

GENERATING AND TRANSLATING THE EVIDENCE:

ENHANCING THE UPTAKE OF SYSTEMATIC REVIEWS

John Wallace

BA (Mod), MSc (B'ham), MB, BAO, BCh, MSc (Oxon), MRCPsych

Clinical Psychologist and Consultant Psychiatrist

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE

REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

AWARDED BY THE UNIVERSITY OF OXFORD.

GENERATING AND TRANSLATING THE EVIDENCE: ENHANCING THE UPTAKE OF SYSTEMATIC REVIEWS

John Wallace, Kellogg College

A thesis submitted in Michaelmas Term, 2013, in partial fulfilment of the requirements for the degree of Doctor of Philosophy awarded by the University of Oxford

The theme of this project was synthesis and the thesis encompasses knowledge generation and knowledge translation. Systematic review methodology was employed. The initial two systematic reviews compared antidepressant medication and cognitive-behaviour therapy for the acute treatment of depression. A further comparison of a combination of the two interventions with each treatment on its own was also conducted, with the bulk of the evidence favouring the psychotherapy.

Moving to the topic of knowledge translation, the main theme of the thesis, the barriers, facilitators, and interventions impacting on systematic review uptake were identified. The evidence from these three systematic reviews, using diverse methodologies, was then combined to identify the interventions that overcame specific obstacles and built on highlighted facilitators in order to improve the uptake of evidence from systematic reviews. Juxtaposing barriers and facilitators alongside effectiveness studies in this final, mixed-methods systematic review allowed a number of interventions to be recommended. The synthesis also allowed strategies to be highlighted that required further development.

Interventions with a statistically significant effect such as educational visits, summaries of systematic reviews, and targeted messaging, addressed a wide range of the identified barriers and facilitators. These interventions were recommended. Promising uptake strategies

requiring further development were also identified. Furthermore, large gaps in the evidence base regarding systematic review utilization were highlighted. Fewer of the facilitators identified as part of this project, such as the medico-legal protection provided by systematic reviews, appear to have been built on in order to increase review uptake. Finally, all the preceding evidence was drawn on in order to develop a proposal focused on improving the uptake of evidence from systematic reviews and meta-analyses.

This doctoral project offers a menu or range of evidence-based factors that can be considered by organisations and researchers when planning strategies aimed at increasing the uptake of pre-appraised, synthesized evidence.

GENERATING AND TRANSLATING THE EVIDENCE:
ENHANCING THE UPTAKE OF SYSTEMATIC REVIEWS

Chapter 1	**Introduction**	**1**
Chapter 2	**Literature review**	**32**
Chapter 3	**Methodology**	**82**
Chapter 4	**Systematic reviews comparing antidepressants and CBT**	**135**
Chapter 5	**Systematic review of the barriers to systematic review uptake**	**197**
Chapter 6	**Systematic review of natural facilitators**	**248**
Chapter 7	**Systematic review of interventions**	**287**
Chapter 8	**Systematic reviews of barriers, facilitators and interventions**	**321**
Chapter 9	**A strategy to enhance uptake of systematic reviews**	**346**
Chapter 10	**Conclusion**	**373**

Word count: 82,426

List of Tables **Page**

2.1 CBT and antidepressants: previous systematic reviews 41
2.2 Combination treatment versus monotherapy: previous reviews 49
2.3 Barriers and facilitators: previous systematic reviews 53
2.4 Interventions enhancing evidence uptake: previous systematic reviews 65
4.1 Characteristics of included studies: antidepressant versus CBT systematic review 148
4.2 Included studies: combination treatment versus monotherapy 150
4.3 Summary of findings, fixed-effect model, antidepressants versus CBT 151
4.4 Summary of findings, random-effects model, antidepressant versus CBT 154
4.5 Summary of findings, fixed-effect model, sensitivity analysis 158
4.6 Summary of findings, random-effects model, sensitivity analysis 159
4.7 Summary of findings, fixed-effect model, combination versus CBT 163
4.8 Summary of findings, fixed-effect model, combination versus antidepressants 165
4.9 Summary of findings, random-effects model, combination versus CBT 167
4.10 Summary of findings, random-effects model, combination versus antidepressants 170
4.11 Sources of heterogeneity: antidepressants versus CBT 183
4.12 Sources of heterogeneity: combination treatment versus monotherapy 184
5.1 Search of PubMed and Embase: systematic review of barriers 213
5.2 Disciplines participating: systematic review of barriers 215
5.3 Characteristics of included studies: systematic review of barriers 216
5.4 Methods and quality: systematic review of barriers 220
5.5 Lack of awareness and the studies citing this barrier 224
5.6 Lack of familiarity and the studies citing this barrier 226
5.7 Lack of usefulness and the studies citing this barrier 229
5.8 Lack of motivation and the studies citing this barrier 229
5.9 Lack of access and the studies citing this barrier 230
5.10 Environmental barriers and the studies citing them 232
5.11 Lack of use and the studies citing this barrier 233
5.12 Number of barriers investigated by each study 236
5.13 Barrier category and barrier descriptive findings 237
6.1 Individuals contacted in course of facilitators' review 256
6.2 Textbooks searched in course of facilitators' review 256
6.3 Data collection sheet 259
6.4 Duplicates: facilitators' review 284
6.5 Included studies: systematic review of facilitators 263
6.6 Discipline of participants: systematic review of facilitators 264
6.7 Discipline of participants in each individual study of facilitators 265
6.8 Characteristics of included studies: systematic review of facilitators 266
6.9 Facilitators assessed by each study 268
6.10 Perceived facilitators of systematic review uptake: knowledge 270
6.11 Perceived facilitators of systematic review uptake: attitude 271
6.12 Perceived facilitators of systematic review uptake: behaviour 272
6.13 Ordered list of detected facilitators to evidence uptake from systematic reviews 273
6.14 Study methods: systematic review of facilitators 285
7.1 PubMed search: systematic review of interventions 294

7.2 Types of interventions enhancing systematic review uptake 301
7.3 Description of interventions 305
7.4 Risk of bias assessment and results: systematic review of interventions 307
7.5 Type of behaviour targeted to enhance uptake of systematic reviews 309
8.1 Synthesis matrix of barriers, facilitators and interventions 344

