

How to carry out a literature search for a systematic review? A practical guide to obtaining published and unpublished studies

Lauren Z. Atkinson,¹ Andrea Cipriani ^{1,2}

¹Department of Psychiatry, University of Oxford, Warneford Hospital, OX3 7JX, Oxford, UK

²Oxford Health NHS Foundation Trust, Warneford Hospital, Oxford, UK

Correspondence to:

Andrea Cipriani
Department of Psychiatry
University of Oxford
Warneford Hospital
OX3 7JX
Oxford
UK
Tel: +44 (0)1865 618228
Email: andrea.cipriani@psych.ox.ac.uk

Learning objectives

- Understand the purpose of conducting a literature search and its integral part of the literature review process.
- Become aware of the range of sources that are available to search the literature, including electronic databases of published data, and trial registries to identify unpublished data.
- Understand how to develop a search strategy and apply appropriate search terms to interrogate electronic databases or trial registries.

Abstract

Performing an effective literature search to obtain the best available evidence is the basis of any evidence-based discipline, in particular evidence based medicine. However, with a vast and growing volume of published research available, searching the literature can be challenging. Even when journals are indexed in electronic databases, it can be difficult to identify all relevant studies without an effective search strategy. It is also important to search unpublished literature to reduce publication bias, which occurs from a tendency for authors and journals to preferentially publish statistically significant studies. This article is intended for clinicians and researchers who are approaching the field of evidence synthesis and would like to perform a literature search. It aims to provide advice on how to develop the search protocol and the strategy to identify the most relevant evidence for a given research or clinical question. It will also focus on how to search not only the published but also the unpublished literature using a number of online resources.

Introduction

A literature search is distinguished from, but integral to a literature review. Literature reviews are conducted for the purpose of (a) locating information on a topic or identifying gaps in the literature for areas of future study, (b) synthesizing conclusions in an area of ambiguity and (c) helping clinicians and researchers inform decision making and practice guidelines. Literature reviews can be narrative or systematic, with narrative reviews aiming to provide a descriptive overview of selected literature, without undertaking a systematic literature search. By contrast, systematic reviews use explicit and replicable methods in order to retrieve all available literature pertaining to a specific topic to answer a defined question (Higgins and Green, 2011). Systematic reviews therefore require a priori strategies to search the literature, with predefined criteria for included and excluded studies that should be reported in full details in a review protocol.

Performing an effective literature search to obtain the best available evidence is the basis of any evidence-based discipline, in particular evidence based medicine (McKeever et al., 2015; Sackett, 1997). However, with a vast and growing volume of published research available, searching the literature can be challenging. Even when journals are indexed in electronic databases, it can be difficult to identify all relevant studies without an effective search strategy (Hopewell et al., 2007). In addition, unpublished data and 'grey' literature (informally published material such as conference abstracts) are now becoming more accessible to the public. It is important to search unpublished literature to reduce publication bias, which occurs from a tendency for authors and journals to preferentially publish statistically significant studies (Dickersin and Min, 1993). Efforts to locate unpublished and grey literature during the search process can help to reduce bias in the results of systematic reviews (Song et al., 2010). A paradigmatic example demonstrating the importance of capturing unpublished data is that of Turner et al., 2008, who showed that only using published data in their meta-analysis led to effect sizes of antidepressants that were one third larger (32%) than effect sizes derived from combining both published and unpublished data. Such differences in findings from published and unpublished data can have real-life implications in clinical decision

making and treatment recommendation. In another relevant publication, Whittington et al. (2004) compared the risks and benefits of selective serotonin reuptake inhibitors (SSRI's) in the treatment of depression in children. They found that published data suggested favourable risk-benefits profiles for SSRIs in this population, but the addition of unpublished data indicated risk outweighed treatment benefits. The relative weight of drug efficacy to side-effects can be skewed if failing to search for, or include, unpublished data.

This article is intended for clinicians and researchers who are approaching the field of evidence synthesis and would like to perform a literature search. It aims to provide advice on how to develop a search strategy to identify the most relevant evidence for a given research or clinical question. It will also focus on how to search not only the published but also the unpublished literature using a number of online resources. A working example about efficacy of treatment interventions is used here to demonstrate the search techniques outlined in the article, however the overarching methods are purposefully broad in order to be accessible to all clinicians and researchers, regardless of their research or clinical question.

