrent falls increases with the number of risk factors below:
  - previous fall
  - polypharmacy (4 or more drugs)
  - alcohol >1 unit/day
  - poor mobility/gait
  - psychotropic drug use
  - orthostatic hypotension
  - balance disorders
  - visual impairment
  - hearing impairment
  - cognitive impairment
    • (http://www.bhps.org.uk/falls/documents/Medicn&RiskOfFalls.pdf)
Aims of causality assessment

• Aim to answer the following questions:
  - did the drug cause this ADR?
  - does the drug increase the risk of this ADR?

• And therefore:
  - how to decrease the occurrence of this ADR?
Single case causality

• Criteria generally used:
  - known event (possibly for related drug)
  - plausible timing
  - de/re-challenge
  - exclusion of other causes
  - typical ADR
Single case causality

- Problems with these criteria:
  - known event: not good for signal detection
  - plausible timing: after drug was taken?
  - de/re-challenge: may not have occurred
  - exclusion of other causes: may be multifactorial
  - ‘typical’ ADR: only a small list of these
Case series causality

• Additional criteria available:
  - strength of association
  - specificity of event
  - temporal relationship
  - dose response
  - consistency of reporting

• Direct application of Bradford Hill criteria
  • Perrio et al. DrugSafety 2007;30(4):333-246
Strength of association

• Strength = quantitative measure of the association between a drug and an ADR
• Useful in analysing large ADR databases
• Disproportionality analysis:
  - how does the reporting of this ADR for this drug compare to the reporting of this ADR in general (or this ADR for similar drugs)?
Disproportionality

- VigiBase (WHO database managed by UMC)
  - 6,194,555 reports [15 Feb 2011]
  - 206,208 reports of nausea
  - 3.3% of VigiBase reports mention nausea
Disproportionality

<table>
<thead>
<tr>
<th></th>
<th>total</th>
<th>nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluvoxamine</td>
<td>7861</td>
<td>1235 (16%)</td>
</tr>
<tr>
<td>VigiBase</td>
<td>6,194,555</td>
<td>206,208 (3.3%)</td>
</tr>
</tbody>
</table>

- increased reporting of nausea with fluvoxamine
  - is it due to the drug?
  - is it due to the disease under treatment?
  - other explanation?
Disproportionality measures

• A number of different measures of disproportionality:
  - PRR (European Medicines Agency)
  - ROR (Netherlands)
  - EBGM (US FDA)
  - IC (UMC)

• All work on the same data
• Give broadly similar results
Disproportionality measures

• Disproportionality usually compares one drug to whole database (or all other drugs)
• However, can also compare between individual drugs (eg, within a class), helping to control for confounders
• Note in the following example:
  - absolute report numbers don’t matter
  - however, there is a catch!
Statins and rhabdomyolysis

<table>
<thead>
<tr>
<th></th>
<th>total</th>
<th>rhabdomyolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerivastatin</td>
<td>14,474</td>
<td>5,389 (37%)</td>
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<tr>
<td>simvastatin</td>
<td>35,578</td>
<td>3,203 (9.0%)</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>34,200</td>
<td>1,691 (4.9%)</td>
</tr>
<tr>
<td>lovastatin</td>
<td>14,108</td>
<td>297 (2.1%)</td>
</tr>
<tr>
<td>VigiBase</td>
<td>6,194,555</td>
<td>17,742 (0.29%)</td>
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</table>
Ranolazine - ARF

• Ranolazine (treatment of chronic angina) – acute renal failure
• 12 reports in VigiBase, found through routine statistical screening
Ranolazine - ARF

<table>
<thead>
<tr>
<th></th>
<th>renal failure acute</th>
<th>all reactions</th>
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<tbody>
<tr>
<td>ranolazine</td>
<td>12</td>
<td>567</td>
</tr>
<tr>
<td>all drugs</td>
<td>35,971</td>
<td>6,194,555</td>
</tr>
</tbody>
</table>

- ranolazine:
  - 12/567 (2.1%) reports mention acute renal failure
- whole database:
  - 35,971/6,194,555 (0.58%) reports mention ARF
- ARF reported 3.6 times more often for ranolazine than for database as a whole
Specificity of event

• Specificity of event, ranolazine + ARF:
  - rhabdomyolysis (3 reports)
  - pneumonia / sepsis (2 reports)
  - multiple drug overdose
  - obstructive uropathy
  - myocardial infarction
  - urinary tract infection
  - no cause specified (3 reports)
Specificity of event

• Many ADRs have multiple etiologies
  – consider: organ failure, confusion, oedema
• Generally, drugs cause adverse reactions through specific mechanisms
• Totality of information available from a case series may be a better guide to mechanism than a single report
Temporal relationship

- Causality assessment generally considers plausibility of time to onset of ADR
- What is ‘plausible’?
- Some are well-described:
  - anaphylaxis (minutes to hours)
  - alopecia (several weeks)
  - solid organ tumours (years)
Time to onset

• Data from VigiBase – single suspect drug, all dates available:
  - agranulocytosis 5484 reports
  - angioedema 20,930
  - hepatitis 8961
  - serum sickness 1908
  - SJS 6531
  - TEN 2067
  • Khodabakhshi, G. MSc thesis.
Time to onset

Time to onset for each ADR

- Agranulocytosis: 35 days
- Angioedema: 1 day
- Hepatitis: 19 days
- Serum sickness: 8 days
- Stevens-Johnson syndrome: 8 days
- Toxic epidermal necrolysis: 7 days

Time To Onset (days)
TTO - agranulocytosis

Top ten reported ATC groups for agranulocytosis

Most frequent ATC groups
TTO - angioedema

Top ten reported ATC groups for angioedema

Time To Onset (days)

A01AD  C01EB  C09AA  D10AX  G02CC  J01CA  M01AB  M01AE  M02AA  S01BC

Most frequent ATC groups
Dose response

• Difficult to examine dose relationship on a single report:
  - usually only drug/no drug
  - presence of other risk factors

• Risk factors for rhabdomyolysis with statins
  - dosage in reports compared to dosage on prescriptions
Consistency

- ADRs often have multiple risk factors
- Rhabdomyolysis with statins:
  - age
  - dose
  - renal/hepatic/thyroid dysfunction
  - hyperkalemia
  - interacting drugs
- 58% simvastatin reports had 3+ risk factors!
- Case series is useful in establishing if reaction also occurs in the absence of other risk factors
Consistency

• Clustered reporting presents a problem for signal detection:
  – form of selection bias
  – may be one clinic, one study, or local publicity

• Signal detection at UMC routinely adds additional selection criteria:
  – must have reports from 2 or more countries
  – i.e., geographical consistency
Conclusion

• Assessing causality on individual cases is complicated by missing information or knowledge; confounding; selection biases; ...

• A case series may supply additional information, which may require a different approach to causality assessment
Thank you!