List of Figures **Page**

4.1 Flow chart: CBT versus antidepressants 141
4.2 Flow chart: Combination therapy versus monotherapy 142
4.3 CBT Vs Antidepressants, fixed-effect model, BDI, continuous data 152
4.4 CBT Vs Antidepressants, fixed-effect model, BDI, dichotomous data 152
4.5 CBT Vs, Antidepressants, fixed-effect model, HDRS, continuous data 153
4.6 CBT Vs Antidepressants, fixed-effect model, HDRS, dichotomous data 153
4.7 CBT Vs Antidepressants, BDI, random-effects model, continuous data 155
4.8. CBT Vs Antidepressants, BDI, random-effects model, dichotomous data 155
4.9 CBT Vs Antidepressants, HDRS, random-effects model, continuous data 156
4.10 CBT Vs Antidepressants, HDRS, random-effects model, dichotomous data 156
4.11 CBT Vs Antidepressants, BDI, R-Es, dichotomous data, Rush excluded 160
4.12 Combination Vs CBT, BDI, fixed-effect model, continuous data 164
4.13 Combination Vs antidepressants, BDI, F-E model, continuous data 166
4.14 Combination Vs antidepressants, BDI, F-E, dichotomous data 166
4.15 Combination Vs CBT, BDI, random-effects model, continuous data 168
4.16 Combination Vs CBT, BDI, random-effects model, dichotomous data 168
4.17 Combination Vs CBT, HDRS, random-effects model, continuous data 169
4.18 Combination Vs CBT, HDRS, random-effects model, dichotomous data 169
4.19 Combination Vs antidepressants, BDI, random-effects, continuous data 171
5.1 Flow chart: barriers to review uptake 214
5.2 Percentage reporting lack of awareness of The Cochrane Library: 225
5.3 Lack of awareness of The Cochrane Database of Systematic Reviews 225
5.4 Percentage reporting lack of familiarity with systematic reviews 227
5.5 Percentage reporting lack of familiarity with meta-analysis 227
5.6 Percentage reporting lack of usefulness of systematic reviews 229
5.7 Percentage reporting lack of access to The Cochrane Library 231
5.8 Percentage reporting lack of use of The Cochrane Database of Systematic Reviews 234
5.9 Percentage reporting lack of use of The Cochrane Library 234
6.1 Flow chart: facilitators of systematic review uptake 261
6.2 Most cited facilitators of systematic review uptake 274
6.3 Number of studies highlighting less cited facilitators 275
7.1 Flow chart: interventions enhancing systematic review uptake 300
7.2 Number of studies investigating each intervention enhancing review uptake 304
8.1 Overview of mixed-knowledge synthesis: barriers, facilitators, interventions 334

Acknowledgements

I wish to acknowledge the encouragement of Dr David Berman, Professor of Philosophy, Trinity College Dublin; Ms Susan Keating, Editor, Irish Arts Review, State Apartments, Dublin Castle, Dublin; Dr Charles Byrne, Irish Health Service Executive-West; Lady Pamela Lea, Chelsea, London; and Professor Michael Clarke, Director of the MRC all-Ireland Hub for Trials Methodology Research, Queen's University, Belfast, Ireland.

CHAPTER ONE

INTRODUCTION

CONTENTS

1.1 Knowledge generation 3

1.2 Objectives of the research 4

1.3 Essentials of the research design 5

1.4 Context of first two systematic reviews 9

1.5 Academic background of writer 16

1.6 The science of synthesis 17

1.7 Knowledge translation 21

1.8 Systematic reviews in mental health care 28

1.9 Summary 29

1.1 Knowledge generation and translation

Questions occur in the context of an already-formed body of knowledge. The background to the thesis is outlined here and this writer attempts to place the various elements of this doctoral project in context while setting a rationale for the research undertaken. The problems targeted, the knowledge gaps addressed, the objectives of the research, and the reasons for the methodology chosen, are detailed. The background outlined here also explains why the questions addressed are so important.

The conclusion of this thesis describes how the identified knowledge gaps about important problems were bridged and how, in doing so, original, incremental contributions were made.

The initial focus of this thesis is knowledge generation. The emphasis then shifts to the main theme of the project: knowledge translation. The knowledge generation section involves a comparison of medication and psychological therapy in the field of mental health, using systematic review methodology. This is consistent with a belief that evidence of effectiveness derived from a study of groups is more reliable than that derived from personal experience (Gray, 2013).

Following the reviews of mental health therapies, barriers and facilitators to the translation of knowledge generated by systematic reviews were identified by this writer. These were later juxtaposed with interventions, also identified by this writer, that were aimed at promoting evidence uptake from pre-appraised, integrative reviews and meta-analyses.

Drawing on the results of the six reviews, a strategy is outlined for enhancing the uptake of evidence from systematic reviews, meta-analyses, and the databases associated with them, in the field of mental health.

1.2 Objectives

By 2030, clinical depression is set to rise from the third to the second leading cause of the global disease burden (WHO, 2012). The condition is associated with significant disability, mortality and healthcare costs (Anglin et al. 2013). Depression also adversely affects social functioning (De Silva et al. 2013). The primary objective of the first systematic review presented here was to assess the effectiveness of cognitive-behaviour therapy (CBT) relative to antidepressants in depressive disorder. The second systematic review aimed to assess the relative effects of combination therapy (CBT and antidepressants) versus single therapy (CBT or antidepressants) in the treatment of depression.

Clinical practice does not always reflect best evidence. This may be because of unconscious acts of omission, information overload, or the inaccessibility of evidence (Arditi et al. 2012). Having generated knowledge, the next important step is to make sure that the research evidence is translated to decision makers for practical use.

The primary objective of the third and fourth systematic reviews was to identify the barriers and natural facilitators to evidence uptake from systematic reviews, drawing on data derived from diverse study types such as surveys, interviews, and focus groups. The aim of the fifth systematic review was to identify interventions aimed at enhancing uptake of review evidence, utilising outcome-evaluation studies.

Finally, the pragmatic objective of the sixth review was to juxtapose the identified interventions, aimed at enhancing systematic review uptake, with the highlighted barriers and facilitators. This final review allowed this writer to identify barriers and facilitators that had been addressed by the selected interventions. The review also indicated promising interventions that could be developed further and also highlighted the barriers and facilitators that had not been addressed by any of the identified interventions.

A proposal for a strategy, in the field of mental health, to improve uptake of systematic reviews was developed in the final section of this thesis. This drew on the knowledge gained from each discrete element of the research conducted as part of this project.

1.3 Essentials of the research design

Methods

The theme of this thesis was synthesis. Systematic review methodology was the method employed. Where appropriate with interventions studies, a meta-analysis was also executed. The six reviews drew on evidence from a wide range of study designs, including surveys, focus groups, interviews, mixed-methods, and intervention-outcome studies. The criteria for considering studies for the individual reviews were outlined in each case. The types of studies eligible, types of participants used, the objectives of the reviews, and outcome measures are discussed in some detail in the relevant sections.

Search Methods

An unknown proportion of research is never formally published (Heneghan and Godlee, 2013). An extensive effort was made to track all relevant studies for the reviews outlined here. The various methods used to identify studies are summarized in each systematic review. The bibliographic databases searched, the dates and the periods addressed, and any constraints, were explicitly stated. Grey literature sources, such as internal reports and conference proceedings, are described together with the references lists that were targeted. Experts and topic specialists who were contacted were also listed.

Data collection and analysis

The methods used to apply the selection criteria are outlined. The process of data extraction from published reports is also described. Safeguarding against bias is central to presenting evidence (Ransohoff et al. 2013). Accordingly, recommended tools for assessing risk of bias are identified and made explicit.

For intervention studies, the effect measure was stated and unit of analysis issues were explored, together with the strategies for dealing with missing data. In all the systematic reviews, approaches to addressing clinical heterogeneity are detailed, together with how the writer determined whether conducting a meta-analysis was considered appropriate or not. Publication and other reporting biases were also addressed. The models used, fixed-effect and random-effects, are identified for the reviews dealing with interventions where appropriate. Analyses aimed at determining whether conclusions are robust to decisions

made during the review process, using sensitivity analysis, are documented. Studies excluded from the individual reviews are listed.

Results

A summary of the search results is described for each particular investigation. The summary included references retrieved by electronic searches and an outline of how many were considered as potentially eligible after screening. A 'Characteristics of included studies' table' is used to give a succinct summary of information about each included study (Higgins and Green, 2008).

The risk of bias in the included studies was explored. Where appropriate, ratings on each criterion are reported in the 'Risk of bias' tables under a number of headings such as allocation, blinding, incomplete outcome data, selective reporting, and other potential sources of bias, depending on the nature of the primary studies included in the systematic review.

