Principles of signal detection

Marie Lindquist
Pharmacovigilance endpoints

- What we do should support good decision making in relation to medication therapy
  - to maximise treatment effectiveness
  - to reduce risks
  - to prevent harm or minimise its impact

- We must consider the needs of
  - Individual patients and health care professionals
  - The population in general
What do we need to do

- Our job is to find and communicate
  - new information on medicines or their use which is
    - relevant
    - important
  - and has an impact on how the drug may or may not be used
There are many definitions of ‘signal’

- WHO (1991)
- Meyboom (1997)
- Amery (1999)
- CIOMS VIII (2010)
- and many others
Hypothesis based on reported clinical concerns (e.g. from adverse reaction case reports) or other data

- Facts
- Assessments

Value judgement

Decision Action
The questions to answer

✓ What is an important observation
  ✓ With an impact on drug use and patient safety
✓ How do we find the information
✓ How do we analyse it
✓ When do we have enough information to decide on an action
✓ What is the best action
What is an important observation

• When known, the observation will improve therapy
  – for certain individuals
  – for the exposed population as a whole

Consider how the information will be used
What to look for

• Problems related to inherent drug characteristics
  - the active ingredient
    • common for all products with the same active ingredient
  - the product
    • can differ between products e.g. if reaction is caused by an excipient

• Problems related to medicines use
  - Overdose
  - Interactions
  - Medication error

• Quality problems
  - sub-standard drugs, counterfeiting

• Antimicrobial resistance?
Indicators

- Unusual/unexpected features
- An increase in severity/seriousness
- An increase in reporting
## Epidemiology basics

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposed</strong></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td><strong>Non-exposed</strong></td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

### Frequency
- **Incidence** = # cases developing over a defined time period
- **Prevalence** = # cases at a given point in time

### Risk
- **Absolute risk (exp)**
  \[
  \frac{A}{A+B}
  \]
- **Reference risk (non-exp)**
  \[
  \frac{C}{C+D}
  \]
- **Relative risk**
  \[
  \frac{\text{Risk (exp)}}{\text{Risk (non-exp)}}
  \]
With case reports alone, we cannot

• Calculate incidence/prevalence
  - Do not know the frequency of the ADR*)
  - Do not know the size and characteristics of the exposed population

• Calculate relative risk
  - Do not know the frequency of the reaction among the non-exposed
  - Do not know the size and characteristics of the non-exposed population

*) due to (variable) under-reporting
So, a signal

- is only the starting point of a process
- does not tell us how many patients will be affected (of all exposed)
- does tell us that some patients may be affected
How do we find the signals

- Manual observation and clinical judgement
- Automated signal detection methods
Manual investigations + clinical judgement

• Clinical review
  - all cases at data entry, and 'flag' relevant associations

• Literature review
  - search for hypotheses generated from other sources

• Monitor reporting trends and patterns
  - by substance, medicinal product or areas of importance
Increased reporting?

- Many reports for new drug
- Increased frequency of reporting for old drug
- More reports than for other drugs in general
- More reports than for other drugs used for the same indication
- More reports than for other drugs with similar chemical structure/pharmacological action
Observing the unexpected?

• Reactions that were not anticipated based on existing knowledge
• Known reaction, but more serious cases coming in
• Special groups affected
  – e.g. elderly, children
• Other unusual/unexpected features
How can we get the most out of the data we have?
Introducing quantitative signal detection methods

- Looking at reporting frequencies
  - relative to a background of other reports
  - to identify associations that stand out from the background
Quantitative signal detection methods

• Providing a measure of unexpectedness
  - using statistical calculations of ‘disproportionality’
  - based on observed/expected ratio
## Quantitative signal detection methods

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed population</td>
<td>Drug X+ ADR Y</td>
<td>Drug X+ Other ADRs</td>
</tr>
<tr>
<td>Non-exposed population</td>
<td>Other drugs + ADR Y</td>
<td>Other drugs+ Other ADRs</td>
</tr>
</tbody>
</table>
Quantitative signal detection methods

- Exposed population
  - Drug X+ ADR Y
  - Other drugs + ADR Y

- Non-exposed population
  - Other drugs +
  - Other ADRs

- Cases
- Controls
  - Drug X+ Other ADRs
  - Other drugs + Other ADRs
Advantages

• Unbiased
• Can be more or less automated
• Works for screening of large amounts of case reports
  - depending on implementation method
Which method should we use?

• All measures give similar results
  – Certainly when there is a large number of cases
  – All based on unexpectedness relative to the rest of the data set

• Difference in the implementation within signal detection process
How do we analyse the information

• Documentation level
  – Are all relevant facts present?
  – Data quality!

• Medical importance of the signal
  – Degree and duration of harm caused

• Credibility of cases
  – Result and accuracy of individual causality assessment, e.g. dose response

• Credibility of signal
  – Enough independent cases? Pointing in the same direction? Plausible mechanism of action?
Other assessments

• Confounding
  - Other risk factors than drug present?

