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BEYOND MEDLINE

Reducing Bias Through Extended Systematic Review Search

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Abstract

Objective: To evaluate the sensitivity and precision of various extended search methods in identifying randomized controlled trials (RCTs) for systematic reviews.
Method: Prospective analysis of extended search methods (specialized databases or trial registries, reference lists, hand-searching, personal communication, and Internet) used in two systematic reviews of RCTs. The gold standard was the total number of RCTs identified by major databases (MEDLINE, EMBASE, etc.) and extended search strategies combined. Sensitivity was the proportion of all known RCTs identified by any extended search method. Precision reflected the proportion of all items uncovered by any extended search method that actually were RCTs.
Results: The extended search identified 94 additional RCTs for the systematic reviews beyond those identified with the major databases. Specialized databases and trial registries had the highest sensitivity and precision for the lipid-lowering project (13.6% and 52.7%, respectively; $p < .05$) followed by scanning of reference lists (7.2% sensitivity and 41.9% precision; $p < .05$). Hand-searching was more effective than personal communication and Internet searching (1.7% sensitivity and 12.2% precision; $p < .05$). The acupuncture project had slightly different results, with the specialized databases and trial registries tied with the review of reference lists for highest sensitivity (14.2%). The precision followed the same trend as the lipid-lowering project (17.6% specialized databases; 8.3% reference lists; $p < .05$). A post-hoc analysis showed that 75 of the 94 RCTs were indexed in the major databases but missed by the major database search.
Conclusions: Extended searching identified additional RCTs for the systematic reviews beyond those found in major databases. Specialized databases and trial registries were most effective. An important number of RCTs were missed by the major database search. Timing and accuracy of indexing may explain this finding. The definitive measure, whether there is an association between the method used to uncover RCTs, the quality of the items uncovered and their impact on systematic review results, is yet to be determined.

Keywords: MEDLINE, Information storage and retrieval, Randomized controlled trials, Review literature

Although trials with statistically significant findings are likely to be published in MEDLINE (11;26;32;38), a search in MEDLINE will generally fail to identify all possible randomized controlled trials (RCTs) (1;3;6;9;11;19;23;36;37). Up to 63% of all available RCTs may be missed by a search strategy limited to MEDLINE (2;9). Expanding the literature search beyond MEDLINE ensures a more comprehensive and unbiased identification of RCTs (1;9;11;27;38). An extended literature search, conducted in a systematic

manner, is a key distinction between traditional reviews and systematic reviews. Systematic reviews are summaries of the available research evidence on a certain health technology. They are based on systematic search and appraisal methods that reduce bias and chance effects and provide more reliable information on which to make decisions (2;19).

Systematic reviews therefore depend on the ability of literature search strategies to identify available research evidence. Literature search protocols should seek not only to identify all relevant literature within the major databases (e.g., MEDLINE), but also to secure relevant material, sometimes described as gray literature, from outside usual sources. Suggestions and recommendations have been published for expanding the search strategy beyond MEDLINE (4;13;14;20;25;31;33;39). Protocols based on these recommendations generally require that researchers:

- Search the subject-specific and specialized electronic databases;
- Search the gray literature (government reports, monographs, indices and directories, health newsletters, and other reports) (28);
- Hand-search key journals;
- Scan reference lists of trials, reviews, and systematic reviews;
- Identify conference proceedings; and
- Consult with other researchers in the topic area.

To date, there has been no evaluation of the effectiveness of many of these extended search methods.

While there is some evidence on the effectiveness of hand-searching (1;9;17;18) and trial registries (6;34;35), this evidence is mostly indirect. Hand-searching and trial registries have been used as the gold standard in studies evaluating the effectiveness of major database search strategies. Hand-searching may not be an appropriate gold standard, since the study by Milne and Thorogood (24) shows that trials can be missed even by hand-searching journals. The journals hand-searched were generally limited to those indexed in MEDLINE. These studies suggest that indexing problems in MEDLINE, for example, may explain why 18% to 22% of citations were missed by a MEDLINE search alone (9;37). They also emphasize the importance of the text words and MeSH words used (9). Overall, the usefulness of hand-searching will be influenced by the number and appropriateness of the journals hand-searched (9).

