Existing Evidence in Published Literature for Drug-Condition Pairs

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Background

- Literature provides evidence from a variety of sources (e.g. clinical trials, case reports, observational studies, etc.)
- Even though the number of published studies on drug safety has increased considerable in the last years, we believe many drug-condition pairs have not been investigated

Objectives

- To quantify using an automated search strategy the extent to which literature is readily available to explore evidence about potential drug-outcome associations

Methods

DATA

- Two methods to access data (**Figure 1**):
  - **Search Method 1** – RISmed (publicly available R-package) to search/download English content from PubMed that has the "Humans" MeSH tag and specific drug-condition tags or terms in title/abstract
  - **Search Method 2** – Query copy of U.S. National Library of Medicine® (NLM) MEDLINE looking for articles with specific drug-condition tags

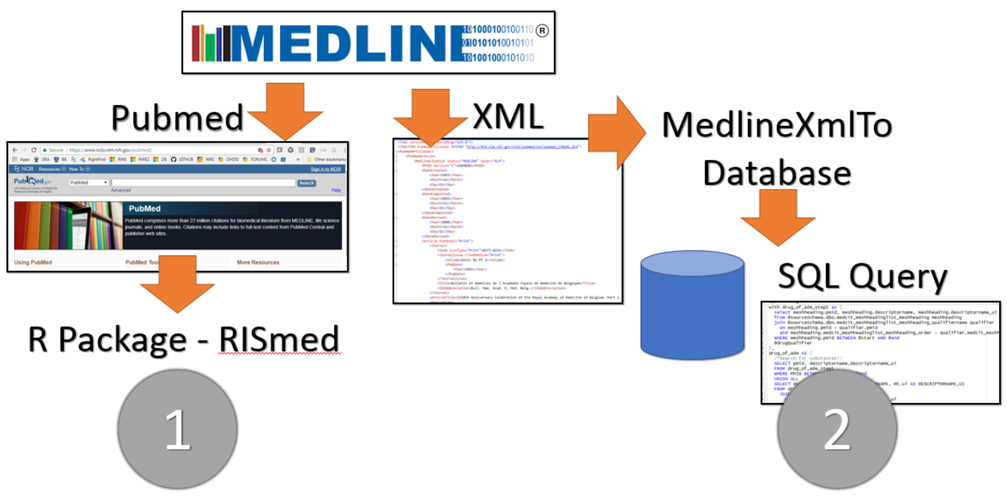


FIGURE 1 – Published Literature Search Strategies

EVALUATED SET OF DRUGS & CONDITIONS

- Identified **"all drugs"** as MeSH codes with >=100 patient exposures in Truven Health MarketScan® Commercial Claims & Encounters Database in year 2015
- Identified **"all conditions"** as MeSH codes with >=100 MEDLINE articles, associated with qualifier "chemically induced", and not used for animal research/experimentation
- Summarized patterns of published evidence across:
  - "all drugs" / "all conditions"
  - subgroup analysis based on "all drugs" / 23 conditions* of pharmacovigilance interest (Trifirò et al.)

* While there are 23 conditions, "Cardiac valve fibrosis" did not have a good MeSH map and was not explored while "Aplastic anemia/pancytopenia" was split into 2 conditions

SEARCHING FOR EVIDENCE

Evidence was assessed by 3 search strategies with varying degrees of sensitivity:

1. **Broad PubMed Search** – leveraging *Search Method 1* to identify all publications returned by searching for a given drug-condition pair
2. **Co-occurrence of MeSH Terms** – leveraging *Search Method 2* selection of all publications in which both the drug and condition MeSH tags were found
3. **Co-occurrence of MeSH Terms with Adverse Event Qualifiers** – same as above but drug qualified with "adverse effects" and conditions "chemically induced" (Avillach et al.)

SEARCH EXAMPLE

Using PMID 26948245 in **Abstract 1** as an example of an article that meets both search strategies for D000069283-"Rituximab" & D009503-"Neutropenia"

Scand J Rheumatol. 2016 Oct;45(5):404-7. doi: 10.3109/03009742.2016.1138318. Epub 2016 Mar 7.