Defining the clinical question

The review question will guide the search strategy, but also the conclusions that can be drawn from the review based on which studies or other forms of evidence are to be included and excluded from the literature review. A narrow question will produce a narrow and precise search, perhaps resulting in too few studies to base a review, or be so focused that the results are not useful in wider clinical settings. Using an overly narrow search also increases the chances of missing important studies. A broad question may produce an imprecise search with many false positive search results. These search results may be too heterogeneous to evaluate in one review. Therefore from the outset, choices should be made about the remit of the review which will in turn affect the search.

A number of frameworks can be used to break the review question into concepts. One such framework is the PICO framework (Population, Intervention, Comparator and Outcome) framework,

developed to answer clinical questions such as the effectiveness of a clinical intervention (Richardson et al., 1995). It is noteworthy that 'outcome' concepts of the PICO framework are less often used in a search strategy due to being less well defined in the title and abstracts of available literature (Higgins and Green, 2011). Whilst PICO is widely used, it is not a suitable framework to identify key elements of all questions in the medical field and minor adaptations are necessary to enable the structuring of different questions. Other frameworks exist that may be more appropriate for questions about health policy and management, such as ECLIPSE (Expectation, Client group, Location, Impact, Professionals, Service) (Wildridge and Bell, 2002) or SPICE (Setting, Perspective, Intervention, Comparison, Evaluation) for service evaluation (Booth, 2006). A detailed overview of frameworks is provided in Davies (2011).

Scoping search

Before conducting a comprehensive literature search, a scope of the literature using just one or two databases (like PubMed or Medline) can provide valuable information as to how much literature for a given review question already exists. A scope search may reveal whether systematic reviews have already been undertaken for a review question. Caution should be taken however as systematic reviews that may appear to ask the same questions may have differing inclusion and exclusion criteria of studies included in the review. In addition, not all systematic reviews are of the same quality. If the original search strategy is of poor quality methodologically, original data is likely to have been missed and the search should not simply be updated (see the comparison between Naughton (2014) and Caddy (2015) about ketamine for treatment resistant depression).

Search strategy

The first step in conducting a literature search should be to develop a search strategy. Quoting the relevant scientific literature, the search strategy should pre-define how relevant literature will be identified. The search strategy should include the identification of sources to be searched (list of

databases and trial registries) and key words used in the literature (list of key words). The search strategy should be documented as an integral part of the systematic review protocol. Just as the rest of a well conducted systematic review, the search strategy used needs to be explicit and detailed such that it could be reproduced using the same methodology, with exactly the same results, or updated at a later time. This not only improves the reliability and accuracy of the review but also means that if the review is replicated, the difference in reviewers should have little impact, as they will use an identical search strategy. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was developed to standardise the reporting of systematic reviews (Moher et al., 2009). The PRISMA Statement consists of a 27-item checklist to assess the quality of each element of a systematic review (items 6, 7 & 8 relate to the quality of literature searching) and also to guide authors when reporting their findings.

Sources to search

There are a number of databases that can be searched for literature but the identification of relevant sources is dependent on the clinical or research question (different databases have different focuses, from more biology to more social science oriented), and the type of evidence that is sought (i.e., some databases report only randomised controlled trials).

- MEDLINE and Embase are the two main biomedical literature databases. MEDLINE contains more than 22 million references from more than 5,600 journals worldwide. In addition, the MEDLINE In-Process & Other Non-Indexed Citations database holds references before they are published on MEDLINE. Embase has a strong coverage of drug and pharmaceutical research and provides over 30 million references from more than 8,500 currently published journals, 2,900 of which are not in MEDLINE. These two journals however are only available to either individual subscribers or through institutional access such as universities and hospitals. PubMed, developed by the National Center for Biotechnology Information of the US National Library of Medicine, provides access to a free version of MEDLINE and is

accessible to researchers, clinicians and the public. PubMed comprises medical and biomedical literature indexed in MEDLINE but provides additional access to life science journals and e-books.

In addition, a number of subject and discipline specific databases exist.

