

Large-scale drug repositioning by safety signals using the **OpenVigil 2 pharmacovigilance data analysis tool**

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Introduction

Drug discovery is an expensive and long-lasting process which is frequently halted due to unforeseen issues. Repositioning of known drugs for new indications is therefore an expedient alternative to traditional drug discovery, i.e. the research on new compounds. Drug repositioning candidates are found accidentally by serendipity, e.g. clinical observation, or systematically by targeted searches, e.g. assessing (dis-)similarities in pharmacogenomics, biological pathways and chemical structures (Ashburn TT. Nat Rev Drug Discov. 2004).

Pharmacovigilance, introduced after the thalidomide tragedy, provides early detection of adverse drug reactions by statistical approaches to detect "signals" of disproportionality, i.e. a deviation between expected and observed frequencies of a drug-event-pair. Advanced computational techniques and growing data foundation move pharmacovigilance into a proactive direction as its statistical methodologies can be used to identify inverse and thus desirable safety signals, i.e. "adverse events" that occur less frequently than expected (Böhm R et al. PLoS One. 2016). OpenVigil 2 was used to screen for drug repositioning candidates via disproportionality analyses (DPA) using reporting odds ratio (ROR).

Results

Screening pharmacovigilance data revealed a multitude of putative candidate drugindication-pairs (e.g. > 500 new putative drugs/medicinal products against nasopharyngitis (figure 1) and > 400 new putative indications for acetylcysteine). The top results are visualized in figures 2-5.

Literature research (table below) underpinned most findings by providing either a probable mechanism of action or similar therapeutic observations from clinical trials, case-reports or in vitro experiments.

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Results: Candidates against nasopharyngitis



Fig. 1: Full DPA of the event "nasopharyngitis" arranged by statistical significance (Chi-squared) and clinical relevance (proportional reporting ratio, similar to ROR). PRR values of less than 0.5 denote an occurrence 50% less frequently than expected and Chi-squared>4 significance (green box).



Fig. 2: Leading inverse safety signals of a DPA of the event "nasopharyngitis" sorted by upper bound of the 95% confidence interval of the ROR (error bars)

Results: Candidate drugs against headache



Fig. 3: Leading inverse safety signals of a DPA of the

Discussion

A multitude of signals for putative new indications was easily extractable and interesting candidates were identified. Of note, we identified inverse signals for nasopharyngitis and antipsychotics and an inverse signal for "aspirin" and gynecologic events (grouped in MedDRA as "Fertility disorders"). The latter could not be further explained by the available literature. Pharmacovigilance must be used with caution due to missing or incorrectly coded data (e.g. mix-up of "indication" and "event") and various reporting issues (e.g. under-reporting, biased reporting). Drug dosage and the severity or duration of the adverse events is usually not reported and was thus not analyzed in this study. For most desirable signals detected, convincing affirmative data from other sources or mechanisms of actions could be found in the literature. These confirming literature searches need to be considered biased since the exact methodology was not defined beforehand in a protocol.

Conclusion: OpenVigil 2 (http://openvigil.sf.net) is suitable for hypothesis generation for drug repositioning and thus drug discovery.

event "headache" sorted by upper bound of the 95% confidence interval of the ROR (error bars).

0.2

0.1





Results: Candidate indications for aspirin



Methods

Using OpenVigil 2 (openvigil.sf.net, U.S. American pharmacovigilance data from 2004 to 2018Q3), disproportionality analyses (DPA) for the drugs "aspirin" and "acetylcysteine" and DPAs for the adverse events (AE) "nasopharyngitis" and "headache" based on cases were performed. Results were sorted for ascending disproportionality between expected and observed frequency using reporting odds ratios (ROR) values and their upper and lower bounds of the 95%-confidence interval. In addition, disproportionality signals referring to brandnames were resolved to names of active substances and included as well. Only findings with n > 3 were considered. Obviously confounded signals and terms that could not be used in a clinical context such as chemotherapeutics or narcotics were eliminated. At least the first five inverse safety signals (ROR < 1) with statistical significance (upper bound of the 95%-confidence interval of the ROR < 1) and putative clinical relevance (ROR < 0.5, denoting approx. 50% less reports as expected by chance) were extracted and subsequently analyzed by literature research in MEDLINE and Google Scholar for affirmative data from controlled clinical trials and putative mechanisms of actions.