A study by Hetherington et al. (16) suggests that personal communication permits the identification of unpublished RCTs or additional material for the systematic review (19;22;30;41). Easterbrook et al. (10) also offer indirect evidence to this effect and note that these unpublished studies are more likely to have produced nonsignificant findings. In evaluating publication bias, a series of studies provides some evidence that personal communications with researchers can lead to the identification of additional trials, and that these trials could potentially affect the results of a pooled analysis; in general, unpublished trials often have negative findings (5;7;8).

The sensitivity and precision of scanning reference lists received less attention in the literature. In a study written by Sindhu and Dickson (36), no information was provided for sensitivity/precision analysis, although scanning reference lists was used as a method to uncover additional literature (9). Kleijnen and Knipschild (19) reported that using reference list scanning to supplement MEDLINE and EMBASE searches allowed the identification of additional controlled trials. Scanning was limited to review articles and textbooks. Whether these RCTs could have been identified by other less time-consuming extended methods is unclear. We could find no evaluation of the effectiveness of other recommended

search methods. The purpose of this study is to address these gaps and evaluate relative effectiveness of various extended literature search methods in identifying RCTs for systematic reviews.

METHODS

Extended and major database search strategies were analyzed prospectively for two systematic review projects: a) RCTs of acupuncture in the treatment of addiction; and b) lipid-lowering therapy in the prevention and treatment of coronary heart disease. The major databases searched were MEDLINE, EMBASE, HealthStar, and Current Contents. Additional major databases were searched for acupuncture in order to improve comprehensiveness.

All extended methods were applied concurrently and at random. Items were entered in the database and coded according to the method by which they were found first.

Details of the extended search for each topic are presented in Tables 1 and 2. Specialized databases and trial registries were searched. These included subject-specific databases, library web catalogues, and inhouse databases. Key indexed and nonindexed journals located either through the local academic health sciences library or through Uncover Reveal Table of Contents were hand-searched. Reference lists of the retrieved material were scanned (40).

The Internet was searched using search engines and meta-indexes for peer-reviewed web-related material available through sites such as OMNI (27). Search terms similar to those used in the major database search strategies were applied to these meta-indexes. The Internet search was also used to locate relevant organizations and researchers, who were then contacted by letter, phone, or e-mail. Directories identifying topic-specific research organizations were also used to identify pertinent contacts. A bibliography of identified trials was sent to these researchers and organizations, who were invited to forward relevant material and to advise of any unlisted trials.

Items meeting the inclusion criteria for each project were retrieved and entered into a DB/TextWorks database. Additional information was selected opportunistically from the literature search and entered in the database. Each item was coded to describe the extended method used and the type of document uncovered. Coding was performed independently by one librarian and one researcher, the results compared, and any differences resolved by discussion. Coding categories were mutually exclusive.

RCTs, controlled trials, and other primary research (cohort, case series or case studies) were categorized as primary studies. Systematic reviews, meta-analyses, narrative reviews, reports, and other types of documents were categorized as background information.

Items were coded as systematic reviews based on published definitions: included either a description of the literature search methods used or a critical appraisal of included studies that met systematic review criteria (2;19). Meta-analyses were coded as systematic reviews regardless of whether they were based on an explicit search strategy or appraisal. Narrative reviews included a reference list or bibliography as well as a review of one or more studies. Reports were documents published by governments, agencies, and other organizations, having no bibliographies or reference lists. Items coded as "other" consisted of editorials, news and media items, or other documents that did not include reference lists. Abstracts were coded based on the type of study discussed.

The number of RCTs retrieved, sensitivity, and precision were the effectiveness indicators used to evaluate the extended search methods. The denominator was the total number of RCTs identified by major database and extended search strategies combined. Sensitivity (S) was the proportion of all known RCTs identified by any extended search method. Precision (P) reflected the proportion of all RCTs uncovered by any extended search method (9). The number of RCTs identified by each extended method was also reported.