- PsycINFO covers a range of psychological, behavioural, social and health sciences research.
- The Cochrane Central Register of Controlled Trials (CENTRAL) hosts the most comprehensive source of randomised and quasi randomised controlled trials. Whilst some of the evidence on this register is also included in Embase and MEDLINE, there are over 150,000 reports indexed from other sources, e.g conference proceedings and trial registers, that would otherwise be less accessible (Dickersin et al., 2002).
- The Cumulative Index of Nursing and Allied Health (CINAHL) and British Nursing Index are databases relevant to nursing but this spans literature across medical, allied health, community and health management journals.
- The Allied and Complementary Medicine Database is a database specifically for alternative treatments in medicine.

The examples of specific databases given here are by no means exhaustive but are popular and likely to be utilised for literature searching within medicine, psychiatry and psychology. Website links for the above mentioned electronic databases are available in Box 1, along with a link to further resources available outside of those mentioned in this paper. Box 1 also provides a website link to a number of video tutorials for searching electronic databases. Box 2 shows an example of the search sources chosen for a review of a pharmacological intervention of calcium channel antagonists in bipolar disorder, taken from a recent systematic review (Cipriani et al., 2016).

To conduct a comprehensive search of the literature it has been suggested that two or more electronic databases should be used (Suarez-Almazor et al., 2000). Suarez-Almazor and colleagues demonstrated that in a search of controlled clinical trials (CCTs) for rheumatoid arthritis, osteoporosis and lower back pain, only 67% of available citations were found by both Embase and

MEDLINE. Searching MEDLINE alone would have resulted in 25% of available CCTs being missed and searching EMBASE alone would have resulted in 15% of CCTs being missed. However, a balance between the sensitivity of a search; an attempt to retrieve all relevant literature in an extensive search, and the specificity of a search; an attempt to retrieve a more manageable number of relevant citations, is optimal. In addition, supplementing electronic database searches with unpublished literature searches (see Obtaining unpublished literature) is likely to reduce publication bias. The capacity of the individuals or review team is likely to largely determine the number of sources searched. In all cases, a clear rationale should be outlined in the review protocol for the sources chosen (the expertise of an information scientist is valuable in this process).

Developing a search strategy

Important methodological considerations (such as study design) may also be included in the search strategy. Dependent upon the databases and supplementary sources used, filters can be used to search the literature by study design (see below, Searching electronic databases). For instance, if the search strategy is confined to one study design term only (e.g randomised controlled trial, RCT), only the articles labelled in this way will be selected. However, it is possible that in the database some RCTs are not labelled as such, so they will not be picked up by the filtered search. Filters can help reduce the number of references retrieved by the search, but using just one term is not 100% accurate, especially if only one database is used (i.e., MEDLINE). It is important for systematic reviewers to know how reliable such a strategy can be and treat the results with caution.

Searching electronic databases

Identifying search terms

Standardised search terms are thesaurus and indexing terms that are used by electronic databases as a convenient way to categorise articles, allowing for efficient searching. Individual database records may be assigned a number of different standardised search terms that describe the same or

similar concepts (e.g. bipolar disorder, bipolar depression, manic-depressive psychosis, mania). This has the advantage that even if the original article did not use the standardised term, when the article is catalogued in a database it is allocated that term (Guaiana 2010). For example, an older paper might refer to 'manic depression', but would be categorised under the term 'bipolar disorder' when catalogued in MEDLINE. These standardised search terms are called **MeSH headings** (Medical Subject Heading) in MEDLINE and PubMed, or **EMTREE** in Embase, and are organised in a hierarchical structure (Box 3). In both MEDLINE and Embase an 'explode' command enables the database to search for a requested term, as well as any more specific terms that may be related. Both narrow and broader search terms can be viewed and selected to include in the search if appropriate to a topic. The Yale MeSH analyser tool (<http://mesh.med.yale.edu/>) can be used to help identify potential terms and phrases to include in a search. It is also useful to understand why relevant articles may be missing from an initial search based upon a comparison grid of MeSH terms used to index each article (see Box 1 for a tutorial video link).

In addition, MEDLINE also distinguishes between MeSH headings (MH) and Publication Type (PT) terms. Publication Terms are less about the content of an article but rather about the type of publication, specifying for example a review article, meta-analysis or a randomised controlled trial. Both MeSH headings and EMTREE have their own peculiarities, with variations in thesaurus and indexing terms. In addition, not all concepts are assigned standardised search terms, and not all databases use this method of indexing the literature. It is advisable to check the guidelines of selected databases before undergoing a search. In the absence of a MeSH heading for a particular term, free-text terms could be used.

