Temporal synchrony between drug dispensings and adverse drug events? The example of statins & rhabdomyolysis and metamizole or clozapine & agranulocytosis

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Background and Objective

- Spontaneous reports of adverse events (AE) have the potential to detect unknown and to estimate the frequency of adverse drug reactions (ADRs), among others.
- Main issue: Size of population at risk (= denominator) is unknown!
- A novel method combining spontaneous AE reports and drug dispensing data by employing temporal synchrony analysis may help to detect signals in pharmacovigilance datasets.
- The method was tested for model drugs as a proof of principle.

Method

Drugs and events

- Statins (mono preparations only; simvastatin, lovastatin, rosuvastatin, atorvastatin, pravastatin, fluvastatin): rhabdomyolysis
- Metamizole and clozapine: agranulocytosis

Data collection

- Aggregated monthly adverse event data: German 'ADR database' of the Federal Institute for Drugs and Medical Devices
- Aggregated monthly dispensing data as defined daily doses (DDD), extrapolated from pharmacy claims data of the DAPI database from > 80% community pharmacies at the expense of the German Statutory Health Insurance Funds (= 90% of the German population)
- Time period: 2005 to 2015

Temporal synchrony analyses (see figures below)

1. Set offset between date of AE reports and dispensings by -1 month
2. Smoothing dispensing and AE curves by moving average (actual and following month)
3. Count synchronous peaks of dispensings and AE, report as ratio to overall peaks (‘peaks’)
4. Testing for statistical significance by Monte Carlo randomization, statistical significance: p ≤ 0.05

Results

**Statins**

<table>
<thead>
<tr>
<th>'peaks'</th>
<th>p-value</th>
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<tbody>
<tr>
<td>0.31</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Dispensings of statins in outpatient care and number of spontaneous reports of statin-associated rhabdomyolysis from 2005-2015

Incidence rate: 0.14 per 10,000 person-years

**Metamizole**

<table>
<thead>
<tr>
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<th>p-value</th>
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<tbody>
<tr>
<td>0.36</td>
<td>0.28</td>
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Dispensings of metamizole in outpatient care and number of spontaneous reports of metamizole-associated agranulocytosis from 2005-2015

Incidence rate: 1.4 per 10,000 person-years

**Clozapine**

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<tr>
<td>0.19</td>
<td>0.99</td>
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Dispensings of clozapine in outpatient care and number of spontaneous reports of clozapine-associated agranulocytosis from 2005-2015

Incidence rate: 2.1 per 10,000 person-years

Discussion and Conclusions

- No temporal synchrony detected for all three drugs with the method and the chosen parameters.

References:

Study registered at International Clinical Trials Registry Platform: DRKS00011398, info@dapi.de

Conflict of interest:

None declared.