Methods in Pharmacovigilance

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How can you monitor the safety of drugs after registration?
Post-marketing surveillance

- Hypothesis generation
- Hypothesis confirmation
Hypothesis generation

- Spontaneous Reporting
- Intensified ADR Reporting
- Targeted Reporting
- Cohort Event Monitoring
Hypothesis confirmation

Case control studies | Cohort studies | Randomized Clinical Trials | Meta-analysis
Spontaneous reporting system

- A system to monitor the safety of all medicines on the market
- Voluntary submission of ICSRs by health professionals, pharmaceutical manufacturers and patients to the national pharmacovigilance centre
Spontaneous reporting system

• Requires two initial steps:

A reporter

1. suspects that an undesirable medical event may have been caused by exposure to a medicine

2. reports the suspicion to the national pharmacovigilance centre
What to report?

• Create awareness for reporting
  - You can report
  - You should report
What to report?

- Serious ADRs* (mandatory/not mandatory)
- Severe ADRs
- New drugs
- Unknown (unlabelled reactions)
- ADRs in vulnerable groups (children, pregnant women, elderly)

* fatal, life-threatening, causing permanent disability, prolonging hospitalisation or medically significant
Do you suspect an adverse drug reaction?

Serious reaction?
- Yes → Report
- No → Involves a medicine on additional monitoring (▼)

Involves a medicine on additional monitoring (▼)
- Yes → Report
- No → Unlisted reaction in product information

Unlisted reaction in product information
- Yes → Report
- No → Involves a child

Involves a child
- Yes → Report
- No → Unsure to report?

Unsure to report?
- Yes → Report

MHRA Reporting Reminder
http://www.mhra.gov.uk
What to report?

• Create awareness for reporting
  - You can report
  - You should report
Pros with spontaneous reporting

- Covers the whole population
- Includes all medicines
- Continual monitoring throughout life-cycle of a medicine
- Detects signals of new, rare or serious ADRs
Pros with spontaneous reporting

• Most commonly used method
• Easiest method to establish
• Least labour intensive
• Relatively inexpensive
Cons with spontaneous reporting

- Inherent under-reporting
- Captures only suspected ADRs
- Reporting bias
  - Seriousness, severity
  - New medicine
  - Advertising of product
  - Publicity of specific ADR
Cons with spontaneous reporting

- Denominator unknown
- Difficult to detect
  - delayed ADRs
  - ADRs with high background incidence
<table>
<thead>
<tr>
<th>Source, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous cases</td>
<td>77 (62)</td>
</tr>
<tr>
<td>Spontaneous cases including literature case reports</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>10 (8.0)</td>
</tr>
<tr>
<td>Observational (post-marketing) studies</td>
<td>10 (8.0)</td>
</tr>
<tr>
<td>Literature case reports</td>
<td>8 (6.4)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.6)</td>
</tr>
</tbody>
</table>
Hypothesis generation

Spontaneous Reporting  Intensified ADR Reporting  Targeted Reporting  Cohort Event Monitoring
Intensified spontaneous reporting

• To enhance ADR reporting of specific medicines in early post-marketing phase

• Extension of Spontaneous Reporting Programme

▼ This medicinal product is subject to additional monitoring
The list of medicines under additional monitoring includes medicines authorised in the European Union (EU) that are being monitored particularly closely by regulatory authorities. Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics, together with a short sentence explaining what the triangle means.

The list includes centrally and nationally authorised medicines in the following categories:

- medicines that contain a new active substance that was not contained in any authorised medicine in the EU on 1 January 2011;
- biological medicines authorised after 1 January 2011 - this applies to all biological medicines including biosimilars;
- medicines for which the marketing-authorisation holder is required to carry out a post-authorisation safety study (PASS);
- medicines given conditional approval or authorised under exceptional circumstances and medicines authorised with specific obligations on the recording or monitoring of suspected adverse drug reactions.

A medicine can be included on this list when it is approved for the first time or at any time during its life-cycle.

Medicines containing new active substances or new biologicals remain on the list for five years. Medicines authorised under exceptional circumstances and those with PASSs remain on the list until the conditions have been fulfilled.