Findings

A summary of the main findings of the reviews, in the context of the objective of the individual systematic review, is included. The results of the individual studies, and any statistical summary of these, are included in 'Data and analysis' tables. For the first two systematic reviews, the data are reported, with a confidence interval, as being compatible with either a reduction or an increase in the outcome of interest. For the later reviews based on evidence from focus groups, surveys, interview studies, and intervention studies where meta-analysis is not appropriate, tabulations and narrative synthesis were offered.

Discussion

A summary of the main findings for each systematic review is presented, together with the limitations of the review and the implications for research and practice. The relevance of the evidence to the review question is explored. Whether the studies identified were sufficient to address the review question adequately is discussed in the context of external validity and current practice.

The ability to prevent bias in the review process is explored together with how the studies fit in with the other evidence in the field. The aim is an overall judgement of the internal validity of the results of each review. The writer has estimated whether the evidence identified has allowed a robust conclusion regarding the objectives of the systematic review.

The 'implications for practice' section is intended to be practical and unambiguous (Higgins and Green, 2008). The 'implications for research' section attempts to address clearly how future research might be done and what further research should be done. Any change between the protocol and the actual review is also described together with the rationale for the changes.

Tables

Tables are important to a systematic review. A *Characteristics of included studies* table, as already stated, is presented for each systematic review. Risk of bias tables are included, giving a judgement regarding protection from bias in each study. Characteristics of

excluded studies that might appear to meet eligibility criteria were also maintained together with the reason for exclusion. Any on-going studies were also outlined.

A *Summary of evidence* table is recommended as a means of presenting findings for the most important outcomes (Higgins and Green, 2008). This table gives a summary of the amount of evidence available together with a depiction of the quality of the evidence. Figures such as forest plots and funnel plots, risk-of-bias summaries, search strategies, data collection forms, and details of outcomes such as measurement scales, were also recorded by this writer.

1.4 The context in which the first two systematic reviews were carried out

One of modern medicine's greatest strengths is its evidence base (Gerada, 2013). Systematic reviews are a rigorous and standardized approach to characterizing a body of evidence (Ransohoff et al. 2013). They provide the best means of informing health decision making (Stewart, 2013). Here systematic review methodology was employed to address a knowledge gap regarding the treatment of an important problem in the field of mental health, clinical depression.

Depression is the most common and readily recognised mood disorder and is defined as at least a single depressive episode lasting two weeks (Wallace et al. 2002). Depressive disorder involves a change from ordinary functioning but must also be accompanied by a least four other symptoms such as insomnia or weight loss, to qualify as a formal clinical disorder (Goodwin, 2003).

Major depression is a common, costly, and recurrent disorder that is associated with considerable morbidity and excess mortality (Cuipers et al. 2013). Depression is firmly established as an independent predictor of mortality and cardiac morbidity in patients with coronary heart disease (Freedland et al. 2013). It also causes severe impairment of a person's ability to perform normal social roles (De Silva et al. 2013). Depression has a powerful impact on productivity and the fulfilment of social and familial roles (Cuipers et al. 2012). We know that depression affects a large number of people with the lifetime prevalence estimated between four and twelve percent of the population and a mean age of onset of between 25-35 years (Goodwin, 2003).

The World Health Organisation Global Burden of Disease study ranked depression as the single most burdensome disease in the world among people in the middle years of life (Murray and Lopez, 1996). This rising burden from mental and behavioural disorders imposes new challenges on health systems (Murray et al. 2013). Therefore, the treatment of depressive disorder is of considerable concern to the sufferer and of overriding significance in psychiatry and clinical psychology (Wallace et al. 2002). Depression can be treated with medication or psychological therapy or both.

Treatment of Depression: General Principles

Depression is a condition that causes significant functional impairment and is biologically and psychologically 'toxic' to us (Goodwin, 2003). There is chronic and widespread under-treatment of the condition (Stahl, 2008). Some psychiatrists do not treat depression in accordance with the evidence (Yang et al. 2013). The aim of treatment is full remission and the condition can be addressed with pharmacotherapy, psychotherapy, or a

combination of the two (Cuipers et al. 2012). However, the relative merits of each of these approaches have not been well established.

Pharmacotherapy

The skilful practice of psychopharmacology has many elements. Initially, it involves establishing a proper diagnosis. It is then important to monitor the response of the patient during the course of the treatment. Subjective-rating scales are useful for this but the symptoms may also be classified on a clinician-determined scale. The goals of treatment involve an improvement in symptoms and everyday function.

Sadly, the goal of remission is not usually achieved with the use of a single antidepressant (Stahl, 2008). We naturally try to avoid polypharmacy as it increases the side-effect burden for the patient. In an individual who has had a partial but inadequate response to just one antidepressant despite optimising the dose, the combination of the medication with a second intervention, such as psychotherapy, demands consideration.

McAllister-Williams (2008a) emphasises that many meta-analyses have shown that antidepressants are significantly better than placebo in treating depressive disorder. Any meta-analysis of published data however runs the risk of suffering from publication bias where studies with positive findings are more likely to have been submitted by authors and accepted by editors (McAllister-Williams, 2008a). In a recent systematic review where the reviewers' conclusions challenged the previously reported efficacy of the novel antidepressant agomelatine, none of the negative trials had been published (Koesters et al. 2013). Seven of the thirteen studies included in their review were unpublished and the

review authors concluded that there was evidence of substantial publication bias associated with the drug (Koesters et al. 2013).

Kirsch and colleagues addressing the benefits of antidepressants, tried to avoid publication bias by obtaining all trial data submitted to the United States Food and Drug Administration (Kirsh et al. 2008). The FDA insists that studies are submitted to them irrespective of whether the data are positive or negative, published or unpublished. Kirsch and colleagues argued, in their important review that aimed to reduce publication bias, that antidepressants have a smaller clinical effect than previously reported. Others, addressing the same findings, drew different conclusions and assert that the drugs are effective and have an acceptable harm/benefit ratio (McAllister-Williams, 2008a).

The choice of antidepressant medication is large (Stahl, 2008). Many of the older compounds, such as amitriptyline, imipramine, and clomipramine, are still used in clinical practice and also in studies comparing cognitive-behaviour therapy (CBT) and antidepressants. If the patient has had no response with an antidepressant then the dose can be increased, a new antidepressant used, or the medication combined with another intervention. But we have no way of deciding which intervention should be regarded as best practice (Goodwin, 2003).

Research in modern psychotherapy has begun to standardize and test selected approaches to treatment in a way similar to the way in which antidepressants are assessed in clinical trials. These psychological treatments are now being tested according to standard protocols, by clinicians receiving standardized training, using standardized manuals, together with set interventions of a fixed duration. Furthermore, many psychotherapies are being compared in clinical trials to antidepressants (Stahl, 2008).

Cognitive-behaviour Therapy

Although current treatments are efficacious in a segment of the population with clinical depression, there is a need for alternative and augmentation strategies (Rethorst and Trivedi, 2013). There is now a renewed emphasis on non-pharmacological interventions across a variety of psychiatric conditions (Lawrence et al. 2012). Since the 1970s there has been a steady development of a range of short-term psychological treatments for depressive disorder. Importantly, some of these interventions can be adequately described in reports (Glasziou et al. 2010). The range of psychological interventions and rationales for the treatment of depressive illness is wide, but CBT is both effective and popular.

