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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

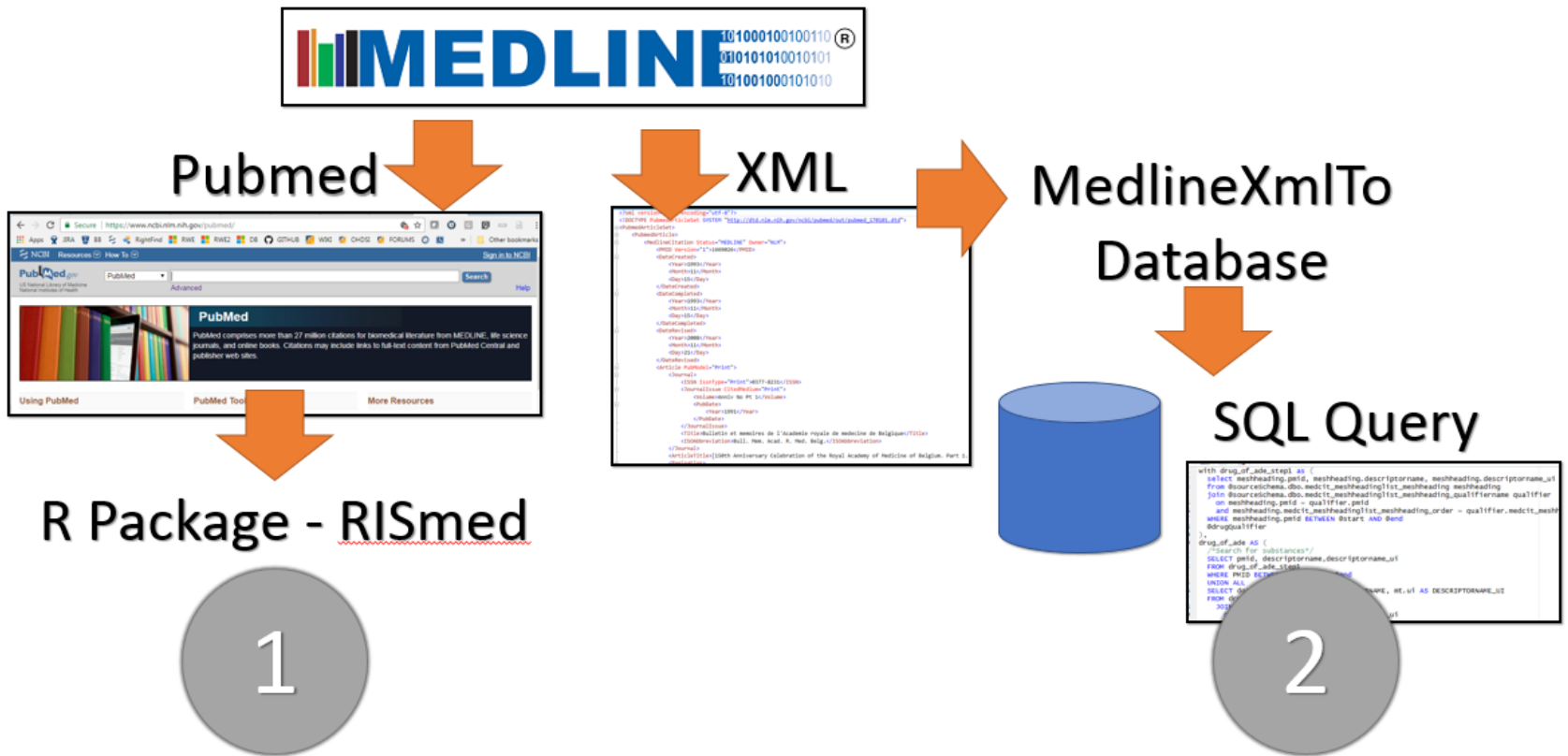


Objectives

- 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 Source





Methods: Drug & Condition Set

- 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



Methods:

Searching for Evidence

- **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.)

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

Knight A¹, Sundström Y², Börjesson O³, Bruchfeld A³, Malmström V², Gunnarsson J².