In addition to these medicines, medicines can be included on the list at the request of the European Commission or a medicines regulatory authority in an EU Member State after consulting the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC).

More information on additional monitoring is available:

- Guideline on good pharmacovigilance practices: Module X - Additional monitoring
- Medicines under additional monitoring: Background information
Hypothesis generation

Spontaneous Reporting  |  Intensified ADR Reporting  |  Targeted Reporting  |  Cohort Event Monitoring
Targeted spontaneous reporting

• Intensified ADR Reporting within a defined cohort
Targeted Reporting

Specific ADR
All ADRs
Specific Medicine(s)
Specific Clinics
Specific Population
Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda

Helen Ndagije · Victoria Nambasa · Elizabeth Namagala · Huldah Nassali · Dan Kajungu · Gordon Sematiko · Sten Olsson · Shanthi Pal
Targeted Reporting

Specific Population
• Specific population: Patient with HIV infection
Targeted Reporting

- Specific Clinics
- Specific Population
TSR Uganda

• Specific population: Patient with HIV infection

• Specific clinics: Regional Pharmacovigilance Centres of Masaka and Mbale
Targeted Reporting

Specific Medicine(s)
Specific Clinics
Specific Population
TSR Uganda

• Specific population: Patient with HIV infection

• Specific clinics: Regional Pharmacovigilance Centres of Masaka and Mbale

• Specific medicines: Tenofovir
Targeted Reporting

- All ADRs
- Specific Medicine(s)
- Specific Clinics
- Specific Population
• Specific population: Patient with HIV infection
• Specific clinics: Regional Pharmacovigilance Centres of Masaka and Mbale
• Specific medicines: Tenofovir
• Specific ADRs: Renal toxicity
Targeted Spontaneous Reporting

- Côte d’Ivoire
- Kenya
- Lao PDR
- Viet Nam
Pros with TSR

• Can utilise existing ADR reporting infrastructure
• Targets specific medicines of interest
• Possible to implement monitoring programme that targets specific issue of concern (ADR, medicine, patient group)
• Captures useful information (less ‘background noise’)
• Denominator known
Cons with TSR

- Under-reporting remains a problem
- Captures only suspected ADRs or known toxicities
- May limit reporting only to specific ADRs
- Relies on diagnostic capability of reporter
Hypothesis generation

Spontaneous Reporting  Intensified ADR Reporting  Targeted Reporting  Cohort Event Monitoring
Cohort Event Monitoring (CEM)

• To gather more information on the safety profile of a new chemical entity in early post-marketing phase

• Observational cohort study design
• Patients enrolled into cohort and actively followed-up during treatment to record all adverse events (not just suspected ADRs).
Cohort

T=1
Cohort Event Monitoring (CEM)

- Characterise known reactions
- Detect signals of unrecognised reactions
- Identify interactions with other medicines and TCAMs
- Detect inefficacy of medicine
- Assess safety in pregnancy & lactation
- Identify risk factors for ADRs
Lareb Intensive Monitoring

- Frequency in real life
- Time course of ADRs
- Management of ADRs
- Risk factors for ADRs
- Quality of life/Severity
Lareb Intensive Monitoring

To gather knowledge about ADRs, such as frequency, type, time course, risk factors and impact of quality of life in order to improve pharmacotherapy and to optimise patient adherence.
Lareb Intensive Monitoring

- Cohort based on first prescription in the pharmacy
- Patient as source of information
- Web-based questionnaires
- Multiple questionnaires in time
Pharmacy

1st dispensing signal

Registration

Questionnaire

LIM-database

Analysis

Automated process
The pharmacy

- One patient, one pharmacy
- Computer signals a first prescription
- Patient is informed about the LIM study
Nieuws

Injectieplaatsreacties bij exenatide gebruik
Exenatide (Byetta® / Bydureon®) is geregistreerd als aanvulling op orale antidi...
11-04-2014   Lees verder

Gebruikt u dapagliflozin (Forxiga®)?
Per 1 september aanstaande zal het nieuwe diabetesmiddel dapagliflozin (Forxiga®) ....
01-08-2013   Lees verder

Komboglyze® gevolgd met Lareb Intensive Monitoring
Het nieuwe diabetesmiddel Komboglyze® (stofnaam saxagliptine met metformine) wordt ...
29-03-2013   Lees verder

Help mee en meldt u aan!