Free-text terms are used in natural language and are not part of a database controlled vocabulary. Free-text terms can be used in addition to standardised search terms in order to identify as many relevant records as possible (Higgins and Green, 2011). Using free-text terms allows the reviewer to search using variations in language or spelling (e.g. hypomani* or mania* or manic* (see truncation and wildcard functions below and Box 4.)). A disadvantage of free-text terms is that they are only

searched for in the title and abstracts of database records, and not in the full texts, meaning that when a free-text word is only used in the main body of text of an article, it will not be retrieved in the search. Additionally, a number of specific considerations should be taken into account when selecting and using free text terms:

- i) Synonyms, related terms and alternative phrases e.g. *mood instability, affective instability, mood lability and emotion dysregulation.*
- ii) Abbreviations or acronyms in medical and scientific research e.g. *magnetic resonance imaging or MRI.*
- iii) Lay and medical terminology e.g. *high blood pressure or hypertension*
- iv) Brand and generic drug names e.g. *Prozac or fluoxetine*
- v) Variants in spelling e.g. English and American English (*behaviour or behavior; pediatric or paediatric*).

Truncation and wildcard functions can be used in most databases to capture variations in language.

- i) **Truncation** allows the stem of a word to be searched that may have variant endings: e.g. a search for *depress** uses truncation to retrieve articles that mention both depression and depressive. Truncation symbols may vary by database, but common symbols include: *, !, or #.
- ii) **Wild cards** substitute one letter within a word to retrieve alternative spellings e.g. *wom?n* would retrieve the terms *woman* and *women*.

Combining search terms

Search terms should be combined in the search strategy using *Boolean operators*. Boolean operators allow standardised search terms and free text terms to be combined. There are three main Boolean operators ('AND,' 'OR,' and 'NOT') (Figure 1).

- OR – This operator is used to broaden a search, finding articles that contain at least one of the search terms within a concept. Sets of terms can be created for each concept, e.g population: (bipolar disorder OR bipolar depression).
- AND – The ‘AND’ operator can be used to join sets of concepts together, narrowing the retrieved literature to articles that contain all concepts, e.g. the population or condition of interest, the intervention to be evaluated: (bipolar disorder OR bipolar depression) AND calcium channel blockers. However, if at least one term from each set of concepts is not identified from the title or abstract of an article, this article will not be identified by the search strategy. It is worth mentioning here that some databases can run the search also across the full texts. For example Science Direct Elsevier and most publishing houses allow this kind of search, which is much more comprehensive than abstract or title searches only.
- NOT – This operator, used less often, can be used to focus a search strategy in order to not retrieve specific literature, e.g. human studies, NOT animal studies. However in certain cases the NOT operator can be too restrictive, for example if excluding male gender from a population, using ‘NOT male’ would also means any articles about both males and females are not obtained by the search..

Conventions of all databases should be checked before undergoing a literature search as functions and operators may differ slightly between them (Cipriani 2016a). This is particularly relevant when using limits and filters. Box 4 shows an example search strategy incorporating many of the concepts described above. The search strategy is taken from Cipriani et al. (2016b) but simplified to include only one intervention.

Search filters

A number of filters exist to focus a search, including language, date and study design or focus filters. Language filters can restrict retrieval of articles to English language, though if language is not an inclusion criteria it should not be restricted to avoid language bias. Date filters can be used to restrict

literature during a specified period, for example if an intervention was only made available after a certain date. In addition, if good systematic reviews exist that are likely to capture all relevant literature (as advised by an information specialist), data restrictions can be used to search additional literature published after the date of those included in the systematic review. In the same way, date filters can be used to update a literature search since the last time it was conducted. Reviewing the literature should be a timely process (new and potentially relevant evidence is produced constantly) and updating the search is an important step, especially if collecting evidence to inform clinical decision making, when publications in the field of medicine are increasing at an impressive rate (Barber et al., 2016). The use of filters will be dependent upon the research question and nature of evidence that is sought through the literature search, and the guidelines of the individual database that is used.

Supplementary search techniques

Google Scholar

Google Scholar allows the use of basic Boolean operators to be used in strings of search terms.

However, the search engine does not use standardised search terms that have been tagged like in other traditional databases and therefore variations of keywords should always be searched. There are a number of advantages and disadvantages to using a web search such as Google Scholar.

