Another perspective in pharmacovigilance

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Definition WHO

The science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem’
An adverse reaction is a response to a medicinal product which is noxious and unintended. This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation;
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.
Did we really change our focus?

• Do we get the most out of our methods?

• Room for improvement of current methods?

• Towards patient oriented information?
Who uses our information?

• Regulatory agencies
• Approval of drugs for marketing
• Healthcare professionals
• Patients
Widening the scope of pharmacovigilance

- Stronger focus on non-serious ADRs

- Information characterising occurrence of ADRs
  - Risk factors
  - Time course, duration outcome
  - Circumstances under which ADRs occur
  - Behaviour towards ADRs

\[\text{Clinical characteristics} \quad \text{Attitude and behaviour}\]
Serious and non-serious ADRs
Information characterising ADRs
## Clinical aspects

<table>
<thead>
<tr>
<th>Clinical aspects</th>
<th>Before</th>
<th>During ADR</th>
<th>Afterwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors, among which genetic polymorphisms and Co-morbidity and concomitant medication</td>
<td>Clinical symptoms</td>
<td>Outcome Sequelae</td>
<td></td>
</tr>
</tbody>
</table>
Theory of reasoned action

Ajzen's Theory of Planned Behaviour

- Attitude
  - Beliefs about the outcomes of certain action
  - Evaluation of the outcome
- Social Influence
  - Understanding of others' beliefs about a certain action
  - Motivation to comply with others' desires
- Perceived Behavioural Control
  - Perceived ability to carry out the action successfully

Intention

Behaviour

Visit GP?

- Treatment desired?
- Bad experience?
- What do others expect from him?
- Feasible to visit GP?
- Practical circumstances

Ajzen's Theory of Planned Behaviour

- Attitude: Beliefs about the outcomes of certain action, Evaluation of the outcome
- Social Influence: Understanding of others' beliefs about a certain action, Motivation to comply with others' desires
- Perceived Behavioural Control: Perceived ability to carry out the action successfully

Intention → Behaviour

Visit GP

Adherence to drug treatment?

- Treatment desired?
- Risk/benefit?
- Previous experiences?
- What do others expect from him?
- Can I stop using the drug?

**Ajzen's Theory of Planned Behaviour**

- **Attitude**
  - Beliefs about the outcomes of certain action
  - Evaluation of the outcome

- **Social Influence**
  - Understanding of others' beliefs about a certain action
  - Motivation to comply with others' desires

- **Perceived Behavioural Control**
  - Perceived ability to carry out the action successfully

**Intention** -> **Behaviour**

Continue or stop treatment?
# Behaviour of healthcare professionals towards ADRs

<table>
<thead>
<tr>
<th>Healthcare professional</th>
<th>Before</th>
<th>During ADR</th>
<th>Afterwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitude and subjective norms</td>
<td>Risk perception Acquiring knowledge on ADRs</td>
<td>Cautiousness Previous experience</td>
<td>Experience</td>
</tr>
<tr>
<td>Behavior</td>
<td>Educational activities Adherence to guidelines Medication errors Off-label prescribing</td>
<td>Diagnostics Treatment of ADRs</td>
<td>Preventive measures Note contraindications Reporting ADRs</td>
</tr>
</tbody>
</table>
# Behaviour of patients towards ADRs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before</th>
<th>During ADR</th>
<th>Afterwards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitude and subjective norms</td>
<td>Risk perception</td>
<td>Level of acceptance</td>
<td>Experience</td>
</tr>
<tr>
<td></td>
<td>Feeling of control</td>
<td>Coping ability</td>
<td></td>
</tr>
<tr>
<td>Behaviour</td>
<td>Adherence</td>
<td>Consumption of care</td>
<td>Consumption of care</td>
</tr>
<tr>
<td></td>
<td>Off-label use</td>
<td>Absenteeism from work</td>
<td>Absenteeism</td>
</tr>
<tr>
<td></td>
<td>Drug misuse or abuse</td>
<td></td>
<td>Adherence to future</td>
</tr>
<tr>
<td></td>
<td>Reading the SmPC</td>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td></td>
<td>Use of social media</td>
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</table>
Can current data sources be used for studying the characterises of ADRs?
Type of reporters

- Healthcare professionals
- Patients
- Nurses and nurse practitioners
- Paramedical personnel
Healthcare professional as source of information