Table 1. Extended Search: Lipid-lowering Drugs

Databases	Web library catalogs (using Library of Congress or MeSH)	Internet peer-reviewed sites
1. Cochrane Library 2. HSTAT (technology assessment guidelines) 3. HSRProj (NLM) 4. Dissertation Abstracts 5. Article1st (OCLC) 6. Papers1st (OCLC)—conferences and paper abstracts 7. TRIP database (evidence-based medicine) 8. NTIS Database 9. CRISP (Computer Retrieval of Information on Scientific Projects) 10. HTA Database 11. LILACS 12. Clinical Trials.gov 13. National Research Register	1. UBC Library Catalog 2. BC Ministry of Health Library Catalog 3. Canadian Institute of Scientific and Technical Information (CISTI) catalog 4. Belinda Database (Buckinghamshire Health Authority Library) 5. HealthPromis (UK web catalog of health promotion 6. National Health Information Center—Health Information Resource Database 7. CHID Online (Combined Health Information Database) 8. WorldCat 9. GAO Web Catalog 10. COPAC (Union catalogues in UK) 11. NLM Locator Plus	1. UK Academic Web Directory 2. UK Social Science Information Gateway 3. OMNI (Organising Medical) Networked Information 4. Medical Matrix 5. Health Communications Network 6. Global Health 7. Health Index 8. Medweb Public Health 9. Medscape

Internet search engines	In-house databases	Directories
1. Google 2. Altavista 3. Northern Lights	1. In-house Catalog	1. ECRI. HealthCare Standards 2. UHC Technology Assessment Monitor

Journals hand-searched	Organizations contacted	
1. *Canadian Journal of Cardiology* 2. *American Journal of Cardiology* 3. *Circulation* 4. *Bandolier* 5. *Evidence-Based Medicine* 6. *Cardiovascular Review Reports* 7. *JAMA* 8. *Annals of Internal Medicine* 9. *British Medical Journal* 10. *ACP Journal Club*	1. US National Institutes of Health 2. University of Ottawa Heart Institute 3. Montreal Heart Institute 4. National Heart Lung and Blood Institute 5. Health Heart Program, St Paul's Hospital, University of British Columbia 6. World Health Organization 7. International Task Force on Coronary Heart Disease 8. International Society of Atherosclerosis 9. Institute of Clinical Evaluation Sciences 10. American Heart Association 11. National Cholesterol Education Program 12. College of Pharmacy and Faculty of Medicine, Dalhousie University 13. American College of Cardiology 14. Ontario Ministry of Health	15. Conseil d'Evaluation des Technologies du Santé 16. Australian Institute of Health and Welfare 17. University Hospital Consortium 18. Health Services Utilization Research Commission 19. Trent Institute for Health Sevices Research 20. Canadian Coordinating Office of Health Technology Assessment 21. International Society for Pharmacoeconomics and Outcomes Research 22. Therapeutics Initiative, UBC 23. National Pharmacy Cardiovascular Council

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$$(S) = \frac{\text{Number of RCTs identified by an extended search method}}{\text{Total number of known RCTs (major databases + extended search)}}$$

$$(P) = \frac{\text{Number of RCTs identified by an extended search method}}{\text{Total number of items identified by the search method}}$$

Chi-square analyses of statistical significance were applied to test differences in proportions. The Epi Info statistical package was used (12). The statistical significance level was set at 0.05.

RESULTS

The extended search uncovered 94 additional RCTs for inclusion in the two systematic reviews: 9 for the acupuncture project and 85 for the lipid-lowering project, respectively. This represented 42.9% for the acupuncture project and 23.5% for the lipid-lowering project of the RCTs included in the systematic reviews (Table 3). The overall precision of the extended search (all methods combined) was 8.9% (n = 9/101) for the acupuncture project and 31.8% (n = 85/267) for the lipid-lowering project.