Google Scholar searches the full text of an article for key words and also searches a wider range of sources that are not found in traditional databases, such as conference proceedings and books, making it a good resource to search for grey literature (Haddaway, 2015). In addition Google Scholar also finds articles cited by other relevant articles produced in the search. However, variable retrieval of content (due to regular updating of Google algorithms and individuals' search history and location) means that search results are not necessarily reproducible and therefore not in keeping with replicable search methods required by systematic reviews. Google Scholar alone has not been

shown to retrieve more literature than other traditional databases discussed in this article and therefore should be used in addition to other sources (Bramer, 2016).

Citation searching

Once the search strategy has identified relevant literature, the reference list of these articles can be searched. This is called '*citation searching*' or '*backward searching*' and can be used to see where particular research led others. This method is particularly useful if the search identifies systematic reviews or meta-analyses of a similar topic.

Obtaining unpublished literature

Conference abstracts

Conference abstracts are considered *grey literature*, i.e. literature that is not formally published in journals or books (Alberani et al., 1990). Scherer and colleagues found that only 52.6% of all conference abstracts go on to publication, and factors associated with publication were studies that had randomised controlled trial designs and the reporting of positive or significant results (Scherer et al., 2007). Therefore, failure to search relevant grey literature might miss certain data and bias the results of a review. Whilst conference abstracts are not indexed in most major electronic databases, they are available in databases such as BIOSIS Previews. However, as many unpublished studies, these data did not undergo the peer review process that is often a tool to assess and possibly improve the quality of the publication.

Searching trial registers and pharmaceutical websites

For reviews of trial interventions, a number of trial registers exist. *ClinicalTrials.gov*

(<https://clinicaltrials.gov>) provides access to information on public and privately conducted clinical trials in humans. Results for both published and unpublished studies can be found for many trials on the register, in addition to information about studies that are ongoing. Searching each trial register

requires a slightly different search strategy but many basic principles described above still apply.

Basic searches on *Clinicaltrials.gov* include searching by condition, specific drugs or interventions and these can be linked using *Boolean operators* (for example, (*bipolar disorder OR manic depressive disorder*) *AND lithium*). Parentheses can be used to build up search terms as shown above, with words within parentheses treated as a unit. More advanced searches allow one to specify in further search fields such as the status of studies, study type and age of participants. The US Food and Drug Administration (FDA) hosts a database providing information about FDA approved drugs, therapeutic products and devices (the FDA (www.fda.gov)). The database (with open access to anyone, not only in the US) can be searched by the drug name, its active ingredient or its approval application number and for most drugs approved in approximately the last 20 years, a review of clinical trial results used as evidence in the approval process are available (some of which remain unpublished). The European Medicines Agency (EMA) hosts a similar register for medicines developed for use in the European Union (www.ema.europa.eu). An Internet search will show that many other national and international trial registers exist which may be relevant search sources dependant on the review question. The World Health Organisation International Trials Registry Platform (WHO ICTRP (www.who.int/ictip)) provides access to a central database bringing a number of these national and international trial registers together. It can be searched in much the same way as Clinicaltrials.gov.

A number of pharmaceutical companies now share data from company sponsored clinical trials. GlaxoSmithKline (GSK) is transparent in the sharing of their data from clinical studies and hosts their own clinical study register (www.gsk-clinicalstudyregister.com), as do Roche (<http://www.roche-trials.com/>). Eli-Lilly provides clinical trial results both on their website and in external registries. However, other pharmaceutical companies such as Wyeth divert users to clinical trial results in external registries. These registries include both published and previously unpublished studies. Searching techniques differ for each company and hand searching through documents is often required in order to identify studies.

Communication with authors

Direct communication with authors of published papers could produce both additional unpublished data omitted from published studies, or other unpublished studies. Contact details are usually available for the corresponding author of each paper in order to make such enquiries. Although high quality reviews do make efforts to obtain and include unpublished data, it does have potential disadvantages; it may be incomplete and is likely not to have been peer-reviewed. It is also important to note that whilst reviewers should make every effort to find unpublished data in an effort to minimise publication bias there is still likely to remain a degree of this bias in the studies selected for a systematic review.