- Met de aanmeldcode op de achterkant van de folder meldt u zich aan voor het onderzoek. Heeft u geen folder gekregen van uw apotheek, maar wilt u wel deelnemen? Neemt u dan contact op.
- U kunt deelnemen als u minder dan 2 weken geleden gestart bent met het geneesmiddel.
- Bij de aanmelding krijgt u enkele vragen over geneesmiddelengebruik. Het invullen bestaat uit 4 korte stappen en duurt ongeveer 5 tot 10 minuten.
- Bekijk de demo aanmelden en enquête invullen voor meer informatie.
- Benieuwd wat er met uw gegevens gebeurt? Lees dan ons privacyreglement.

Klik op de knop om te starten
Questionnaires

- Patient characteristics
- Drug use
- ADRs
- Quality of life
Questionnaires

• Number of questionnaires per study is flexible

• Timing of questionnaires is flexible

• Collection of longitudinal data
The drug

• New chemical entities (NCE’s)
• Drug whose safety are being discussed
• More than one drug can be monitored
• Length of the study depends on the drugs being monitored
<table>
<thead>
<tr>
<th>Type of drugs</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-diabetic drugs</td>
<td>Bydureon®</td>
</tr>
<tr>
<td>(GLP-1 agonist, DPP-4 inhibitors, SGLT-2 inhibitors)</td>
<td>Byetta®</td>
</tr>
<tr>
<td></td>
<td>Eucreas®</td>
</tr>
<tr>
<td></td>
<td>Forxiga®</td>
</tr>
<tr>
<td></td>
<td>Galvus®</td>
</tr>
<tr>
<td></td>
<td>Janumet®</td>
</tr>
<tr>
<td></td>
<td>Januvia®</td>
</tr>
<tr>
<td></td>
<td>Jentadueto®</td>
</tr>
<tr>
<td></td>
<td>Komboglyze®</td>
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<tr>
<td></td>
<td>Onglyza®</td>
</tr>
<tr>
<td></td>
<td>Trajenta®</td>
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<td></td>
<td>Victoza®</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DOACs</td>
<td>Eliquis®</td>
</tr>
<tr>
<td></td>
<td>Pradaxa®</td>
</tr>
<tr>
<td></td>
<td>Xarelto®</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valdoxan®</td>
</tr>
</tbody>
</table>
Pregabalin study

- Neuropathic pain
- Epilepsy
- Generalised Anxiety Disorder
Pregabalin has been studied in 10 controlled clinical studies of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

Pregabalin has been studied in 3 controlled clinical studies of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.
Pregabalin study

- Neuropathic pain
- Epilepsy
- Generalised Anxiety Disorder
- Questionnaires at 2 weeks, 6 weeks, 3 months, 6 months
Pregabalin study

- 1373 participants
- 58% female
- Average age 54.5 years
- Range 11-89 years
  - Off label use
Pregabalin study

- Neuropathic pain 1134
- Pain 22
- Fibromyalgia 20
- Herpes zoster 16
- Epilepsy 11
- Back pain 11
- Dystrophy 10
1373 participants

897 (65%) fills in one or more questionnaires

728 (81%) reports at least one ADR
Table II. Reported adverse drug reactions (ADRs) that occurred in more than ten patients

<table>
<thead>
<tr>
<th>ADR</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>265 (25.2)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>146 (13.9)</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>72 (6.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>96 (6.5)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>57 (5.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>47 (4.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>43 (4.1)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>43 (4.1)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>41 (3.9)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>33 (3.1)</td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>32 (3.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (3.0)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>21 (2.1)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>20 (1.9)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>17 (1.6)</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>17 (1.6)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>16 (1.5)</td>
</tr>
<tr>
<td>Oedema</td>
<td>15 (1.4)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>13 (1.2)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>11 (1.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>10 (1.0)</td>
</tr>
</tbody>
</table>
Signal

