Systems complementary to spontaneous reports

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UMC Pharmacovigilance Course Module IIA. May 11, 2011
Outline

• Prescription-event monitoring
• Longitudinal observational databases
• Strengths and weaknesses of each system
Individual case safety reports

• Strengths
  – Cover a very large population
  – Rapidly available to the analyst
  – Communicate important clinical concerns

• Limitations
  – Haphazard data collection
  – No information on drug usage or event rates in unexposed
  – 'Snapshots in time'
Prescription-event monitoring

• Idea
  – Actively collect information on all adverse events in cohort exposed to a drug of interest

• Main differences vs spontaneous reports
  – Collect information on all patients in cohort (not just those with suspected ADR)
  – Register all adverse events (not just suspected ADRs)
  – Seek information on adverse events prior to drug exposure (for comparison)
Enrolment

• Ideally, a random sample among those patients prescribed the drug of interest
  – For example, throw a die and include patient if 5 or 6
  – Non-compliance may not be random and can introduce biases!

• Continue enrolment until the predefined size of the cohort has been reached
Data collection

Follow up visits

Observation or comparator periods depending on study design
Analysing prescription-event data

• Enhanced spontaneous reports-type analysis
  – Number of exposed patients known
  – More information on risk factors, co-medications etc
  – Sometimes possible to go back to reporter for more information

• Adverse event profiles
  – Comparison to other drugs
  – Comparison across time periods
Screening prescription-event data

• What to compare rates in observation period to?
  – Other drugs
  – Other time periods for the same drug

• Differences between drugs
  – Demographics
  – Underlying disease

• Differences between time periods
  – Period length
  – Patients may be more observant to adverse events when on drug
  – Certain events (lethal) impossible prior to prescription
  – Chronic conditions potentially problematic
Prescription-Event Monitoring

• Intensive Medicines Monitoring Programme (IMMP)
  New Zealand 1977
• Prescription Event Monitoring (PEM)
  UK 1980
• Prescription Event Monitoring in Japan (J-PEM)
  Japan 1990s
• Cohort-Event Monitoring (CEM)
  WHO 2007
Longitudinal patient records

• Another source of information on real world use and effects of medicines
• No active effort on behalf of medical professional to provide information
  – Use administrative system for managing patients
• Listings *over time* for each patient of
  – Medical diagnoses
  – Drug prescriptions
  – Administrative information (test results, lifestyle, ...)

- [Image]
- [Image]
Simplified patient histories
Temporal patterns

• In a time period after the prescription of a given drug, what medical events occur...
  – disproportionally often (possible ADRs)
  – disproportionally rarely (possible beneficial effects)

• Must distinguish true temporal association from general tendency to occur in the same patient histories!

• OBS! Temporal association does not imply causality
Event history data
Raw histogram

- Provides some sense of temporal association
- ... but sensitive to
  - recording biases
  - censoring
Observed vs expected

- Provides a baseline based on how the medical event is registered relative to prescriptions of other medicines
- Emphasises absolute difference between observed and expected
Shrinkage O/E ratio

• Consider the IC shrinkage O/E ratio (on log₂ scale)

\[ IC = \log_2 \frac{Obs + 1/2}{Exp + 1/2} \]

• +1/2 pulls ratio to 1 and the IC to 0
  – Reduces risk of false alerts

• Differs from the unshrunk log observed-to-expected ratio primarily for rare events

• Positive values -> more events than expected

• Negative values -> less events than expected
Chronograph

- Shrinkage obs/exp ratio
  - Emphasize relative difference
  - Robust for rare events
- Observed vs Expected
  - Emphasises absolute difference
  - Clear empirical basis
Example: nifedipine-flushing

- Example of a transient increase
Example: nifedipine—swelling

- Example of a persistent increase
- Interpretation of persistence not straightforward
Example: sibutramine–malaise

- Example of decreased rate of registration
- Beneficial effect?
A prospective discovery

- Temporal association between risperidone and pneumonia highlighted prospectively
- Similar pattern for group of atypical antipsychotics shown here
- Not in UK SPC in 2008 – but added in 2009
- Latent diagnosis?

Star et al. BJGP 2010.
Challenges

• Sample size
  – Large numbers of patients required to identify rare events
  – Pooling data will lead to heterogeneity

• Missing data
  – Not all medicines taken and medical events experienced are going to be recorded – cf. underreporting!

• Signal-to-noise ratio – lack of clinical suspicion

• Inaccurate event times
  – Delayed diagnoses may resemble adverse drug reactions

• Reversed causality!
# Comparison of approaches

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<th>Breadth</th>
<th>Event rates in exposed</th>
<th>Event rates in un-exposed</th>
<th>Broad capture of drugs and events</th>
<th>Under-recording</th>
<th>Biases</th>
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<tbody>
<tr>
<td>Spontaneous reporting systems</td>
<td>Global</td>
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<tr>
<td>Prescription-event monitoring</td>
<td>~10,000 patients per drug studied</td>
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<tr>
<td>Longitudinal observational databases</td>
<td>1-100 million patients</td>
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Key points

• No single method can be relied upon exclusively in global adverse drug reaction surveillance
• Individual case reports represent the first line of evidence and provide powerful means of recognising the unexpected
• Cohort-event monitoring allows quantification of adverse event rates and solicits information on events that may not otherwise be reported
• The analysis of longitudinal patient records can detect a wide variety of temporal patterns relating medical diagnoses to drug prescriptions
References


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