

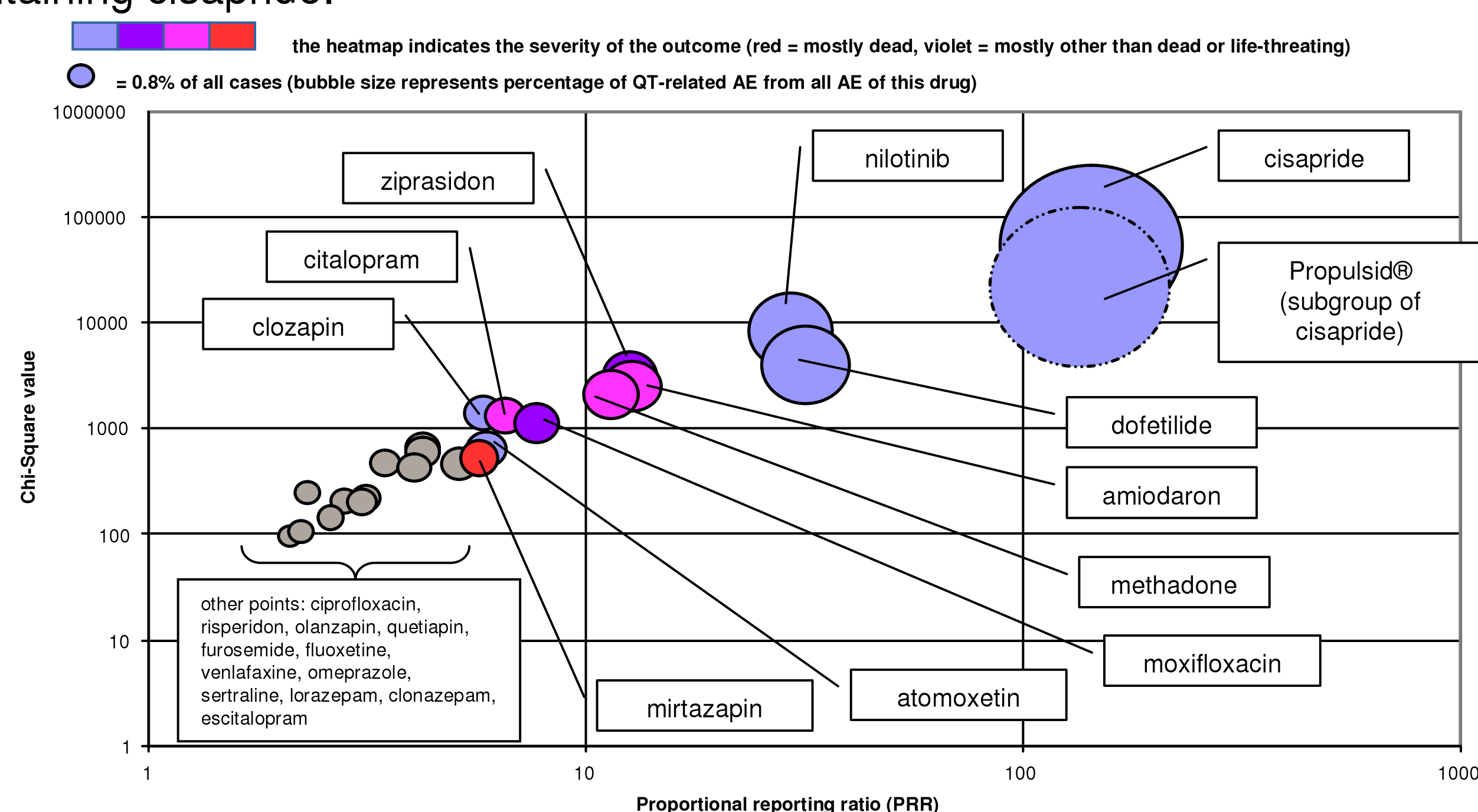


Background

Clinical routine often requires the information which drug in the medication list of a patient is most likely evoking an adverse event (AE) or which combinations of drugs carry the risk for drug-drug-interactions (DDI). Data for this usually derive from the pharmacokinetic and -dynamic profile of a drug that is assessed during preclinical development and clinical trials. However, rare adverse events are not detected during clinical trials, and the potential targets as well as the metabolic pathways are only incompletely known. This is why spontaneous reporting was introduced to sample reports of unexpected behavior of drugs. The resulting pharmacovigilance data are not suited either for calculating risks or establishing causal relationships between one (or more) drug(s) and AE. Instead the data can be analyzed to generate hypotheses and test them at bench or bedside. The pharmacovigilance data analysis tool OpenVigil 2 (openvigil.sf.net) offers unique analysis options to address the clinical questions mentioned above. In comparison to other tools that operate on FDA data, OpenVigil 2 uses cleansed data which leads to more precise results in pharmacovigilance data mining.

