ELSEVIER

Journal of Clinical Epidemiology 65 (2012) 827−834

Journal of Clinical Epidemiology

Search strategies−identified reports on ‘‘off-label’’ drug use in MEDLINE

Bita Mesgarpour[a,b], Markus Müller[a], Harald Herkner[b,*]

[a]*Department of Clinical Pharmacology, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, 1090 Vienna, Austria*
[b]*Department of Emergency Medicine, Medical University Vienna, General Hospital, Währinger Gürtel 18-20, 1090 Vienna, Austria*

Accepted 29 January 2012

Abstract

Objective: We developed search strategies that facilitate the identification of studies on ‘‘off-label’’ drug use in the bibliographic database OvidSP MEDLINE.

Study Design and Setting: We compiled a gold standard reference set of reports classified as relevant or not relevant to off-label drug use. We conceived search queries, including search words and word strings. We searched MEDLINE via OvidSP from 1948 to 2011. In comparison with the gold standard, we determined sensitivity and precision of search queries and their combinations. We attempted to achieve the highest possible sensitive search strategy and an optimal balance of sensitivity and precision.

Results: Our gold standard set contained 4,067 relevant documents overall of 6,785 records, among those 2,177 could be retrieved from MEDLINE. The most sensitive single term was ‘‘off label*.af.’’ (overall sensitivity 40.9%, sensitivity within MEDLINE 76.4%, and precision 84.4%). A combination of 31 search queries had the maximum overall sensitivity of 53.3% (sensitivity within MEDLINE 99.5%) at a precision of 60.3%. A search strategy with the maximum precision (84.0%) yielded a sensitivity of 49.0% (sensitivity within MEDLINE 91.5%).

Conclusion: We empirically developed two versions of optimized sensitive search strategies, which can achieve reasonable performance for retrieving off-label drug use documents in OvidSP MEDLINE.

Keywords: Off-label use; Drug labeling; Bibliographic databases; Information retrieval; MEDLINE; Sensitivity

1. Introduction

It is well known that a large number of licensed medications are used routinely for unapproved indications or dosages, routes of administration, or age groups [1−4]. These applications of medicines which are not described in their package insert are called ‘‘off-label usage’’ [5,6]. It should be differentiated from using unlicensed, unregistered, or ‘‘compassionate use’’ medicines, which have not been evaluated or approved by the regulatory authorities. Prescribing medications outside their licensed indications is legal according to many countries’ laws and regulations [7,8]. However, off-label use of medicine is generally not recommended unless validated by high-quality evidence, within the context of a formal research proposal and exceptional use, justified by individual clinical circumstances [9].

Because the benefit/risk profile of ‘‘off-label’’ drug usage has not been approved by a regulatory body, an extensive exploration of evidences seems well advised. Compendia and drug information references typically include drug information on off-label indications [10]. Nonetheless, new data are continuously reported in the literature which can only be retrieved through bibliographic databases, in which health professionals and researchers frequently pursuit their information requirements.

Application of search strategies or search filters is the requisite for a comprehensive search in biomedical databases, such as MEDLINE. In recent years, there is an increasing list of studies which have developed search strategies in terms of methodological search filters, such as randomized controlled trials, systematic reviews, diagnosis, etiology, prognosis, and treatment [11] and content search strategies, such as mental health, occupational health intervention, and adverse effects [12−14].

The present study presents the development of sensitive search strategies to improve the retrieval of off-label drug use studies in MEDLINE.

* Corresponding author. Tel.: +43-1-40400-3956; fax: +43-1-40400-1965.

E-mail address: harald.herkner@meduniwien.ac.at (H. Herkner).

0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2012.01.020

What is new?

- Studies on "off-label" drug use are not easy to detect in electronic literature databases because of variation in description and diversity in study type.
- Two versions of optimized sensitive search strategies are developed using two sets of gold standards.
- These search strategies could improve sensitivity and precision of search on off-label drug use studies in OvidSP MEDLINE.

2. Methods

2.1. Search and data management

We searched MEDLINE via OvidSP from 1948 to 2011, last updated in 28 February 2011. We chose MEDLINE because its usage is widely accepted by clinicians, health care researchers, and librarians. OvidSP interface was selected because of its flexible and customizable feature [15]. We designed a Microsoft (MS) Access database and stored the characteristics of retrieved records, such as author(s), title, journal, and publication year by each search query. They were split into two MS Access tables, which were linked by a key field; the first one contains record information including relevancy and the second one contains search queries data. We used the presence–absence data to represent retrieval records related to each search query. Thus, relevancy and retrieval status of the records retrieved by a search query was specified as "one" and the rest of records as "zero" in a column.

2.2. Assessment of the relevance of documents

We regarded documents as relevant if they referred to any human drug outside the licensed use, including different dose, indication, route of application, or used for another age group. We identified the relevancy of documents from the abstract or full-document appraisal as necessary. We excluded documents related to medical devices, veterinary drugs, herbal medicine, surgical procedures, or nonpharmacological interventions. We did not apply any language restrictions, but methodwise we excluded book series and videos.

2.3. Construction of a gold standard

We developed the gold standard based on a systematic and sensitive search of OvidSP EMBASE in addition to OvidSP MEDLINE for documents that fulfilled our criteria of an off-label drug use study. We removed duplicate records from the relevant citations retrieved from these two bibliographic databases and merged them in the third table of our developed MS Access database. This enabled us to construct two by two tables to calculate the appropriate test properties for each search query and their combinations.

We used two types of gold standard sets: (1) the whole set of documents from searching EMBASE and MEDLINE and (2) the subset of documents that are covered in MEDLINE.

2.4. Development of search queries

Based on the definition of off-label use of medications, we compiled an initial list of search words and word strings, including the medical subject heading (MeSH) "Off-Label Use." To expand the search terms, we determined the frequency analysis of titles and abstracts of 500 random relevant documents in the gold standard set using Textalyser, a web-based text analysis tool (http://textalyser.net/index.php?lang=en#analysis). It led to identification of some specific word strings, such as "appropriate indication," "unlicensed drug use," or "approved by the fda" which were appeared in the title or abstracts of relevant documents.

To develop a more sensitive search, we tried application of different fields in OvidSP, particularly ".af." for all searchable fields. We also truncated certain words—for example, "label," "labeled," "labeling," and "labels" all will be found by the truncated search term "label*." We used the adjacent operator, adj[Number], to find the most sensitive combination of proximate words—for example, the search query "label adj3 indication" will retrieve "off-label indication," "out of label indication," "off-label or pending indication," "no indication of label," "outside their labeled indication," and so on. To improve the precision of search, we applied the search technique of combination with the Boolean "NOT" and in consequence, excluded irrelevant documents from nonspecific search terms, such as "unlicense." For this purpose, we identified the frequent word terms and strings in irrelevant retrieved citations by manual review. Ultimately, we compiled a list of 73 search queries for retrieving the reports of off-label drug use (see Appendix A on the journal's website at www.jclinepi.com).

2.5. Evaluation of search queries and strategies

We determined the sensitivity, precision, and number needed to read (NNR) of search queries in OvidSP MEDLINE by using diagnostic test method as shown in Tables 1 and 2. Furthermore, we found out the sensitivity and precision of search queries combination, demonstrated by the "cumulative sensitivity" and "cumulative precision." The sensitivity or "recall" of a search was defined to its capacity to identify as many as the total number of known documents, which were possible. The precision