Table 2. Extended Search: Acupuncture for Addiction Treatment

Databases	Web library catalogs (using Library of Congress or MeSH)	Internet peer-reviewed sites
1. Cochrane Library 2. HSTAT (technology assessment guidelines) 3. HSRProj (NLM) 4. Dissertation Abstracts 5. Article1st (OCLC) 6. Papers1st (OCLC)—conferences and paper abstracts 7. TRIP database (evidence-based medicine) 8. Ebsco Academic Search 9. Ebsco Canadian MAS 10. Alcohol and Alcohol Problems Science Database (ETOH) 11. ACUBASE (France) 12. CRISP (Computer Retrieval of Information on Scientific Projects) 13. Clinical Trials.gov 14. National Research Register	1. UBC Library Catalog 2. BC Ministry of Health Library Catalog 3. Canadian Institute of Scientific and Technical Information (CISTI) catalog 4. Belinda Database (Buckinghamshire Health Authority Library) catalogue of health promotion) 5. HealthPromis (UK web catalogue of health promotion) 6. National Health Information Center—Health Information Resource Database 7. CHID Online (Combined Health Information Database) 8. WorldCat 9. GAO Web Catalog 10. COPAC 11. NLM Locator Plus	1. UK Academic Web Directory 2. UK Social Science Information Gateway 3. OMNI 4. Medical Matrix Networked Information) 5. Health Communications Network 6. Global Health 7. Health Index 8. Medweb Public Health 9. Medscape

Internet search engines	In-house databases	Directories
1. Google 2. Altavista 3. Northern Lights	1. In-House Catalog	1. ECRI. HealthCare Standards 2. UHC Technology Assessment Monitor

(continued)

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Table 2. (*Continued*)

Journals hand-searched	Organizations contacted	
1. *Alternative Medicine Journal* (peer-reviewed) 2. *Alternative Therapies in Health and Medicine* (peer-reviewed) 3. *Journal of Substance Abuse Treatment* 4. *JAMA* 5. *American Journal of Acupuncture* 6. *Journal Alternative of and Complementary Medicine* 7. *Annals of Internal Medicine* 8. *Lancet* 9. *British Medical Journal*	1. US National Institutes of Health, Office of Alternative Medicine (also known as the National Center for Complementary and Medicine) 2. Center for Complementary Alternative Medicine 3. Center for Addiction and Alternative Medicine 4. The University of Texas Center for Alternative Medicine Research 5. Tzu Chi Institute for Complementary and Alternative Medicine (Bc) 6. National Acupuncture Detoxification Association 7. Richard and Hinda Rosenthal Center for Complementary & Alternative Medicine—Rosenthal Center Directory of Databases 8. Research Council for Complementary Medicine 9. Centre for Addiction and Mental Health 10. The National Institute on Alcohol Abuse and Alcoholism 11. Centre for Addiction Studies (UK)	12. NIDA Organization 13. Canadian Centre on Substance Abuse 14. Foundation for Traditional Chinese Medicine (UK) 15. Hooper Detox Centre 16. National Academy of Acupuncture 17. BC Women's Hospital 18. Vancouver Richmond Health Board (Detox Committee) 19. The Acupuncture Association of BC 20. Evergreen Treatment Services 21. Ministry for Children and Family (BC) 22. Hennepin Country Medical Center 23. Merle West Center for Medical Research 24. Lincoln Medical and Mental Health Center 25. Yosan University of Traditional Chinese Medicine

Table 3. Extended Search: Overall Results

	Acupuncture		Lipid-lowering	
	Total items (%)	RCTs (%)	Total items (%)	RCTs (%)
Extended	101 (47.6)[a]	9 (42.9)	267 (33.0)[a]	85 (23.5)
Major database	111 (52.4)[a]	12 (57.1)	543 (67.0)[a]	276 (76.5)
Entire bibliography	212	21[a]	810	361[a]

[a] $p < .05$ for differences between projects.

The search of specialized databases and trial registries and the review of reference lists were the most effective methods of identifying RCTs for the acupuncture project (33.3% each). The search of specialized databases and trial registries was by far the more effective method utilized to uncover RCTs for the lipid-lowering project at 57.6%, followed by the review of reference lists (30.6%) ($p < .05$) (Table 4). Hand-searching and personal communications produced 11.1% and 22.3%, respectively, of the RCTs ($p < .05$) for the acupuncture project versus 7.1% and 3.5%, respectively, found through extended methods for the lipid-lowering project. As noted above, personal communications produced a larger number of RCTs in the acupuncture project ($p < .05$). There were no significant differences between the effectiveness of hand-searching and personal communications, or between personal communications and Internet.