Conclusion

Developing a search strategy is a key part of review process, and the quality of the systematic reviews depends a lot on the quality of the literature search, as the evidence retrieved from the search will ultimately be the basis of informed decisions of conclusions made. In this way, sources should be selected to minimise the possibility of bias and supplementary search techniques should be used in addition to electronic database searching to ensure an extensive review of the literature has been carried out. It is worth reminding that developing a search strategy should be an iterative and flexible process (Higgins and Green, 2011) and only by conducting a search strategy by his/her own will one learn about the vast literature available, and how best to capture it.

Acknowledgements: We thank Sarah Stockton for her help in drafting the article. Andrea Cipriani is supported by the NIHR Oxford cognitive health Clinical Research Facility.

Declaration of interest: In the past two years Andrea Cipriani has served as an expert witness for a patent litigation case about quetiapine extended release. Lauren Atkinson: none.

Box 1. Website links of search sources to obtain published and unpublished literature

Electronic Databases

Medline/PubMed: www.ncbi.nlm.nih.gov/pubmed

EMBASE: www.embase.com

PsychINFO: www.apa.org/psycinfo/

The Cochrane Central Register of Controlled Trials (CENTRAL): www.thecochranelibrary.com

The Cumulative Index of Nursing and Allied Health (CINAHL): www.cinahl.com/

British Nursing Index: www.bniplus.co.uk/

The Allied and Complementary Medicine Database: www.bl.uk/collections/health/amed.html

Grey Literature Databases

BIOSIS Previews (part of Thomson Reuters Web of Knowledge: <http://ipscience.thomsonreuters.com/>)

Trial registries

Clinicaltrials.gov: www.clinicaltrials.gov/

Drugs@FDA: www.accessdata.fda.gov/

European Medicines Agency (EMA): www.ema.europa.eu

The World Health Organisation International Trials Registry Platform (WHO ICTRP): www.who.int/ictcp

GlaxoSmithKline clinical study register: www.gsk-clinicalstudyregister.com

Roche clinical trial results database: <http://www.roche-trials.com/>

Eli-Lilly clinical trial results: www.lillytrials.com/results/ctr_toc.pdf

Please see the below links for further resources outside of those mentioned in this paper:

http://libguides.kcl.ac.uk/ld.php?content_id=17678464

<https://dml.georgetown.edu/core>

<https://hsl.lib.umn.edu/biomed/help/nursing>

The below link provides a series of tutorial videos:

For searches in electronic databases: <http://library.buffalo.edu/hsl/services/instruction/tutorials.html>

For using the Yale MeSH Analyzer tool <http://library.medicine.yale.edu/tutorials/1559>

Box 2. Example of search sources chosen for a review of calcium channel antagonists in bipolar disorder (Cipriani et al., 2016)

Electronic databases searched:

- Embase
- Medline
- Medline In-Process and Other Non-Indexed Citations
- PsycINFO
- CENTRAL

Box 3. Search terms and hierarchical structure of *MeSH* (Medical Subject Heading) in MEDLINE and PubMed.

Search for MeSH heading: 'Bipolar Disorder'

Tree Number(s): F03.084.500

MeSH Unique ID: D001714

Entry Terms:

- Bipolar Disorders
- Disorder, Bipolar
- Psychosis, Manic-Depressive
- Psychosis, Manic Depressive
- Manic-Depressive Psychosis
- Manic Depressive Psychosis
- Affective Psychosis, Bipolar
- Bipolar Affective Psychosis
- Psychoses, Bipolar Affective
- Psychosis, Bipolar Affective
- Psychoses, Manic-Depressive
- Manic-Depressive Psychoses
- Psychoses, Manic Depressive
- Mania
- Manias
- Manic State
- Manic States
- State, Manic
- States, Manic
- Depression, Bipolar
- Bipolar Depression
- Manic Disorder
- Disorder, Manic
- Manic Disorders

All MeSH Categories

Psychiatry and Psychology Category

Mental Disorders

Bipolar and Related Disorders

Bipolar Disorder

Broad category

Narrow category

Box 4. Example of a search strategy about bipolar disorder using Medline (Cipriani et al., 2016).

The search strategy follows the PICO framework and includes MeSH terms, free text key words, and a number of further techniques such as truncation that have been outlined above. Numbers in bold brackets are number of citations retrieved by each search.

