# Using the OpenVigil 2 pharmacovigilance tool for guidance for clinical decisions involving newly occurring adverse events

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http://openvigil.sf.net

## The Problem – Where‘s that detoriation of the patient‘s condition coming from?

?

If a new event is regarded to be caused by the medication, further information which drug is the most likely is needed.
**We compare summary of product characteristics (SPC), the SIDER Side Effect Resource, OpenVigilFDA and OpenVigil 2 as possible sources of information.**
SPCs and SIDER – which relies on data from SPCs – cannot be entirely trusted, unfortunately (fig. 1).

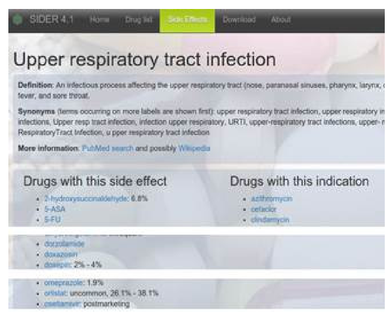


Fig. 1: SIDER-output for adverse event "Upper respiratory tract infection" for drugs orlistat and doxazosine although a statistical signal and a pharmacological rationale is missing (ref. 1)

## Our solution: OpenVigilFDA at bedside

## Case reports: Liver damage (gGT↑)

A patient at a radiotherapy ward developed increasing gamma-glutamyltransferase (gGT) blood levels. Ultrasound did not reveal filiae in the liver.

OpenVigilFDA was used to rank the RRR of all drugs of the patient for this adverse event (fig. 2, cf. material and methods below). **Pantoprazole was identified as the most likely agent** and subsequently stopped. Omeprazole and ranitidine showed comparable associations with increased gGT (fig. 3, tab. 1). Therefore, a magaldrate was chosen for this patient. **The condition improved**.

Of note, we used this approach successfully for a similar patient who also developed an increased gGT while on pantoprazole and for yet another patient where dipyrone (INN: metamizol) was identified.

***Open Vigil* FDA analysis of the drug in a list being most likely associated with an event 'GAMMA-GLUTAMYLTRANSFERASE+INCREASED'**

No background correction used.
Extracting data (this can take 15-80 seconds)...Show/Hide

Copy table below to clipboard

| Term | Count |
|---|---|
| Total number of reports with event GAMMA-GLUTAMYLTRANSFERASE+INCREASED | 11185 |
| Percentage this event of all events | 0.18958 |
| All reports (all events/drugs) (total) | 5899773 |

Table of measures of disproportionality for each drug and the specified adverse event:
Interpretation: Large RRR values indicate overproportional reporting of this reaction for this drug. Consider stopping this drug first.

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| substance_name | DE | D | percentage_DE_of_D | RRR | percentage_DE_of_E |
|---|---|---|---|---|---|
| PANTOPRAZOLE | 228 | 62968 | 0.36209 | 1.90992 | 2.03844 |
| LORAZEPAM | 154 | 54873 | 0.28065 | 1.48034 | 1.37684 |
| METOCLOPRAMIDE | 65 | 35623 | 0.18247 | 0.96246 | 0.58114 |
| LEVOTHYROXINE | 234 | 125222 | 0.18687 | 0.98568 | 2.09209 |

Query execution time is 6.87 seconds.

Fig. 2: rDPA-data for gGT increased

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| substance_name | DE | D | percentage_DE_of_D | RRR | percentage_DE_of_E |
|---|---|---|---|---|---|
| OMEPRAZOLE | 397 | 117877 | 0.33679 | 1.77648 | 3.5494 |
| PANTOPRAZOLE | 228 | 62968 | 0.36209 | 1.90992 | 2.03844 |
| LANSOPRAZOLE | 220 | 47503 | 0.46313 | 2.44287 | 1.96692 |
| RANITIDINE | 147 | 46055 | 0.31918 | 1.6836 | 1.31426 |

Query execution time is 6.44 seconds.
Date & time of this analysis: 2016-02-24 16:19:32

Fig. 3: rDPA-data for common antacida

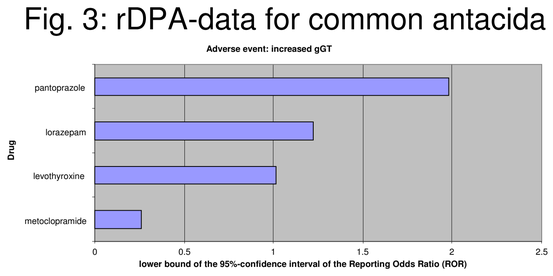


Fig. 4: rDPA-diagramme for gGT increased

**Comparison with other data:**

OpenVigil 2 uses cleaned data obtained by other cleaning procedures than OpenVigilFDA. The lower-bound of the 95%-confidence interval of the ROR was calculated (fig. 4).

All data are summarized in tab. 1:

**Tab. 1: Comparison of frequencies and risks for gGT increased**

| Drug | SPC | SIDER | OpenVgilFDA [RRR] | OpenVigil 2 [lb ROR] |
|---|---|---|---|---|
| Pantoprazole | Uncommon (0.1-1%) | Yes (no frequency data) | 1.9 | 1.97 |
| Lorazepam | No | No | 1.48 | 1.22 |
| MCP | No | No | 0.96 | 0.25 |
| L-Thyroxine | No | No | 0.98 | 1.01 |
| Omeprazole | Uncommon (0.1-1%) | No | 1.78 | 1.63 |
| Ranitidine | Rare (0.01-0.1%) | No | 1.68 | 0.96 |

**Summarizing, all methods deliver comparable results. While it takes several minutes to operate OpenVigil 2 or SIDER or to download all relevant SPCs, OpenVigilFDA can provide this information within a few seconds.**

## Case reports: Thrombocytopenia

A patient at a neurosurgery ward developed spontanous bleedings and thrombocytopenia during treatment with three anticonvulsants.