CBT essentially focuses on modifying maladaptive, distorted thinking. It is concerned with the 'here and now', tends to be time-limited and have clear aims. This makes it a useful, short-term, structured psychotherapy. Indeed, CBT for depression has long been referred to as one of the most widely used, influential and consistently tested of all psychological treatments (Fennell, 1989). CBT usefulness in reducing symptom severity in severe mental health conditions has been demonstrated (Morrison et al. 2013).

CBT is an elegant interweaving of both cognitive and behavioural techniques. The number of therapy sessions required varies from 6 to 20 highly structured, one-hour interventions. CBT sessions are usually followed by behavioural assignments where new ideas are tested. This opens the way for changes in behaviour as well as thinking. The short-term, structured nature of the intervention makes it particularly suitable for empirical investigation. As a result, CBT now has an extensive research base and CBT has become a major orientation of many practicing psychotherapists.

Comparison

There is a debate about the effectiveness of antidepressants and psychotherapy in the treatment of adult depression (Wagner, 2005). Although there is agreement that antidepressants are effective in treating depression, the effectiveness of cognitive-behaviour therapy is also important. To estimate the effectiveness of a talking therapy, we can compare it with a reference treatment. A reference treatment, in this case an antidepressant, is one that has been already found to be effective in a particular patient population.

In a number of conditions, psychological interventions are rarely offered (Eccleston et al. 2013). There remains a bias in high-impact journals towards neurobiological sciences (Kingdom, 2013). Some believe that psychotherapies such as CBT have been underused to treat depression (Markowitz, 2008). There is clearly a need for alternatives to pharmacotherapy.

There are a number of situations in which CBT may be obviously preferable to antidepressant medication. These situations include the management of the patient who does not like tablets, is unable to tolerate medication due to their side effects, or who is pregnant. CBT can be of particular benefit with children and adolescents. Apart from these situations, the choice between antidepressants and CBT often rests simply on the preferences of the patient and therapist. Clearly, more evidence on which to base clinical recommendations would be an advantage.

Importance of Issue

In Western countries antidepressant drugs and CBT dominate the treatment of depression. The comparative effectiveness of CBT and medication is of importance to both clinicians and patients. Clinicians need to think carefully before choosing a treatment for a patient with depression (Markowitz, 2008).

Antidepressant medication is the most common treatment for depressive illness used by general practitioners. The time and skill required for CBT is unlike that required for the general management of depressed patients in primary care. Larger time investments may be deemed justified if CBT is more cost effective, more effective clinically, and more acceptable to patients (Scott and Freeman, 1992).

How much time and money each treatment costs and how they are valued by patients, is important. All specialist strategies such as CBT involve at least twice as many appointments and from 4 to 14 times more face-to-face contacts with a psychotherapist than a general practitioner favouring antidepressants (Scott and Freeman, 1992). Contact with a specialist therapist can cost four times as much as the time that general practitioners spend with patients (Scott and Freeman, 1992). If CBT is more demanding in terms of time and money, then we need to know if the cost is justified. It may be justified if CBT is more clinically effective.

Reviews

The initial segment of this thesis involved conducting two related systematic reviews that were designed to address important and clinically relevant questions regarding the

treatment of clinical depression (Wallace et al. 2014a). The reviews, within the context of a positivistic epistemology, looked at two treatment modalities: pharmacological and cognitive. These are the two treatments currently used in real life, clinical settings.

The first systematic review looked at antidepressants alone versus CBT alone in the treatment of depressive disorder. The second systematic review looked at combined treatment versus CBT alone, or antidepressants alone, in the treatment of depression.

Although there is a consensus that antidepressants are effective in the management of depression, the beneficial effect of CBT is also substantial. The objective of the secondary research conducted here was to complete a systematic review and meta-analysis of all randomised controlled trials and controlled clinical trials in which the efficacy of antidepressants was compared with CBT in the treatment of depressive illness.

It has been suggested that it should be established whether combination treatment of antidepressants and CBT is superior to single therapy (Keller et al. 2000). A second systematic review and meta-analysis was conducted of all randomised controlled trials and controlled clinical trials in which antidepressants and CBT were combined for the treatment of depression and where this 'combination treatment' was compared with either treatment alone. The aim was to test the hypothesis that combining antidepressants and CBT was more effective in treating depression than either of these mono-therapies alone.

1.5 Reflexive account

It is important that clinicians are aware of their own beliefs and preferences (Peile et al. 2013). This writer had a background in psychology and clinical psychology prior to

studying medicine and psychiatry. This led to an interest in the relative effects of psychological and pharmacological interventions in the field of mental health and especially the impact of their combination.

This writer trained initially as a CBT therapist while a postgraduate psychology student with the psychology department at Birmingham University. Following qualification as a doctor, training was again undertaken in CBT while a specialist registrar in psychiatry at University College London. This writer has also attended the CBT workshops at the Centre for Cognitive Therapy at the Warneford Hospital, Oxford University.

This writer has completed the Certificate in Psychopharmacology, over two years, with the British Association for Psychopharmacology in Cambridge.

1.6 The science of synthesis

Evidence-based healthcare has taken root as one of the central pillars of modern medicine (Heneghan and Godlee, 2013). The vast investment in biomedical research during the last 5 decades has led to important advances in health care. Despite the availability of a large amount of relevant, biomedical evidence, a gap can exist between the optimal practice suggested by the evidence and routine patient care (Wallace, 2012a).

Reviews of summarised evidence have become an essential tool for clinicians who want to keep up to date with the wide-ranging and fast accumulating evidence in their field (Gartleher and Flamm, 2013). As it is impossible to read every single research article, systematic reviews have become a quick and efficient way to keep pace with recent

developments (Wallace, 2012b). They make large quantities of information palatable. Since the 1990s when systematic review methodology was in its infancy, methods for searching, selecting, and meta-analysing data have advanced beyond recognition (Heneghan and Godlee, 2013).

Systematic review is a fundamental scientific activity. It is important that clinical decisions are not based solely on one or two studies without taking account of the whole range of information that might be available on a particular topic. Systematic reviews address a fuller spectrum of evidence than do narrative reviews (Strech et al. 2013). Pre-appraised, integrative reviews seek to empower clinicians by quickly providing them with review evidence most relevant to a specific clinical question. Systematic reviews may be better than a single study but clinical decisions are often based on results derived from one famous study rather than any comprehensive assessment of all the available evidence.

Despite its widespread acceptance as a mechanism for rational decision making, evidence-based healthcare remains in many ways an ideal rather than a fully-fledged reality (Heneghan and Godlee, 2013). Evidence-based medicine is a form of information management in which high-quality knowledge is produced and then quickly disseminated. The systematic review is an essential part of this process. Systematic reviews consist of a clearly formulated question and use explicit methods to identify, critically appraise and analyse data from all the relevant research in order to address a clinical problem (Sackett et al. 1996). A meta-analysis is one statistical technique that can be used in an overview in order to integrate the results of included studies. It is essentially a form of data synthesis or statistical pooling (Mitchell et al. 2012a).

A review may not necessarily include a meta-analysis. However, if the systematic review can pool the data from the included studies, it can greatly increase the statistical power of the research (Deeks et al. 2008). This pooling may increase the chance of detecting a real effect of a treatment as statistically significant, if it exists (Bowers, 2008).

It is hoped that systematic reviews may go some way to settling controversies arising from apparently conflicting studies regarding, for instance, the relative effectiveness of medication and psychotherapy. Because systematic reviews provide the most powerful evidence available, they have become extremely important to decision makers, attracting a high citation rate (Tyrer, 2008).