Reverse Disproportionality Analysis

Methods: Reverse Disproportionality Analysis (DPA) for at least one of the adverse events “electrocardiogram qt corrected interval prolonged” or “electrocardiogram qt prolonged” or “electrocardiogram qt interval abnormal” was performed. The 4D-diagram below shows overproportional reporting (x-axis), statistical significance (y-axis), fraction of all reported AE for a drug (bubble size) and severity of outcome (color heatmap) of the 23 drugs that most likely induce QT changes. The brandname “Propulsid” is also included as an example of a subclass of all drugs containing cisapride.



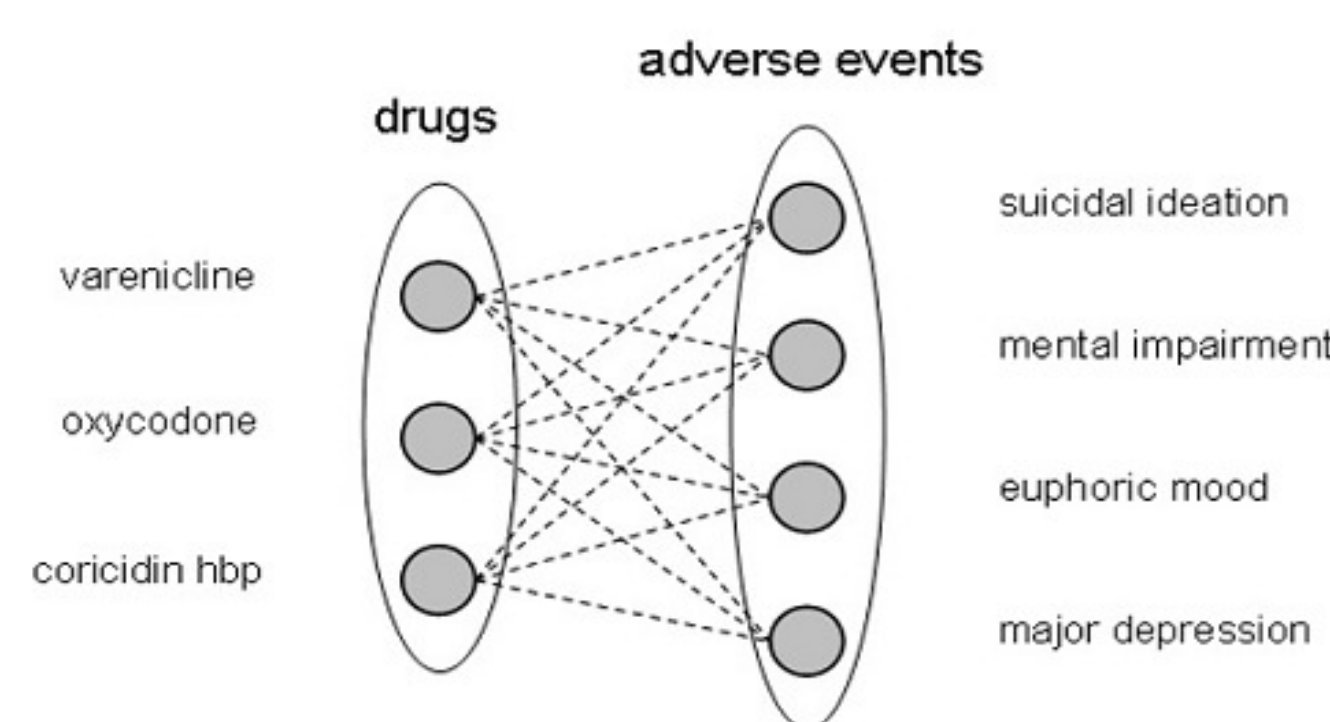
Results: According to this biased analysis (cf. OpenVigil cave-at document!) cisapride confers the highest risks for QT prolongation. QT changes are less commonly reported with mirtazapine but those reported were overproportionally associated with deadly outcome.