Late-onset neutropenia after rituximab in ANCA-associated vasculitis.

Knight A[1], Sundström Y[2], Börjesson O[3], Bruchfeld A[3], Malmström V[2], Gunnarsson I[2].

Author information

Abstract

BACKGROUND: Rituximab (RTX) is being used increasingly in anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV). Late-onset neutropenia (LON) and risks of infections have been observed following RTX therapy in rheumatological diseases including granulomatosis with polyangiitis (GPA) but data on microscopic polyangiitis (MPA) are lacking.

METHOD: We studied the occurrence of LON in 59 AAV (47 GPA/12 MPA) patients treated with RTX. Patient charts were retrospectively reviewed for the occurrence of LON and clinical data were extracted and included in the analysis.

RESULTS: Seven of the total 59 patients (11.9%) developed LON after a median time of 86 days (range 56-168 days) since their latest RTX treatment. Of these seven LON patients, 5/47 (10.6%) had a diagnosis of GPA and 2/12 (16.7%) of MPA. Three of the patients developed LON after the first RTX treatment and four had received repeated courses. Five LON patients developed infectious symptoms. Six of the patients were hospitalized. Retreatment with RTX was given in three cases without further LON episodes.

CONCLUSIONS: LON is a potentially severe side-effect of RTX occurring in both GPA and MPA and may develop after both single and repeated treatment courses. As infections are commonly seen, the condition requires an increased awareness. No predisposing factors for LON were identified.

MeSH terms
Adult
Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis/drug therapy
Antirheumatic Agents/adverse effects*
Female
Granulomatosis with Polyangiitis/drug therapy*
Humans
Male
Microscopic Polyangiitis/drug therapy*
Middle Aged
Neutropenia/chemically induced*
Rituximab/adverse effects*

Substances
Antirheumatic Agents
Rituximab

1. **Broad PubMed Search** – [Red Highlights] Selected not only for the MeSH tags but for the MeSH name text found in the title and abstract
2. **Co-occurrence of MeSH Terms** – [Blue Highlights] Contains both MeSH tags
3. **Co-occurrence of MeSH Terms with Adverse Event Qualifiers** – [Green Highlights] Contains both MeSH tags with qualifiers

ABSTRACT 1 – Example PubMed Article with Meets Both Search Criteria for "Rituximab" & "Neutropenia"