• Bias
  - Selection, publication, measurement bias present?
How do we know when we have enough information

• We don’t!
What is the best action

- New data
- Data compilation
- Signal detection
- Signal analysis

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Possible actions

- Wait and see
- Seek more information
- Do studies
- Raising awareness/warning
- Restrictive measure
- Withdrawal

{ Signal strengthening

{ External communication
Actions
Wait and see

- Is this ever a realistic option?
- Likely risk very low
- Symptoms not severe, or easy to treat
- Notional probability of causality less than 50/50
Seek more information

- To strengthen signal
  - Estimate reporting rates by adding drug use denominators
    - Sales data or prescription data provides an exposure surrogate
  - Use patient record databases for hypothesis testing
Reporting rates

Can give an indication of

- The size of the problem (incidence estimate)
- Differences between the target drug and its comparator drugs
- Differences between geographical areas
- Differences over time (if longitudinal data is used)
Reports of carbamazepine and Stevens Johnson syndrome in WHO database

<table>
<thead>
<tr>
<th>Country</th>
<th># reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>318</td>
</tr>
<tr>
<td>United States</td>
<td>155</td>
</tr>
<tr>
<td>Germany</td>
<td>144</td>
</tr>
<tr>
<td>Malaysia</td>
<td>129</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>104</td>
</tr>
<tr>
<td>Spain</td>
<td>37</td>
</tr>
<tr>
<td>Sweden</td>
<td>31</td>
</tr>
<tr>
<td>Canada</td>
<td>28</td>
</tr>
<tr>
<td>Switzerland</td>
<td>16</td>
</tr>
<tr>
<td>Italy</td>
<td>10</td>
</tr>
<tr>
<td>Netherlands</td>
<td>8</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
</tr>
</tbody>
</table>
## Adding sales data

<table>
<thead>
<tr>
<th>Country</th>
<th># reports sum</th>
<th>KG sales sum</th>
<th># reports/mill DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>129</td>
<td>4,705.9</td>
<td>27.4</td>
</tr>
<tr>
<td>Thailand</td>
<td>318</td>
<td>28,797.7</td>
<td>11.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>31</td>
<td>95,036.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Switzerland</td>
<td>16</td>
<td>53,641.7</td>
<td>0.3</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>104</td>
<td>604,275.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Netherlands</td>
<td>8</td>
<td>53,917.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Germany</td>
<td>144</td>
<td>990,518.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Spain</td>
<td>37</td>
<td>307,818.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Canada</td>
<td>28</td>
<td>258,180.9</td>
<td>0.1</td>
</tr>
<tr>
<td>United States</td>
<td>155</td>
<td>2,086,026.5</td>
<td>0.1</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
<td>44,577.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Italy</td>
<td>10</td>
<td>448,681.8</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Reporting rates using prescription data

In addition, analyses can be made involving

- Patient age
- Gender
- Indication
- Dosage
To consider

• Direct comparisons drugs/countries should not be made
  – without investigating possible reasons for differences

• The choice of comparator drug/s is important
  – problems if not used for the same indication, or if the severity of
    the disease treated is different
  – analyses should be made at similar times in their marketed lives

• Biases in denominator and numerator can be different
  – e.g. under-reporting in numerator and not in denominator
To consider

• Method only useful when there is a relatively large amount of reports
  - particularly when involving more variables than drug/country/year

• 'Push button' merging of the different data sets is not possible
  - more or less extensive manual mapping/data washing needed
Remember

- Combining drug use data and spontaneous ADR data is helpful when analysing signals
  - But reporting rate ≠ incidence
  - Gives a more or less good estimate of incidence
  - Need data on background rate of disease to compare risk in exposed/non-exposed populations
# Hypothesis testing using health care databases

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<tr>
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<td><strong>Controls</strong></td>
</tr>
<tr>
<td>Drug X+ Diagnosis Y</td>
<td>Drug X+ Other diagnoses</td>
</tr>
<tr>
<td>No/other drugs + Diagnosis Y</td>
<td>No/other drugs + Other diagnoses</td>
</tr>
</tbody>
</table>

Provide both numerator and denominator data

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To consider

• Diagnoses ≠ ADRs
  - no bias

• Longitudinal data
  - patients their own controls

• No selection/exclusion of patients based on preset criteria, but
  - Subset of total population

• Complete set of numerators/denominators
  - only if all people in database coverage area registered as patients, and
    - database coverage representative for total population
    - database size enough to include rare drugs/ diagnoses
Spontaneous reporting or formal epidemiological studies?

- Case report
- Case series
- Signal => Hypothesis
- Analysis
  - Reporting frequency
  - Causality
  - Incidence/prevalence
  - Risk

- ?
- ?

- Hypothesis
- Study design
- Study execution
- Analysis
  - Incidence/prevalence
  - Risk
  - Causality
Time to communicate

Signal detection

Data compilation

New data

Signal analysis

Communication
Time to communicate

1. Signal detection
2. Data compilation
3. Signal analysis
4. New data
5. STOP
Communication principles

• The right message
  – At the right time
• To the right audience
  – By the right medium
• Consequences
  – Message received?
  – Message understood?
  – Followed up?
  – Acted on appropriately?
To consider

• Importance of signal
  – Seriousness and public health impact

• Prevention
  – Can the reaction be avoided?
  – Identifiable risk groups?

• Predictability
  – Can the reaction be predicted?
  – Any early indicators?
To consider

• **Treatment**
  - What treatment is available?
  - Is it effective?

• **Alternatives**
  - What therapeutic alternatives are available?
  - Are they equal/better/worse?

• **Damage control**
  - If the signal is ultimately proven false, can the damage caused be reversed/rectified?
Always provide

- The best possible description of the nature of the hypothesis
- Clear information about all the available facts and assessments made
- An open account of value judgements made
- The reason for action
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What we should do!

- Signal detection
- Data compilation
- New data
- Signal analysis
- Information
- Communication
- Follow up
- Feedback loops in place?
- Impact assessment