The Propulsid-example shows that this and all other analyses can also be done on subsets, e.g., one drug class or all brands containing a certain drug. These data could identify risk factors in supposedly inactive excipients of pharmaceutical products.

Detection of Drug-Drug-Interactions

Background: The capability of OpenVigil to mine for multiple data items at the same time allows to search for signs of drug-drug-interactions (DDI) or adverse event syndromes, respectively, in pharmacovigilance data.

This illustration of an ADE bicluster (from Harpaz 2011) shows how DDI and syndromes could be detected using pharmacovigilance data:



Methods: Re-calculation of published results: Harpaz 2010 describes 52 records containing the drugs “Darvocet” and “Varenicline” and the AE “nausea”, “insomnia”, “memory impairment”, “fatigue” and “abnormal dreams” in the FDA AERS data for 2008.

Results: OpenVigil 2 finds only 12 records (unique reports) in the FDA AERS data from the year 2008. This is due to the very conservative data validation and importing process during which duplicate reports are detected. However, still, those 12 unique reports originate from only 2 cases as can be seen when looking at the raw data.

Using OpenVigil 1 to search the unfiltered raw data of 2008 reveals all 52 reports¹.

However, these 52 reports also originate from only 2 cases².

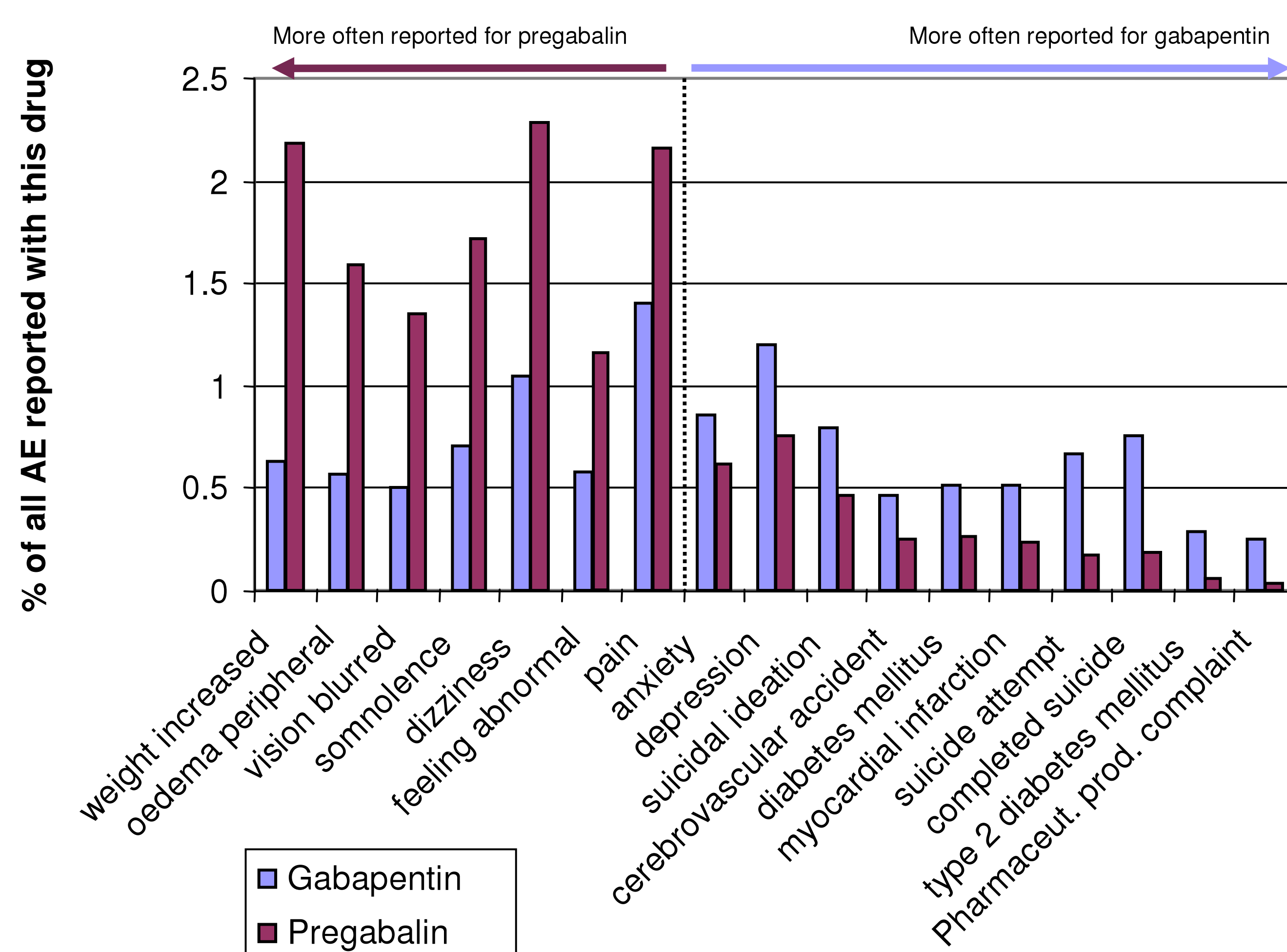
This suggests that Harpaz et al. do not correct for multiplicates of the same case or report.