Author information

Abstract

BACKGROUND: Rituximab (RTX) is being used increasingly in anti-neutrophil cytoplasmic 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*

Retrospective Studies

Rituximab/adverse effects*

Substances

Antirheumatic Agents

Rituximab

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

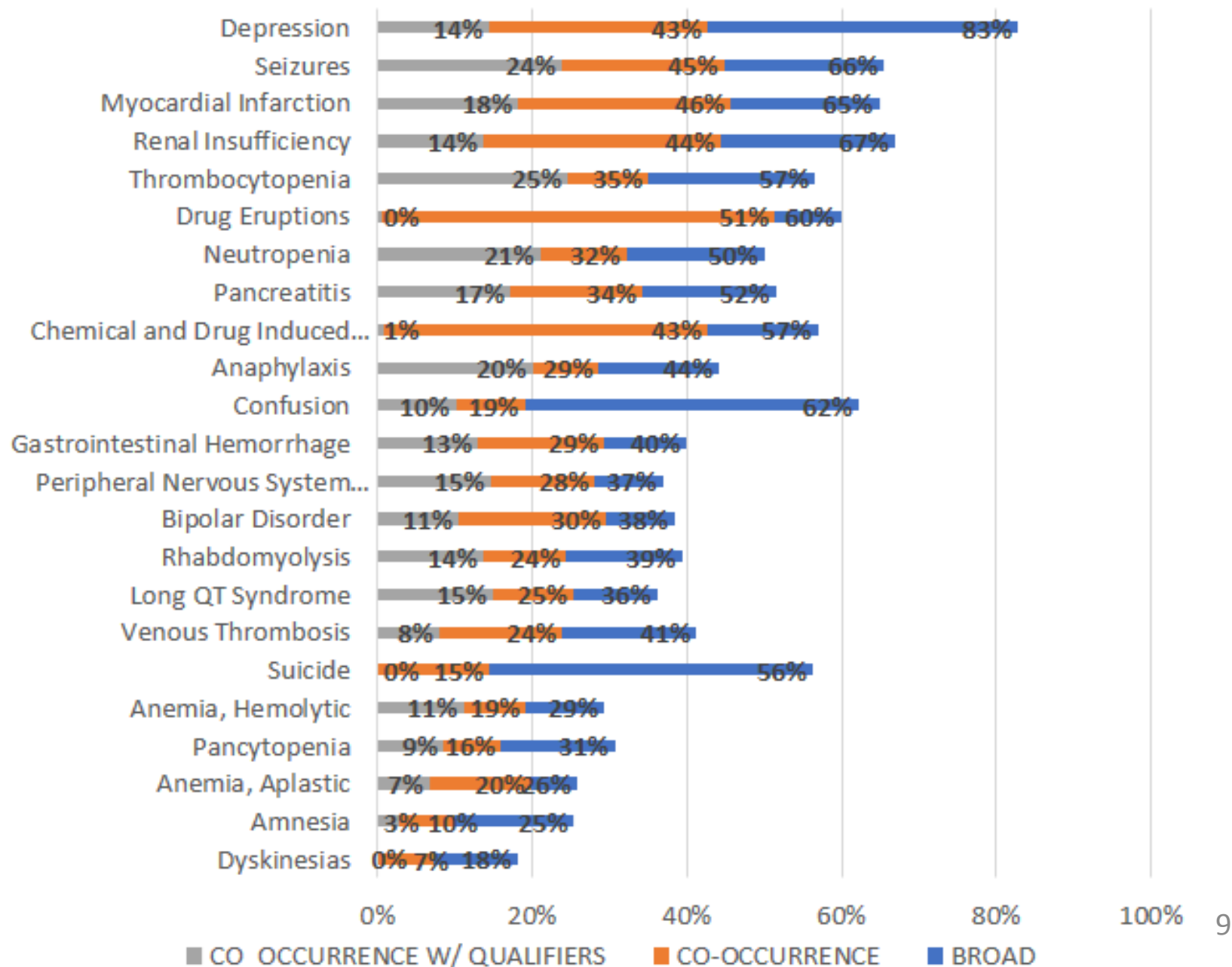


Results

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 - % of Broad Pubmed Search Drugs with Evidence for 23 Conditions 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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- Poster Presented at ICPE



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PowerPoint Presentat



Citations

- Trifirò G, Pariente A, Coloma PM, Kors JA, Polimeni G, Miremont-Salamé G, Catania MA, Salvo F, David A, Moore N, Caputi AP, Sturkenboom M, Molokhia M, Hippisley-Cox J, Acedo CD, van der Lei J, Fourrier-Reglat A; EU-ADR group. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? *Pharmacoepidemiol Drug Saf.* 2009 Dec;18(12):1176-84. doi: 10.1002/pds.1836. PubMed PMID: 19757412.
- Avillach P, Dufour JC, Diallo G, Salvo F, Joubert M, Thiessard F, Mouglin F, Trifirò G, Fourrier-Réglat A, Pariente A, Fieschi M. Design and validation of an automated method to detect known adverse drug reactions in MEDLINE: a contribution from the EU-ADR project. *J Am Med Inform Assoc.* 2013 May 1;20(3):446-52. doi: 10.1136/amiajnl-2012-001083. Epub 2012 Nov 29. PubMed PMID: 23195749; PubMed Central PMCID: PMC3628051.