Database: Ovid MEDLINE(R) <1946 to June Week 2 2016>

Search Strategy:

Population search:

- 1 "bipolar and related disorders"/ or bipolar disorder/ (34752)
- 2 ((bipolar or bi polar) adj5 (disorder* or depress*)).tw. (23079)
- 3 ((cyclothymi* or rapid or ultradian) adj5 cycl*).tw. (4884)
- 4 (hypomani* or mania* or manic* or mixed episode* or rcbd).tw. (15999)
- 5 1 or 2 or 3 or 4 (47621)

MeSH categories from hierarchy (Box 2.)

Free text synonyms and related terms with truncation

Boolean operator 'OR' to retrieve all citations including any of these search terms

Intervention search - general terms:

- 6 exp calcium channel blockers/ (76291)
- 7 calcium channels, l-type/ (6706)
- 8 calcium channels/ (24446)
- 9 (((calcium or ltcc) adj2 (antagonist* or block* or channel* or inhibit*)) or ccb or ccbs or dhp receptor*).tw. (51396)

Abbreviations of terms

Intervention search - terms for example drug/drug class of interest:

- 10 dihydropyridines/ (4566)
- 11 dihydropyridine*.tw. (8337)
- 12 isradipine/ (1339)
- 13 (dynacirc or icaz or carboxylate or isradipin or isrodipin* or lomir or prescal or vascal).tw. (12932)
- 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (132982)

Comparison (RCT) filter search:

Explode function to retrieve related terms to 'clinical trial'

- 15 exp clinical trial/ or exp "clinical trials as topic"/ or cross-over studies/ or double-blind method/ or placebos/ or random allocation/ or single-blind method/ (1040841)
- 16 (clinical adj2 trial*).tw. (236171)
- 17 (crossover or cross over).tw. (60468)
- 18 (((single* or doubl* or trebl* or tripl*) adj2 blind*) or mask* or dummy or doubleblind* or singleblind* or trebleblind* or tripleblind*).tw. (186739)
- 19 (placebo* or random*).tw. (810249)
- 20 animal/ not human/ (4230831)
- 21 15 or 16 or 17 or 18 or 19 (1545540)
- 22 21 not 20 (1393739)
- 23 5 and 14 and 22 (74)

NOT operator to exclude animal studies

Boolean operator 'AND' to combine each search concept

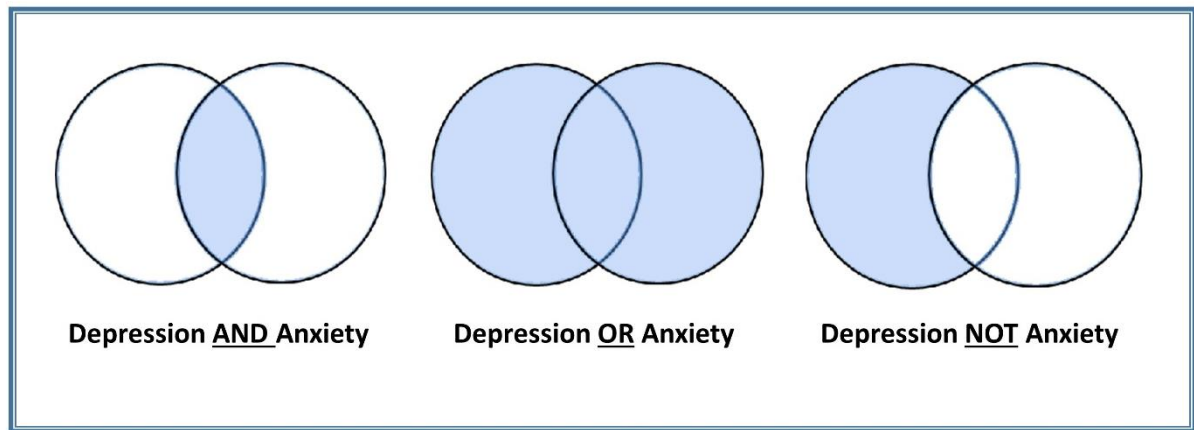


Figure 1. Example of Boolean operator concepts (the resulting search is the light blue shaded area).