Furthermore, their strategy to detect DDIs is flawed since they only include drugs marked as „primary suspect“ and only consider associations with more than 50 reports. The latter is a necessity that arises from the large volume of the FDA AERS data.

SQL Code: 1) SELECT COUNT(*) FROM DEMO WHERE ISR = ANY(SELECT ISR FROM DRUG WHERE DRUGNAME = "DARVOCE") AND ISR = ANY(SELECT ISR FROM DRUG WHERE DRUGNAME = "CHAMPIX" OR DRUGNAME = "CHANTIX" OR DRUGNAME = "VARENICLINE") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "ABNORMAL DREAMS") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "FATIGUE") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "INSOMNIA") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "MEMORY IMPAIRMENT") AND (DSRC="DEMO08Q1" OR DSRC="DEMO08Q2" OR DSRC="DEMO08Q3" OR DSRC="DEMO08Q4");
2) SELECT COUNT(DISTINCT CASENO) FROM DEMO WHERE ISR = ANY(SELECT ISR FROM DRUG WHERE DRUGNAME = "DARVOCE") AND ISR = ANY(SELECT ISR FROM DRUG WHERE DRUGNAME = "CHAMPIX" OR DRUGNAME = "CHANTIX" OR DRUGNAME = "VARENICLINE") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "ABNORMAL DREAMS") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "FATIGUE") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "INSOMNIA") AND ISR = ANY(SELECT ISR FROM REAC WHERE PT = "MEMORY IMPAIRMENT") AND (DSRC="DEMO08Q1" OR DSRC="DEMO08Q2" OR DSRC="DEMO08Q3" OR DSRC="DEMO08Q4");