- HCP provide information on
  - Seriousness of ADRs
  - Diagnosis
  - Differential diagnosis
  - View of HCP may differ from the patient’s view
Patient as source of information

- Patient reported outcomes provide information on
  - Severity of ADRs
  - Symptoms of ADRs
  - Time course and outcome
  - Impact on the QOL
  - Medical confirmation may be needed
Can current signal detection techniques be used for studying the characteristics of ADRs?
Case by case analysis

- Enables the study of characteristics events, depending on the type of reporter

- Motivation of the reporter contributes to the detection of signals

- Reports from patients generally more detailed than from healthcare professionals but provide other type of information
Source, n (%)

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<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td>Spontaneous cases</td>
<td>77</td>
<td>(62)</td>
</tr>
<tr>
<td>Spontaneous cases including literature case reports</td>
<td>13</td>
<td>(10)</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>10</td>
<td>(8.0)</td>
</tr>
<tr>
<td>Observational (post-marketing) studies</td>
<td>10</td>
<td>(8.0)</td>
</tr>
<tr>
<td>Literature case reports</td>
<td>8</td>
<td>(6.4)</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>(5.6)</td>
</tr>
</tbody>
</table>

Signals of special interest count, n (%)

<table>
<thead>
<tr>
<th>Signal</th>
<th>n</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Drug interaction</td>
<td>13</td>
<td>(10)</td>
</tr>
<tr>
<td>Medication error</td>
<td>2</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Off-label use</td>
<td>2</td>
<td>(1.6)</td>
</tr>
<tr>
<td>In utero exposure</td>
<td>2</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Accidental exposure</td>
<td>1</td>
<td>(0.8)</td>
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Active follow up on reported cases

• Additional questionnaires after submitting case reports
• Dedicated questions about the ADR experienced
  – Clinical aspects
  – Impact of the ADRs
  – Attitude and behaviour to ADRs and (future) drug treatment
Active follow up after spontaneous reporting

Fig. 2. Time between the onset of fever and complete recovery from fever following immunization with Influenza A (H1N1) vaccine Pandemrix® in children aged 6 months to 4 years who reported fever after both administrations.

Active follow up after spontaneous reporting

Fig. 3. Responders to questionnaire 1 (Q1) and questionnaire 2 (Q2) in relation to the height of fever following the first vaccination and the decision to receive the second dose. T = temperature.

## Main focus of HCP reports

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<tr>
<td>Clinical characteristics</td>
<td>X*</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Attitude &amp; behaviour physician</td>
<td>X*</td>
<td>X</td>
<td>X*</td>
</tr>
<tr>
<td>Attitude &amp; behaviour patient</td>
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* Active follow up may be needed
## Main focus of reports from patients

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* Active follow up may be needed
Disproportionality analysis

Case by case

• Value of the individual report
• Frame of reference: experience of reporter and assessor
• Signal refers to the selected cases
• Causal relationship

Disproportionality analysis

• All reports contribute ‘equally’
• Frame of reference: (part of) dataset
• Signal also refers to other reports in the dataset
• Statistical dependency
Main focus of disproportionality analysis

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<td></td>
<td></td>
</tr>
<tr>
<td>physician</td>
<td></td>
<td></td>
<td></td>
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Use of observational databases

- Can be used for the studying most of the serious events
- Not all ADRs are coded; ADR usually no “reason for encounter”
- Additional analysis of free-text may be needed
- Promising developments
  - Eu-ADR
  - Sentinel
  - OHDSI
  - Etc.
# Main focus of observational databases

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Use of prospective cohort studies

• Can be tailored to get the desired information
• May enable monitoring ADRs and related aspects over time
• Examples
  – PEM
  – LIM
  – (IMMP)
  – Cohort event monitoring
Main focus of prospective cohort monitoring

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Use of social media

• Exchange of experiences on social media
• Does not depend on reporting
• Real time monitoring
• Medical confirmation may be needed, risk for bias

• September 2014 start IMI WEB-RADR project
Main focus ADR info social media

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In conclusion
Evidence based driven information on drug-ADR

Practice driven information

Demand driven information

True pharmacovigilance
Another perspective..
Thank you for your attention!
There is still a big gap between our knowledge of ADRs and their occurrence, course and impact on the lives of patients in daily practice.
A change to a more patient oriented approach in pharmacovigilance is needed