Systematic reviews should accurately reflect the underlying evidence (Ransohoff et al. 2013). In controversial areas, the conclusions drawn from a given body of research may be associated more with the speciality of the reviewer than with the available evidence (Lang and Secic, 2006). In contrast, a systematic review is governed by formal rules that are established for each step of the process in advance. Consequently, bias is reduced, the process made transparent, the results reproducible, and the validity of the review can be verified.

How science takes stock

It is part of the mission of The Cochrane Collaboration to promote the accessibility of systematic reviews of the effects of healthcare interventions (Higgins and Green, 2008). Cochrane reviews strive to address the needs of all decision makers including patients (Gartleher and Flamm, 2013). In the era before pre-systematic reviews, clinicians deferred to hospital experts whose position and allegiance were not known. Systematic

reviews, on the other hand, attempt to take account, in an explicit fashion, of a whole range of relevant findings in a particular area. They aim to provide a summary of all studies addressing a set question while simultaneously placing the studies in a particular context. A meta-analysis, pooling the results of the different primary studies, may give an improved reflection of reality.

Systematic reviews can induce a sense of humility by illustrating the inadequacy of the existing evidence (Tyrer, 2008). Research in any one area may be weak and so evidence synthesis will often draw attention to important knowledge gaps. Systematic reviews allow clinicians to move above all the evidence, overview the research terrain, and summarise the many elements of a complex puzzle. Systematic reviews can help with difficult decision making. They can also direct the flow of clinical research towards relevant problems (Egger et al. 2001a).

This is regarded by some as the age of the systematic review (Tugwell et al. 2012). A review may be aggregative or configurative (Gough and Thomas, 2013). Regardless of type, these reviews require a substantial investment of resources (Ransohoff et al. 2013). However, lack of use of systematic reviews and meta-analyses constitutes a serious problem (Tetzlaff et al. 2009). Systematic reviews, especially up-to-date Cochrane reviews, are not consistently used in the development of clinical practice guidelines (Al-Ansary et al. 2013). Cochrane reviews suffer the same fate of other systematic reviews in that the information they offer remains unused due to the perception that they are not immediately relevant (Gartleher and Flamm, 2013).

While systematic review methodology has many advantages, the uptake of evidence from the resultant reviews is slowed by many obstacles (Wallace et al. 2012a). The lack of

identification of the obstacles that hinder review uptake constitutes a significant knowledge gap. Lack of awareness of the enhancers of systematic review use also poses a serious challenge (Wallace et al. 2012b). Selection of interventions that increase review use is important (Wallace, 2013). The identification, in the later chapters of this thesis, of the barriers but also the facilitators and interventions moderating systematic review usage, constitutes a considerable and original contribution to addressing an important knowledge deficit (Wallace et al. 2014b). Their identification helps to fill a knowledge gap that impacts on the translation of evidence from research into everyday practice.

1.7 Knowledge Translation

The importance of research evidence to clinical decision making is accepted on an intellectual level and is largely unquestioned. It is assumed that simply by funding research an eventual improvement in healthcare will occur. In practice however, behaviour often diverges from evidence-based recommendations (Oxman et al. 1995). Though we know that it is important for clinicians to adhere to evidence-based methods, this is frequently difficult due to often unsubstantiated talking points coming from advertising and the Internet (Matson, 2013).

Good clinical knowledge is not necessarily used. Some evidence can take many years to find its way into clinical practice (Balas and Boren, 2000). Research evidence is frequently not reflected in guidelines, expert advice, and clinical practice (Murthy et al. 2012). This denies patients the benefits of advances in medical research. Failure to translate successful research into practice is a major cost to the public and a substantial waste of resources (Glasziou et al. 2014).

The gap between what is known and what is implemented needs attention. It also requires action and the strengthening of research and dissemination efforts (Cuipers et al. 2012). Adoption of an innovation is not an instantaneous act. It is a process that occurs over time (Dobbins et al. 2001a). The discipline of knowledge translation (KT) is increasing in importance. KT describes efforts to facilitate the transfer of high-quality evidence from research into clinical practice throughout the careers of practitioners. It represents a process whereby research information is not only received but also acted upon (Straus et al. 2009). Knowledge translation interventions have the potential to improve clinical practice and patient care (Kastner and Straus, 2012).

Several factors have increased the need for better knowledge dissemination in medicine and psychiatry. The growth of science and technology, increased media attention to scientific discoveries, and the demand for political accountability, have all intensified the demand for better dissemination and utilization of research evidence in healthcare settings (Dobbins et al. 2001b). There is a fracture between knowledge and utilisation. There is also a realisation that strategies accelerating the use of research should run alongside knowledge creation (Lang et al. 2007). In the area of mental health, it is acknowledged that there is a major challenge in the translation of scientific advances into clinical practice, with a route from evidence to action that is efficient, rapid, and explicit (Geddes and Carney, 2001).

Terminology

While KT is currently topical in healthcare, the concepts behind the discipline are not new. Many terms are used to describe the process of moving evidence to practice. Diffusion refers to the clinician's natural, unaided adoption of practices and policy.

Dissemination refers to the communication of information to clinicians to improve their knowledge and skills. It is more active than diffusion. Implementation is more active still. It involves effective communication strategies that identify and overcome the barriers to change, using effective techniques in the practice setting. Adoption refers to a decision maker's intellectual commitment to change their practices. It can also refer to the actual alterations in practice (Davis and Taylor-Vaisey, 1997). All these related terms imply that it is necessary to move beyond the simple publication or diffusion of evidence to the routine active use of research knowledge by clinicians.

The evidence pipeline

The uptake of evidence can have a number of phases. Pathman described 4 stages of the evidence-to-action process (Pathman et al. 1996). First, the clinician needs to be aware of evidence, then agree with it, then adopt it, and then adhere to the evidence in practice. There is often a steady decline or loss of information at each of these steps however. So, even with high rates of transfer of evidence in the early stages, there may be little impact on eventual patient outcomes.

In a schema adopted from Glasziou and Haynes, the evidence pipeline represents the trajectory that research evidence, represented as water, must take to be incorporated into clinical practice (Glasziou and Haynes, 2005). The research evidence leaks gradually from the evidence pipeline where a number of factors, or barriers, contribute to its evaporation and dissipation. KT interventions can be viewed as attempts to overcome these barriers and reduce the evaporation and dissipation of research evidence as knowledge moves towards the patient from its source.

From bench to bedside

It is important then to look at the initial problem of getting the relevant evidence into the clinical pipeline, how this can be improved, and then develop methods for reducing blockages and leakages at each stage. Interventions designed to change practice should be based on an accurate assessment of the factors that support or impede targeted healthcare outcomes (Cochrane et al. 2007). The accuracy of the assessment is directly related to the future impact of the intervention (Bloom, 2005). If we accept this finding, then it is vital to identify barriers and facilitators to knowledge uptake prior to implementing a strategy to improve evidence use.

Barriers and facilitators to evidence uptake

Obstacles or barriers to the application of best evidence and the development of innovative approaches to overcoming these obstacles fall squarely within the field of knowledge translation. Researchers have attempted to examine the barriers to change with the long-term aim of understanding how the knowledge gaps can be narrowed and closed (Cochrane et al. 2007). By highlighting the barriers it may be possible to target an intervention to overcoming the specific obstacle identified.