AE-profiles of drugs of same drug class

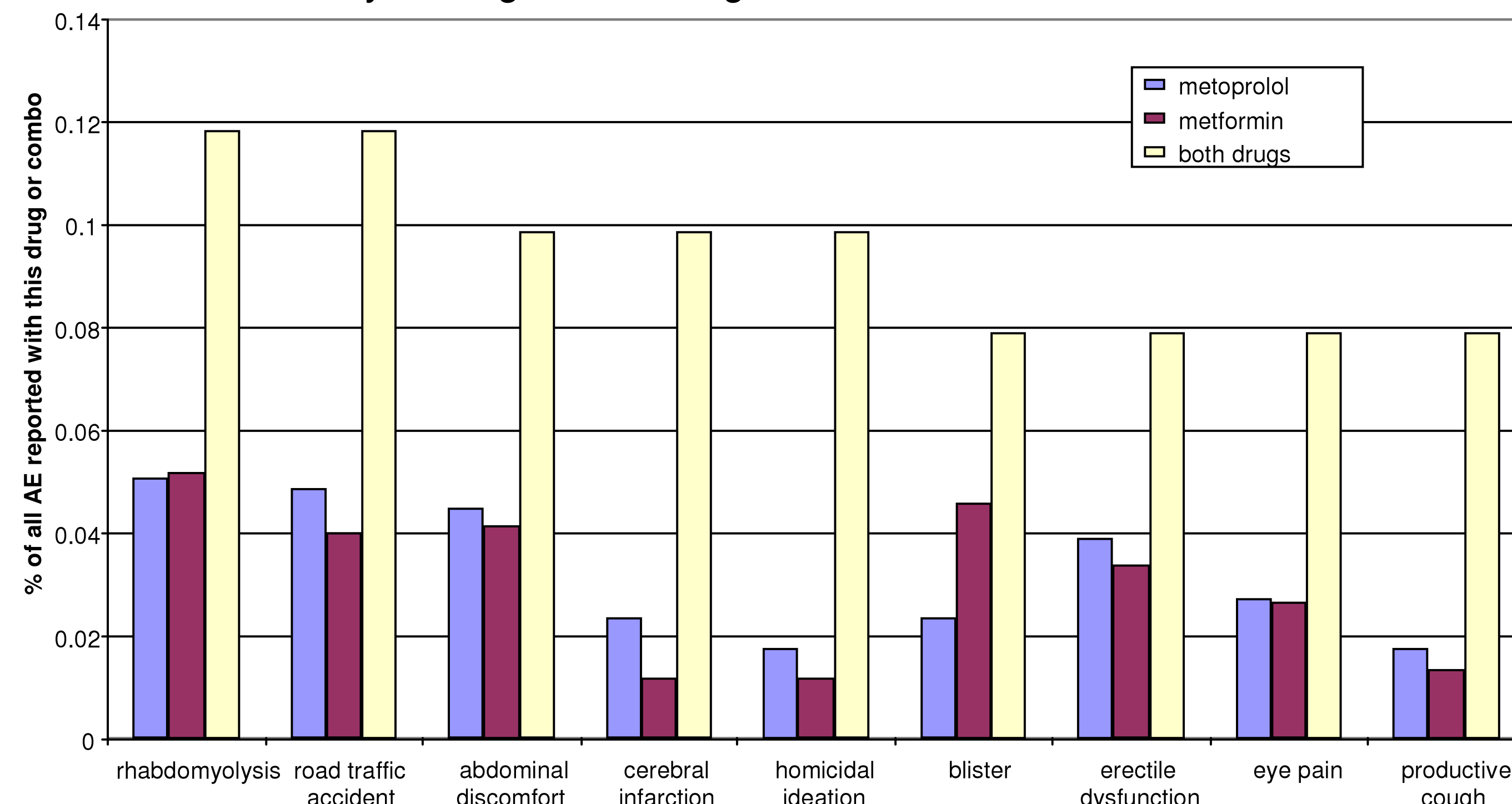
Methods: Numbers of reports for AEs reported with either of two drugs with a highly similar range of applications (i.e., pregabalin and gabapentin) were extracted. The most extreme differences in relative numbers for the same adverse events of these drugs were visualized:



Results: It appears that weight increase is predominantly an AE seen with pregabalin but not so much with gabapentin. On the other hand, gabapentin appears to confer a much higher risk for anxiety/depression/suicide. This is one method of ranking drugs within their class and to screen for the safest treatment option. Data like these provide the physician an additional decision guidance which drug of a class should be used.

Since the bi-clustering technique described by Harpaz is extremely dependent on computing power and memory, OpenVigil 2 does currently not offer a hypothesis-free detection of DDI. Instead, pre-defined combinations of drugs or events (= bi-clusters) can be analyzed, e.g., commonly used drugs:

Methods: Numbers of reports for AEs reported with either of two drugs which are frequently prescribed together (i.e., metformin and metoprolol) and the numbers of reports for the combination of these drugs were extracted. The most extreme differences in reporting between each of the drugs alone and the combination acquired by calculating the fraction of all drug-event-associations and by sorting and filtering this list was visualized:



Results: The above listed AE could be due to a drug-drug-interaction. As with all pharmacovigilance data, results have to be interpreted with caution: The higher incidence of AEs might be caused by the more severe illness of patients receiving both instead of just one drug.