OpenVigilFDA was used to rank all drugs of the patient for the adverse event (fig. 5).

**Levetiracetam was stopped. The condition improved.**

***Open Vigil* FDA analysis of the drug in a list being most likely associated with an event 'THROMBOCYTOPENIA'**

No background correction used.
Extracting data (this can take 15-80 seconds)...Show/Hide

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| Term | Count |
|---|---|
| Total number of reports with event THROMBOCYTOPENIA | 36012 |
| Percentage this event of all events | 0.64946 |
| All reports (all events/drugs) (total) | 5544906 |

Table of measures of disproportionality for each drug and the specified adverse event:
Interpretation: Large RRR values indicate overproportional reporting of this reaction for this drug. Consider stopping this drug first.

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| substance_name | DE | D | percentage_DE_of_D | RRR | percentage_DE_of_E |
|---|---|---|---|---|---|
| LEVETIRACETAM | 729 | 26517 | 2.74918 | 4.23302 | 2.02433 |
| LACOSAMIDE | 39 | 5081 | 0.76757 | 1.18185 | 0.1083 |
| LAMOTRIGINE | 339 | 45242 | 0.7493 | 1.15373 | 0.94135 |

Query execution time is 4.29 seconds.

Fig. 5: rDPA-data for thrombocytopenia

**Comparison with other data:**.

**Tab. 2: Comparison of frequencies and risks for thrombocytopenia**

| Drug | SPC | SIDER | OpenVgilFDA [RRR] | OpenVigil 2 [lb ROR] |
|---|---|---|---|---|
| Levetiracetam | Uncommon (0.1-1%) | Common (1-10%) | 4.23 | 4.15 |
| Lacosamide | No | No | 1.18 | 0.7 |
| Lamotrigine | Very rare (< 0.01%) | Rare (0.01-0.1%) | 1.15 | 1.16 |

**A case of isolated thrombocytopenia:**

A female patient at a radiotherapy ward developed an isolated thrombocytopenia, i.e., no concomitant anaemia or neutropenia. Based on our previous experience with bone marrow damaging radiooncologic treatments, this could not be explained.
In this case, OpenVigil 2 was used to rank all drugs (fig. 6). Dexamethasone appears to confer the highest risk. Since dexamethasone is used generally at our ward in patients with failing bone marrow due to the radiooncologic therapy, we assumed this signal to be caused by confounding. **Cefpodoxime** could be **stopped** because antibiotic treatment was no longer neccessary. **The condition improved.**

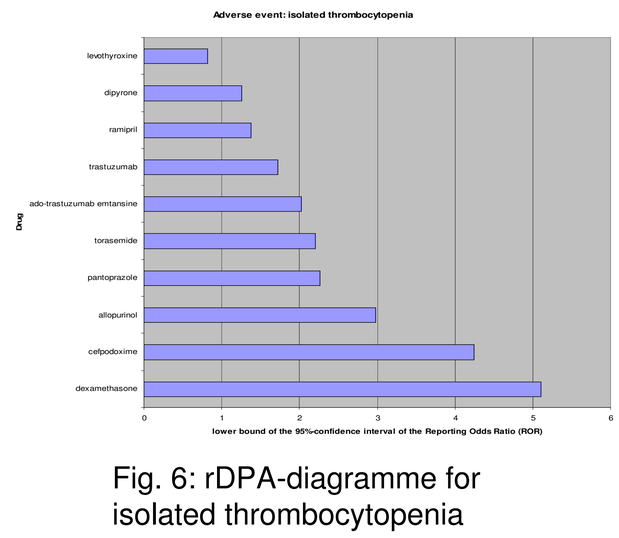
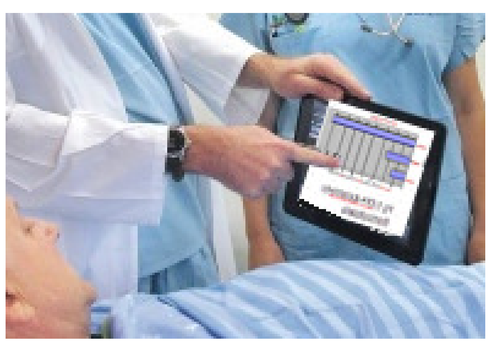



Fig. 6: rDPA-diagramme for isolated thrombocytopenia



**Material and Methods.** Individual German SPCs, SIDER and OpenVigil 2 and OpenVigilFDA were used to extract information on the frequency and association of drugs and certain adverse events. These OpenVigil tools operate on U.S. american pharmacovigilance data. All data were extracted Dec 2015 to Feb 2016 using the latest datasets. We use a reverse disproportionality analysis (rDPA) to extract the Reporting Odds Ratio (ROR, an adaption of the Odds Ratio) or the Relative Reporting Ratio (RRR, in magnitude and explanatory power similar to ROR) for assessing the strength of the possible association. The lower bound of the ROR (lb ROR) is used for very conservative signal generation. Where applicable, multiple adverse event terms were concatenated with Boolean logic (AND, NOT, …) and confounders were eliminated.

**Literature**: 1. Böhm R., Herdegen Th. Dtsch Apoth Ztg 2009, 149(32), S. 3623. [Risk of infection and liver damage by orlistat] Infektionsrisiko und Leberschädigung unter Orlistat