• New association
• Interactions
• Information about latencies
• Information about recovery
• Information about frequencies
<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
</tr>
<tr>
<td>Frequency not known</td>
<td>Hypersensitivity, angioedema, allergic reaction</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Appetite increased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Rare</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Euphoric mood, confusion, irritability, libido decreased</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Disinhibition, elevated mood</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>Dizziness, somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia</td>
</tr>
</tbody>
</table>
Signal

- Headache
  - frequency higher than SmPC
  - Withdrawal not always necessary for recovery
- Abdominal pain
  - Not mentioned in the SmPC
- Suicidal ideation
- Hypoglycaemia
Table 1. Incidence densities per 1000 person-days per period for the five most frequently reported adverse drug reactions associated with pregabalin use

<table>
<thead>
<tr>
<th></th>
<th>0–14 days</th>
<th>15–42 days</th>
<th>43–90 days</th>
<th>91–180 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>18.0</td>
<td>1.0</td>
<td>0.34</td>
<td>0.05</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7.4</td>
<td>0.53</td>
<td>0.10</td>
<td>0.17</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>4.0</td>
<td>0.32</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.9</td>
<td>0.16</td>
<td>0.09</td>
<td>NA</td>
</tr>
<tr>
<td>Weight increase</td>
<td>1.6</td>
<td>0.38</td>
<td>0.13</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Developments

- Vaccines
- Other inclusion points
Web-based
Intensive Monitoring
a patient based
pharmacovigilance tool

Linda Härmak
PV methods spectrum

Spontaneous Reporting
- Denominator unknown
- Suspected ADRs
- All medicines

Intensified ADR Reporting
- Denominator unknown
- Suspected ADRs
- Specific medicines

Targeted Reporting
- Denominator known
- Suspected ADRs/Specific ADRs
- Cohort specific medicines

Cohort Event Monitoring
- Denominator known
- All events
- Cohort specific medicines

- Essential minimum reporting
- Early post-marketing phase of new drugs
- Profile of ADRs for a specific medicine in a specific popn
- Post-marketing surveillance of a new chemical entity
- WHO Programme for International Drug Monitoring
- UK/EU Black Triangle Scheme
- Profile of ADRs for a specific medicine in a specific popn
- CEM of new antimalarials (ACTs)

WHO Programme for International Drug Monitoring
UK/EU Black Triangle Scheme
Post-marketing surveillance of a new chemical entity
CEM of new antimalarials (ACTs)
<table>
<thead>
<tr>
<th>Method</th>
<th>Medicines</th>
<th>Population</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Reporting</td>
<td>All medicines, life-cycle of product</td>
<td>All exposed individuals but denominator unknown</td>
<td>All ADRs</td>
</tr>
<tr>
<td>Intensified ADR Reporting</td>
<td>Specific medicines</td>
<td>All exposed individuals but denominator unknown</td>
<td>All ADRs</td>
</tr>
<tr>
<td>Targeted Reporting</td>
<td>Specific medicines</td>
<td>Defined cohort</td>
<td>All ADRs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specific ADRs</td>
</tr>
<tr>
<td>Cohort Event Monitoring</td>
<td>Specific medicines</td>
<td>Defined cohort</td>
<td>All Events</td>
</tr>
</tbody>
</table>
Which method?

- A new drug is introduced to the market, A. A has a new mechanism of action compared to other drugs on the market. How would you monitor the safety of A? Why?
A new drug is introduced on the market, B. B is an ACE inhibitor indicated as treatment of hypertension and heart failure. How would you monitor the safety of this drug? Why?

Which method?
There is emerging evidence that drug C, which is used in the treatment of HIV, can cause hepatitis. You want to know more about this ADR. Which method would you choose? Why?
Which method?

- Drug D is a biological drug recently introduced to the market. How would you monitor the safety of D? Why?
Drug E will be introduced into a public health programme, but its safety in this population is not well known. How would you monitor the safety of E? Why?

Which method?