Results

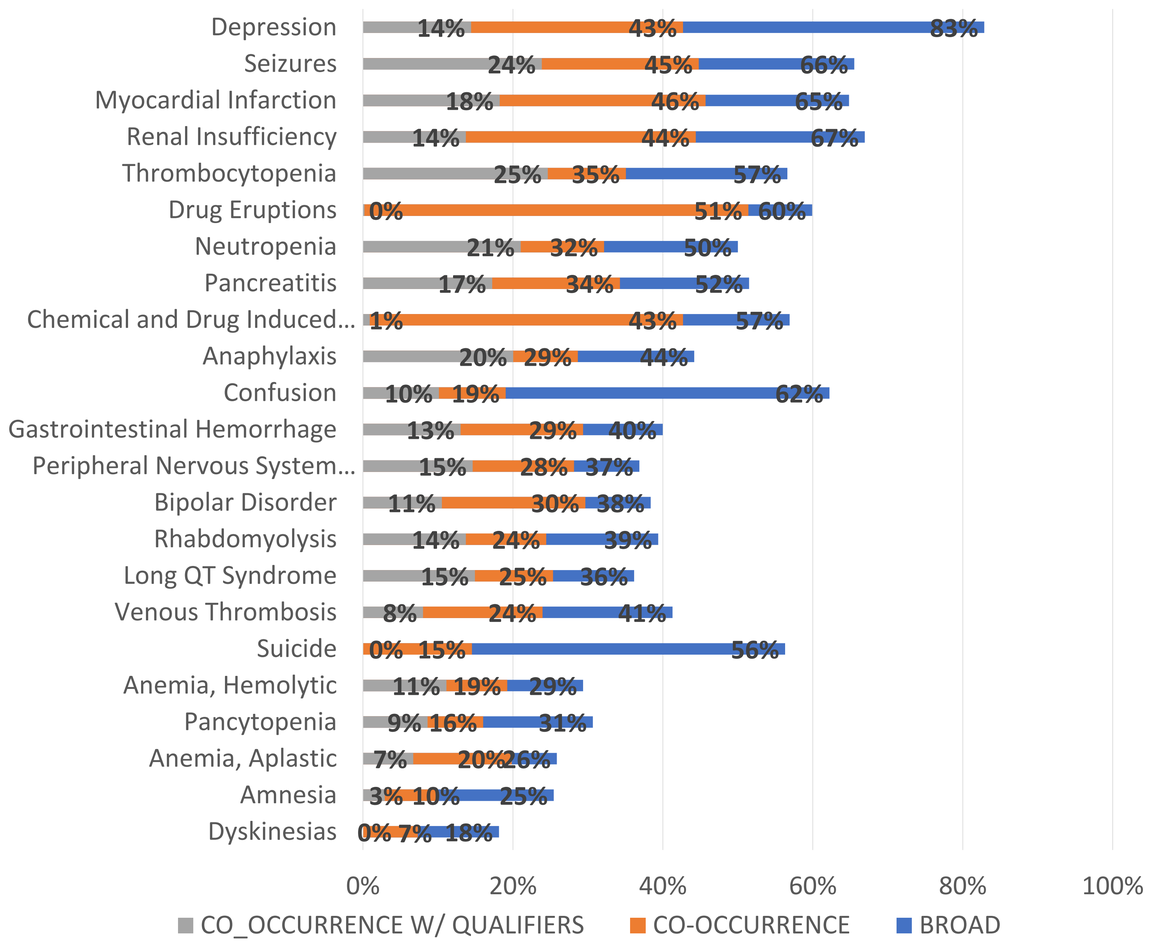
- **Table 1** shows of the possible pairs how many had 1+ article

TABLE 1 – Pairs of Drug-Condition with One or More Publications By Search Type

Evidence Type (n pairs, %)	All Drugs & All Conditions (721 conditions & 998 drugs)	All Drugs & 23 Conditions (23 conditions & 998 drugs)
Drug and Condition Pairs	719,558 (100%)	22,954 (100%)
Broad PubMed Search	216,241 (30%)	10,772 (47%)
Co-occurrence of MeSH Terms	132,109 (18%)	6,673 (29%)
Co-occurrence of MeSH Terms with Adverse Event Qualifiers	37,179 (5%)	2,681 (12%)

- **Graph 1** shows when using the 3 search strategies for the 23 conditions of pharmacovigilance for every drug how many have 1+ articles
  - The strategies are subsets of one another; co-occurrence with qualifiers is within co-occurrence, which is within the broad search
  - The greatest proportions of drug covered for each search strategy:
    - Broad: 83% Depression
    - Co-Occurrence: 51% Drug Eruptions
    - Co-Occurrence with Qualifiers: 25% for thrombocytopenia
  - Suicide and Confusion get associated with many more drugs using the broad search but much less when using the MeSH tags

GRAPH 1 - % of Broad Pubmed Search Drugs with Evidence for 23 Conditions of Interest



Citations

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Conflict of Interest Statement

E. Voss, M. Schuemie, and P. Ryan are full time employees of Janssen R&D, a unit of Johnson & Johnson. The work on this study was part of their employment. They also hold pension rights and own stock and stock options. P. Rijnbeek and J. van der Lei have no conflicts of interest.

Conclusions

- For >50% of drug-condition pairs of potential pharmacovigilance interest, our automated literature approach could not identify any published evidence (either supporting or refuting a potential association) – meaning <50% of the time can a patient/physician find any publication associated to a pair
- A limitation is equal weight was given to all drug-condition pairs as well as no judgement of the quality of the evidence is made
- Understanding where evidence is currently unavailable can support researchers in prioritizing future research

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