Table 4. Extended Search: Methods Used To Uncover RCTs and Other Items

	Acupuncture (%)		Lipid-lowering (%)	
Extended methods	RCTs	All items	RCTs	All items
Personal communications	2 (22.3)[a]	30 (29.8)[a]	3 (3.5)[a]	45 (16.9)[a]
Specialized databases	3 (33.3)	17 (16.8)[a]	49 (57.6)[b]	93 (34.8)[a]
Reference lists	3 (33.3)	36 (35.6)[a]	26 (30.6)[b]	62 (23.2)[a]
Internet	0 (0)	2 (2.0)	1 (1.2)	18 (6.7)
Hand-searching	1 (11.1)	16 (15.8)	6 (7.1)[b]	49 (18.4)
Total	9	101	85	267

[a] $p < .05$ for differences between projects.
[b] $p < .05$ for differences between methods.

The sensitivity and precision results followed similar trends. Sensitivity was the same for specialized databases and reference lists at 14.2%, followed by personal communications (9.5%) for the acupuncture project. Sensitivity was significantly higher for specialized databases (13.6%) than for reference lists (7.2%) or hand-searching (1.7%) ($p < .05$) for the lipid-lowering project (Table 5). The precision of searching the specialized databases and reference lists was significantly higher in the lipid-lowering project (52.7% and 41.9%, respectively,) than the acupuncture project (17.6% and 8.3%, respectively,) ($p < .05$). There were no other significant differences in the sensitivity and precision of the methods between projects.

DISCUSSION

The search of specialized databases and trial registries for the lipid-lowering project had the highest sensitivity and precision of all extended search methods examined. Its relatively low sensitivity (13.6%) was offset by a 52.7% precision. As shown, this result is largely attributable to the search of the Cochrane Library, which contains a well-established trial registry and a cardiology review group. Furthermore, the Cochrane Library provides a more sophisticated search interface for the user, whereas many of the other registries do not provide advanced search capabilities. The precision of specialized databases and trial registries was higher than the 33% reported median precision of MEDLINE search strategies for RCTs (9). This study also supports the continued growth and development of trial registries as an effective means of identifying RCTs for systematic reviews, although sensitivity in our study was lower than anticipated. The sensitivity and precision results for the search of the specialized databases and trial registries for the acupuncture project were 14.2% and 17.6%, respectively. There are very few trial registries dedicated specifically to complementary medicine. The search interfaces are not as complex as those available

Table 5. Sensitivity and Precision of Extended Search Methods for RCTs

	Acupuncture (%)		Lipid-lowering (%)	
Extended methods	Sensitivity	Precision	Sensitivity	Precision
Personal communications	9.5	6.7	0.8	6.7
Specialized database	14.2	17.6[a]	13.6	52.7[a]
Reference lists	14.2	8.3[a]	7.2	41.9[a]
Internet	0	0	0.3	5.6
Hand-searching	4.7	6.3	1.7	12.2

[a] $p < .05$ for differences between projects.

to mainstream topics such as lipid-lowering; therefore, the precision of the search is directly affected. Scanning of reference lists was the second most effective extended search method for the lipid-lowering project. Its sensitivity and precision were 7.2% and 41.9%, respectively, lower than that of specialized databases searches ($p < .05$). While scanning of reference lists identified additional RCTs for the systematic review, it is important to keep in mind the issue of reference bias in published articles (15). It will therefore be essential to examine the impact on systematic review results of RCTs identified through scanning reference lists.

Hand-searching was significantly less effective than searching specialized databases and reference lists, with estimated sensitivity and precision of 1.7% and 12.2%, respectively, for the lipid-lowering project and 4.7% and 6.3%, respectively, for the acupuncture project. In a previous study, Jadad and McQuay (17;18) estimated sensitivity and precision of hand-searching compared with MEDLINE searching at 99% and 2.7%, respectively.