In the past, much of the work has been on the barriers to uptake of evidence from clinical practice guidelines (Cabana et al. 1999). But systematic reviews differ from clinical practice guidelines in a number of important ways, including the emphasis in guidelines on making specific recommendations (Andrews et al. 2013).

Frameworks can be developed to map the process of translating evidence into practice by addressing potential barriers and thus anticipating how knowledge can be sustained and disseminated (Kastner and Straus, 2012). In psychiatry, cited barriers to evidence uptake include a lack of time, difficulties specific to psychiatric research, lack of resources, ingrained habit, insufficient research evidence, and difficulties in disseminating research findings (Lawrie et al. 2000). Some factors, of course, may enhance rather than impede evidence uptake. Research on facilitators of evidence uptake is currently under-developed. We do know that mental health professionals want more relevant, good quality research, more sources of information, and more education (Lawrie et al. 2000).

KT Strategies

Knowledge translation is an active area of innovation (Tugwell et al. 2012). Translating research into practice, however, is a daunting task (Matson, 2013). It requires intellectual rigor, discipline, creativity, clinical judgement, skill, and endurance (Straus et al. 2009). While it is important to facilitate access to evidence, there is little consensus as to the most effective ways to improve uptake of research evidence in general and of evidence from systematic reviews in particular (Dobbins et al. 2009a).

Systematic reviews

KT aims at a seamless linkage between research and routine clinical implementation (Glasziou and Haynes, 2005). Much work has already been done to make evidence-based mental healthcare more accessible and acceptable (McGorry, 2013). Making the best evidence readily available in a clinical setting remains a significant challenge (Geddes, 2001). Knowledge is not enough. Improving research's usability is central (Glasziou,

2013). More effective knowledge and exchange strategies are required but investigation of dissemination and utilisation of research is in its infancy **(**Ciliska et al. 1999).

An aspect of knowledge translation that is largely understated relates to the uptake and impact of knowledge synthesis (Liang et al. 2007). Systematic reviews are a vital part of the cycle of knowledge generation and use (Gough et al. 2013). The generation-and-use cycle cannot work properly without links between research and the users of research (Haynes, 2013). Formal, intermediary processes may be required for some of the uses of knowledge, such as the utilisation of systematic reviews (Gough et al. 2013).

There are strong arguments for using systematic reviews (Tugwell et al. 2012). These pre-appraised, integrative reviews are capable of providing high quality evidence for action. The successful uptake of knowledge from systematic reviews should improve quality of care by decreasing inappropriate variation in clinical practice and expediting the application of effective therapeutic advances to everyday practice (Geddes and Carney, 2001). Good quality systematic reviews should be available for widely-used psychological and pharmacological interventions (Geddes and Carney, 2001). The contribution of systematic reviews is captured by a number of online databases such as The Cochrane Library.

The Cochrane Library

The initial collective vision of the Cochrane Collaboration was to identify randomised controlled trials and to use the findings to prepare systematic reviews to inform healthcare practice and decision-making (Maclehose and Hilton, 2013). The Cochrane Collaboration is now recognised for its well-established record in systematic review methodology. Their

database contains published systematic reviews covering a whole range of healthcare interventions and is a living resource (Maclehose and Hilton, 2013). The Cochrane Collaboration is a unique partnership pursuing answers to the most important questions (Eccleston et al. 2013). As Cochrane reviews are increasingly utilized, they may help bridge the gap between best evidence and optimal healthcare.

Lack of empirical evidence to support effective interventions in the field of knowledge translation is a significant knowledge gap. It is important to promote the availability and value of important information resources such as systematic reviews and to make usage of The Cochrane Library a core activity.

KT Research

The healthcare system relies on continuing medical education to improve the clinical practice of clinicians. A systematic review of lectures, workshops and courses, and their impact on practice and patient outcome revealed that didactic presentations have limited effect (Grol and Grimshaw, 2003).

Programmes that have an interactive approach such as audit with feedback, academic detailing and outreach, together with reminders, seem more effective at changing both physician care and patient outcomes (Lang et al. 2007). Furthermore, the proportion of effective strategies in evidence transfer is believed, by some, to be significantly higher with interventions that include a prospective identification of barriers to change compared with standardized interventions (Chaillet et al, 2006).

Evidence regarding barriers and facilitators can be used to inform local strategies or interventions to improve uptake. It is important to facilitate access and translation but there is little consensus in the published literature as to the most effective ways to reach decision makers and improve research uptake, especially from systematic reviews. It would be helpful to know which interventions enhance uptake of evidence specifically from systematic reviews (Jordans et al. 1998).

Interventions as well as views and perspectives that can aid improved uptake of systematic reviews were identified in this research project. The quality of the diverse contributing research studies was examined. The detected interventions were then assessed in terms of how they overcame the barriers and built on the facilitators identified in this project as impacting on evidence uptake from systematic reviews, meta-analyses and the databases containing them.

1.8 Systematic reviews in mental health

There is increasing interest in the potential contribution of evidence-based medicine to clinical decision-making in psychiatry. However, making the best available evidence readily accessible in a mental health clinical setting continues to be a significant challenge (Yang et al. 2013). Evidence in psychiatry should be both scientifically sound and clinically important (Geddes and Harrison, 1997). Factors such as the conceptual aetiological school to which a clinician subscribes, for example biological versus social, are important but so is evidence.

In psychiatry, a major challenge is to translate scientific advances rapidly into clinical practice (Geddes, 2011). In enhancing the application of existing evidence in psychiatry,

systematic reviews are a major advance (Geddes and Harrison, 1997). Evidence-based medicine in psychiatry needs to demonstrate tangible benefits to patients. Systematic reviews were found not to be available for three of the five most asked questions in this area, and a published meta-analysis was available for only one of these five questions (Lawrie et al. 2001). Reliable evidence even when available is of course not necessarily used (Yang et al. 2013). A consensus is needed on how to deliver clinically useful information, in the form of systematic reviews, in the field of mental health. The gap between research and practice in psychiatry needs to be closed.

1.9 Summary

To this writer's knowledge, the two systematic reviews conducted here on the treatment of depressive disorder differ significantly from others in the field because of their sharp clinical focus and their emphasis on reducing both clinical and methodological heterogeneity.

Moving to the core thesis questions, the aim of the subsequent systematic reviews was to make an incremental and significant contribution to the field of knowledge translation by the systematic identification of barriers to, and facilitators of, uptake of evidence, specifically from systematic reviews and meta-analyses. This was then followed by a synthesis or juxtaposition of these natural barriers and facilitators with the identified interventions. Evaluating complex interventions poses unique challenges (Lawrence et al. 2012). Definitions of complex interventions frequently emphasize that they have multiple interacting components and non-linear causal pathways (Petticrew, 2011). Complexity resides in the number of interacting components; the number of behaviours involved; the numbers of groups targeted by the intervention; the degree of flexibility of the

intervention and the variability of the outcomes (Craig et al. 2008). Nevertheless, the knowledge generated by the synthesis of barriers, facilitators and interventions, was subsequently used to develop a proposal for a strategy to enhance the uptake of evidence from systematic reviews in the field of mental health.

The findings of the reviews described here are intended to help inform the development of future strategies to improve uptake of evidence from systematic reviews by decision makers. All the systematic reviews conducted as part of this project were intended to make incremental and novel contributions to bridging important, identified knowledge gaps regarding relevant problems.