References

- Alberani, V., De Castro Pietrangeli, P. & Mazza, A.M. (1990) The use of grey literature in health sciences: a preliminary survey. *Bulletin of the Medical Library Association*, **78**, 358-363.
- Barber, S., Corsi, M., Furukawa, T.A. *et al* (2016) Quality and impact of secondary information in promoting evidence-based clinical practice: a cross-sectional study about EBMH. *Evidence-Based Mental Health*, **19**, 82-85.
- Booth, A. (2006) Clear and present questions: formulating questions for evidence based practice. *Library Hi Tech*, **24**, 355-368.
- Bramer, W. M., Giustini, D., & Kramer, B. M. R. (2016) Comparing the coverage, recall, and precision of searches for 120 systematic reviews in Embase, MEDLINE, and Google Scholar: a prospective study. *Systematic Reviews*, **5**, 1-7.
- Caddy, C., Amit, B.H., McCloud, T.L., *et al* (2015) Ketamine and other glutamate receptor modulators for depression in adults. *Cochrane Database of Systematic Reviews*, 9, CD011612.
- Cipriani, A., Zhou, X., Del Giovane, C., *et al* (2016a) Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*, **388**, 881-890.
- Cipriani, A., Saunders, K., Attenburrow, M.J., *et al* (2016b) A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. *Molecular Psychiatry*, **21**, 1324-1332.
- Davies, K.S. (2011) Formulating the evidence based practice question: a review of the frameworks. *Evidence Based Library and Information Practice*, **6**, 75-80.
- Dickersin, K., Manheimer, E., Wieland, S., *et al* (2002). Development of the Cochrane Collaboration's CENTRAL Register of controlled clinical trials. *Evaluation & the health professions*, **25**, 38-64.
- Dickersin, K. & Min, Y.I. (1993) Publication bias: the problem that won't go away. *Annals of the New York Academy of Sciences*, **703**, 135-148.

- Guaiana, G., Barbui, C., Cipriani, A. (2010). Hydroxyzine for generalised anxiety disorder. *Cochrane Database of Systematic Reviews*, **12**, CD006815.
- Haddaway, N. R., Collins, A. M., Coughlin, D., *et al* (2015) The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. *PLoS One*, **10**, e0138237.
- Higgins, J.P.T. & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 Available from www.cochrane-handbook.org The Cochrane Collaboration, 2011.
- Hopewell, S., Clarke, M., Lefebvre, C., *et al* (2007). Handsearching versus electronic searching to identify reports of randomized trials. *Cochrane database of systematic reviews*, Mr000001.
- McKeever, L., Nguyen, V., Peterson, S.J., *et al* (2015). Demystifying the Search Button: A Comprehensive PubMed Search Strategy for Performing an Exhaustive Literature Review. *Journal of parenteral and enteral nutrition*, **39**, 622-635.
- Moher, D., Liberati, A., Tetzlaff, J., *et al* (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine*, **6**, e1000097.
- Naughton, M., Clarke, G., O'Leary, O.F., *et al* (2014). A review of ketamine in affective disorders: Current evidence of clinical efficacy, limitations of use and preclinical evidence on proposed mechanisms of action. *Journal of Affective Disorders*, **156**, 24–35.
- Richardson, W.S., Wilson, M.C., Nishikawa, J., *et al* (1995). The well-built clinical question: a key to evidence-based decisions. *ACP journal club* **123**, A12-13.
- Sackett, D.L. (1997) Evidence-based medicine. *Seminars in perinatology*, **21**, 3-5.
- Scherer, R.W., Langenberg, P. & von Elm, E. (2007) Full publication of results initially presented in abstracts. *Cochrane database of systematic reviews*, Mr000005.
- Song, F., Parekh, S., Hooper, L., *et al* (2010) Dissemination and publication of research findings: an updated review of related biases. *Health technology assessment*, **14**, 1-193.
- Suarez-Almazor, M.E., Belseck, E., Homik, J., *et al* (2000). Identifying clinical trials in the medical literature with electronic databases: MEDLINE alone is not enough. *Controlled clinical trials* **21**, 476-487.

- Turner, E. H., Matthews, A. M., Linardatos, E., *et al* (2008). Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *New England Journal of Medicine*, **358**, 252-260.
- Whittington, C. J., Kendall, T., Fonagy, P., *et al* (2004). Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*, **363**, 1341-1345.
- Wildridge, V. & Bell, L. (2002). How CLIP became ECLIPSE: a mnemonic to assist in searching for health policy/management information. *Health Information & Libraries Journal*, **19**, 113-115.