A number of factors explain the result differences. In the present study, journals not indexed in MEDLINE or which were delayed for indexing were hand-searched to identify additional RCTs. Jadad and McQuay (17;18) sought to evaluate the effectiveness of Searching MEDLINE compared with hand-searching of journals indexed in MEDLINE. In addition, we used a more widely defined gold standard, which reduces the absolute effectiveness of any one method.

Personal communications identified a significantly greater number of RCTs for the acupuncture project than for the lipid-lowering project, although sensitivity and precision did not differ significantly. This may reflect the number of journals that publish studies of alternative medicine, the number of RCTs evaluating alternative medicine, and the difficulty of publishing studies of alternative medicine in mainstream medical journals. It should also be noted that while personal communications seemed less effective than other methods, it allowed the identification of unique items not otherwise uncovered.

Only a small number of RCTs were retrieved from the Internet. Most material identified through the Internet took the form of narrative reviews, conference proceedings, and abstracts. The one RCT obtained was an updated conference release of a trial that had already been found through a search of the major databases. This is perhaps not unexpected, since licensing agreements with publishers often limit what researchers can make available on the Internet. New initiatives such as PubMed Central may affect this situation.

Difficulties in acquiring gray literature found by extended methods may have led to an underestimation of the effectiveness of extended searches. Citations from MEDLINE and EMBASE were retrieved with relative ease and at low cost, whereas some gray literature items were expensive and difficult to locate. In addition, the extended search relied on the willingness of organizations and researchers to respond to our call for trials and other relevant information. Unfortunately, not all communications produced a response. The extended search methods were not conducted in sequence and overlap was not taken into consideration when coding; thus, the totals of the various extended search methods used to uncover material for the systematic review may be affected.

The estimated effectiveness of extended search methods depends on the quality of the major database searches. To examine the potential impact of issues surrounding the searching of major databases, we retrospectively determined whether items uncovered by extended search were indeed present in the major databases. We found that 30.0% and 84.7% of RCTs found by extended search methods for the acupuncture project and the lipid-lowering project, respectively, were indexed in MEDLINE, EMBASE, or HealthStar 1 year after this study was completed ($p < .05$). Items identified through conference abstracts or personal communications with researchers that were not published or indexed in the major databases at the time of the initial major database search may have subsequently

been published in the year following the completion of this study. This may explain how some items were missed by the major database search.

The timing of the indexing in these databases may also be partly responsible. The National Library of Medicine makes a concerted effort to have major clinical journals indexed in MEDLINE as soon as possible. However, the lag time for indexing may increase for foreign journals, journals only in print form, and with journal distribution dates (29). Therefore, when major databases were initially searched for the two systematic reviews, journals containing appropriate and relevant material may not have been indexed yet. Relevant items would instead have been identified through the extended search. Current Content searches appear incapable of fully correcting for this lag time. At present, we are investigating the use of PreMedline, which is now integrated with PubMed to address the difficulty.

In addition, while the project-specific search strategies applied to the major databases in this study have not been formally evaluated, they were developed by librarians with extensive knowledge and understanding of the databases, using MeSH headings shown to improve the effectiveness of MEDLINE searches (21). Nevertheless, previously reported indexing problems in major databases may have an impact on our results (1;9).

CONCLUSIONS

The extended search identified 94 additional RCTs for the systematic reviews, or 42.9% for the acupuncture project and 23.5% for the lipid-lowering project of all RCTs included in the two systematic reviews. Search of specialized databases and trial registries was by far the most effective extended method for the lipid-lowering project. It identified the largest number of RCTs and had the highest sensitivity and precision. Reviews of reference lists and the search of specialized databases and trial registries were both equally effective for the acupuncture project. An important overlap was retrospectively observed between RCTs identified by the major database and the extended methods, especially for the lipid-lowering project. The timing and accuracy of indexing may be responsible.

It should be noted that the quality of the items retrieved and the likelihood of these items affecting the results of systematic reviews are yet to be assessed. This will ultimately determine the value of extended search methods.

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