To implement evidence, it is important to prepare well. In order to move knowledge from research to practice it is first necessary to identify a specific problem. Then, the knowledge needed to solve the problem is selected and adapted to local conditions. Next, the knowledge-use determinants, such as obstacles and facilitators are identified. Then the intervention to enhance evidence uptake is selected and tailored to build on the identified facilitators and overcome the emergent barriers. Lastly, the intervention is implemented and strategies put in place to ensure sustained knowledge use.

Knowledge translation is best thought of as a bridge (Lang et al. 2007). Evidence generation and evidence implementation should go hand in hand. To this writer's knowledge, the knowledge translation reviews conducted here are the first systematic reviews of studies investigating and integrating discouraging and encouraging factors to the uptake of evidence specifically from systematic views and meta-analyses. As such, the reviews make an important, incremental contribution to filling an important knowledge gap regarding relevant problems.

The following chapter outlines a review of the literature comparing antidepressants, CBT and their combination. It also offers a literature review of barriers, perceived facilitators and interventions impacting on uptake of evidence from systematic reviews, meta-analyses and the databases containing them. A brief, integrated literature review will also be found associated with each individual systematic review, where appropriate.

CHAPTER 2

LITERATURE REVIEW

CONTENTS

2.1 Psychotherapy, antidepressants and their combination 34

2.2 Psychotherapy versus medication 40

2.3 Combination of medication and psychotherapy 44

2.4 Knowledge Translation 51

2.5 Barriers and facilitators impacting on systematic review uptake 54

2.6 Interventions to enhance systematic review uptake 63

2.7 Synthesis of the barriers, facilitators and interventions 76

2.1 Psychotherapy, antidepressants and their combination

The previous chapter presented an introduction to the background against which the systematic reviews outlined here were conducted. The first two reviews and meta-analyses were concerned with knowledge generation and focused on the treatment of depressive disorder. The aim of the subsequent systematic reviews in this thesis was to systematically identify the barriers to, and perceived facilitators of, uptake of evidence specifically from systematic reviews, meta-analyses and the databases containing them.

This chapter looks at previous reviews addressing the issue of psychotherapy versus medication in the treatment of depression. Systematic reviews of combination therapy versus monotherapy (consisting of psychotherapy or medication alone) are also described.

The literature covering barriers and facilitators impacting on systematic review uptake is then outlined with an emphasis on systematic reviews previously conducted in this area. Reviews of the literature focusing on interventions designed to increase evidence uptake are then described. Lastly, the issue of combining qualitative and quantitative research in bringing the barrier, facilitator and intervention studies together is addressed.

Introduction

The corrosive effect of mental ill health on human happiness has long been recognized and can cast a long shadow over social and economic activity (McGorry, 2013). Depression can cause misery and hardship to the sufferer but also to their carers and

families (Gilbody et al. 2012). Depressive disorder represents one of the most common mental health problems worldwide with a substantial impact in terms of human suffering, impaired functioning, loss of life, and reduced productivity (Li et al. 2012). Symptoms of depression often emerge in childhood and adolescence (Lamers et al. 2012). Patients who have a major depressive episode are at risk of further episodes, and the number of such events significantly increases the risk of subsequent relapse. Up to 50% of individuals with depression may remain depressed or have at least one reoccurrence during follow-up (Eaton et al. 2008).

Depression is also associated with enhanced mortality rates (Markkula et al. 2012). Patients with major depression are more likely to die earlier than those without depression (Gallo et al. 2013). Patients with clinically meaningful symptoms of depression can have significant and long-term impairment in many areas of functioning that equal or exceed those of individuals with chronic physical illness (Bridle et al. 2012). People with depressed mood are also at risk of losing their job and may never work again. The journey from paid employment to welfare, via depression, can be a vicious cycle (Gilbody et al. 2012).

Although substantial progress has been made in the treatment of many chronic conditions, depression continues to cause significant disability and human suffering (Williams and Kuyken, 2012). Primary care and specialist services pick up the pieces when depression strikes (Gilbody et al. 2012). Effective interventions for depression and its potential negative consequences are very much needed (Ayerbe et al. 2013).

Antidepressants are often the first-line treatment for the management of depression in primary care (Wiles et al. 2012). But a substantial proportion of patients with depression

in primary or secondary care fail to respond to adequate trials of antidepressants. Few patients achieve complete remission and medication-resistant depression is common and leads to worse outcomes, including more hospitalizations (Li et al. 2012).

The management of depressive disorder then is of considerable concern to the sufferer and of major significance to a range of disciplines dealing with the condition. The initial challenge is to effectively treat the initial episode so as to prevent depression from turning into a recurrent relapsing condition (Collins et al. 2011). The case to intervene in depression is compelling (Gilbody et al. 2012). And despite the many challenges, effective intervention is not a 'mission impossible' (McGorry, 2013).

Treatment of Depression: General Principles

Across all countries, investment in fundamental research into treating disorders such as depression is disproportionally low relative to the disease burden (Collins et al. 2011). There is chronic and widespread under-treatment of unipolar depression (Stahl, 2008). The aim of treatment is full remission and the condition can be addressed with pharmacotherapy, psychotherapy, or a combination of the two.

The efficacy of psychopharmacological treatments has been called into question (Leucht et al. 2012). Response to antidepressants is certainly variable (Wiles et al. 2012). 'Easy to treat' depression responds to a single antidepressant (Goodwin, 2012). Sadly, remission is not usually reached with the administration of a single treatment (Stahl, 2008). Naturally we try to avoid polypharmacology as it increases the patient's side-effect burden. In an individual who has had a partial but inadequate response to an antidepressant on its own, switching or changing over to a second intervention such as psychotherapy is an option.

McAllister-Williams (2008) emphasises that many reviews with meta-analyses have shown that antidepressants are significantly better than placebo in treating depression. The choice of antidepressants is large and we also can avail of a range of psychological therapies, such as cognitive-behavioural therapy (CBT) that can be effective, or we can combine the two. However, for some time it has been difficult to decide which of these options should be regarded as best practice in terms of treatment choice (Hollon et al. 1992a). The research evidence is said to indicate a broad equivalence of effect between psychological therapies and CBT over a range of depressive severities (NICE, 2010).

Psychotherapy

Since the 1970s there has been a steady development of a range of short-term strategies for dealing with clinical depression. Many patient groups have advocated accessible psychosocial approaches to managing depression (Williams and Kuyken, 2012). 'Broad-brush' interventions, such as counselling, are often offered (Gilbody et al. 2012). Psychosocial interventions are reported to have a positive impact on selected outcome measures (De Silva et al. 2013). Behavioural activation has also been reported to be effective (Kanter et al. 2012). Exercise has also been advocated as a way of reducing depression severity in the elderly (Bridle et al. 2012).

Systematic, directive, structured psychological therapies have been shown to be effective in the treatment of depression (Huntley et al. 2012). Cognitive-behaviour therapy is one such structured psychotherapy (De Silva et al. 2013). The diversity of psychological techniques and rationales for the treatment of depression is extensive, but cognitive-behaviour therapy is one of the most extensively researched and available.

Cognitive-behaviour therapy (CBT) evolved from cognitive therapy, which focused on dysfunctional cognitions or beliefs, and then incorporated components of behaviour therapy. The therapy is a complex interweaving of cognitive and behavioural techniques and the short-term, structured nature of this treatment makes it particularly amenable to empirical investigation. The focus of the therapy is on the constellation of negative thoughts and feelings and how psychological intervention can reduce these for the patient (Williams and Kuyken, 2012).

Although other types of psychological therapy are effective in depression, the most liked is CBT (Huntley et al. 2012). The therapy is becoming the majority orientation of practicing psychotherapists because it is more easily disseminated and implemented than other treatment approaches, and most importantly, because it has a robust evidence base. CBT is advocated for those who have declined low-intensity psychosocial interventions (Huntley et al. 2012). Furthermore, some believe that psychotropic drug efficacy is very small and that psychiatric medication is not worth the burden of the side effects (Leucht et al. 2012).

Doctors and Psychologists

Although biological, psychological, and environmental theories have been advanced, the underlying pathophysiology of depression remains unknown (Anglin et al. 2013). Understandably, different disciplines have varying perspectives on the treatment of depression. The historical legacy of some physical treatments in psychiatry has left them with an image problem (Allan et al. 2012). In addition, some people think that psychiatric disorders are purely psychological conditions that should be treated exclusively with a psychotherapy (Leucht et al. 2012).

In Western countries, medication and psychotherapy dominate the treatment of depression. The comparative effectiveness of medication and talking therapies is of fundamental importance to clinicians and patients alike. The investment of time and skill required for psychotherapies such as CBT is, for some patients, quite unlike routine management. Such increased time investments may be justified if talking therapy is more clinically effective, more cost effective, and more acceptable to patients.

The holy grail of depression treatment is an intervention that is cost effective, well tolerated, minimally invasive, and has no serious side effects (Allan et al. 2012). Effective treatments based on research evidence, influenced by clinical experience and the patient's best interests, are required in order to avoid the corrosive damage that depression can produce (McGorry, 2013).

As it is important to choose the best available treatment for depressive disorder, it is helpful to know the relative merits and outcomes of medication versus psychotherapy in order to inform this decision.

Quality, pre-appraised, integrative reviews

A systematic review is a review of a particular subject undertaken in an objective, systematic way with the purpose of reducing the risk of bias. A meta-analysis is a statistical technique that allows data from individual studies in the systematic review to be pooled with the purpose of enhancing the precision of estimates of treatment effects. It is important that clinical decisions in medicine in general and psychiatry in particular, take account of the whole range of information that might be available on a specific topic. Large, replicated, randomised controlled trials are a good guide to treatment choices. As it

is impossible to read every single research article, systematic overviews have become a quick and efficient way to keep pace with recent developments. Pre-appraised, integrative reviews make large quantities of information more palatable, especially in areas such as the comparison of psychotherapy and medication. Due to the inherent subjectivity and bias proneness of narrative overviews, systematic review methodology was utilized here (Hegeman et al. 2012).

A number of reviews have compared psychotherapy and medication in the treatment of depression and are outlined here.

2.2 Psychotherapy versus medication

DeRubeis and colleagues carried out a systematic review comparing the acute outcome of antidepressant medication and CBT in depressed outpatients from four randomized trials (DeRubeis et al. 1999). Depression in this review was described as being in the severe range. Importantly, the degree of depression suffered by participants in the study could also be described as moderate, depending on the classification system applied. The result of their systematic review indicated that the overall effect sizes comparing antidepressant medication with CBT tended to favour CBT. However, tests comparing the two treatments did not reveal a statistically significant advantage for either modality overall. They concluded that CBT fared as well as antidepressant medication with depressed outpatients, an important finding in itself. They advised that antidepressant medication should not be considered to be superior to CBT for the acute treatment of these depressed individuals (Table 2.1).

Table 2.1. CBT versus antidepressants: previous reviews

Name	No of Studies	Limitations	Result
DeRubeis et al. 1999	4	Severity of depression unclear	CBT favoured
Gerson et al. 1999	60	Indirect comparison of interventions Limited to older individuals	No difference in response rates
Hollon et al. 2005	Not stated	Wide range of psychotherapy and medications employed	CBT as effective as medication
De Maat et al. 2006	10	Variable duration of CBT Severity of depression varied	No difference in response rates
Pinquart et al. 2006	89	A wide range of psychotherapy and medications employed	Both treatments effective

Gerson et al. (1999) compared pharmacological and psychological treatments for depressed older patients (Table 2.1). Psychological treatment encompassed a great variety of talking therapies such as psychodynamic psychotherapy and included CBT. In their overview using indirect comparisons, response rates for the talking therapies did not differ significantly from those for medication. Again psychotherapy appears to perform as well as medication in these older depressed patients. However, this study looked at response rates for antidepressants and psychotherapy in general and they did not use direct comparison studies.

Hollon et al. (2005) looked at the relative efficacy of medication and psychotherapy in adult and geriatric depression and found that while medication typically has a robust and rapid effect, both interpersonal therapy and CBT can be as effective as medication in the acute treatment of depressed patients.

De Maat et al. (2006) found that remission rates did not differ between psychotherapy and pharmacotherapy in the acute treatment of depression. However, the limitations of the review raise concerns about the generalizability of the results. The duration of treatment was relatively short (8-20 weeks); severity of depression was variable; and the dosage of drugs were not standardized. In the long-standing controversy regarding the relative effectiveness of both treatment modalities, De Maat's meta-analysis tends to support the 'no difference' point of view in the acute phase.

Lastly, Pinquart and colleagues carried out a meta-analytic comparison of pharmacotherapy and psychotherapy for the treatment of depression in later life (Pinquart et al. 2006). A wide range of medications were used. Psychotherapy included CBT and other forms of talking therapy. Regarding implications for practice, the authors state that pharmacotherapy and psychotherapy are both effective for treating depression and that treatment choice should be based on contra-indications, treatment access, and patient preferences.

We also know that there are reservations regarding the existing evidence concerning the relative effectiveness of antidepressants and psychotherapy for treating depression in children and adolescents (Cox et al. 2012). The recommended treatment of first choice for children from age 8 years onward and for adolescents is either cognitive-behavioural therapy (CBT) or interpersonal psychotherapy (Dolle et al. 2013). Of antidepressants, fluoxetine is recommended for drug treatment either alone or in combination with CBT. For mild or moderate depression, psychotherapy is recommended; for severe depression, combination therapy is advised (Dolle et al. 2013). However, the serious deficits in existing research on treatment of depression in all age groups are acknowledged (Kisicki and Varley, 2013).

In summary, several reviews have concluded that pharmacotherapy and psychotherapy are equally efficacious in the acute treatment of depression while DeRubeis deduced that psychotherapy outperforms pharmacotherapy (DeRubeis et al. 1999). However, in appraising the research literature, it should be remembered that many studies compared chronic versus non-chronic depression, included patients with varying degrees of severity and often encompassed indeterminate levels of previous treatment. If high quality studies examining psychotherapy are targeted, then the effects for psychotherapy tend to be overestimated in the literature (Cuijpers et al. 2008). Furthermore, most studies had levels of clinical expertise not available in everyday practice. Routinely delivered CBT may not match clinical trial CBT in terms of quality or fidelity. These issues moderate any firm assertions to be made in the area.

Another important limitation of research in this field is the striking methodological and clinical heterogeneity or variation found in most, though not all, reviews and meta-analyses. Treatment duration may be between 4 and 79 weeks, and include primary care patients as well as psychiatric inpatients. Psychotherapy can include anything from social work counselling to interpersonal psychotherapy. Some studies included geriatric and adult patients and encompassed dysthymia (a chronic, low-grade depression) as well as major depression. Not surprisingly, this leads to a great deal of variation between the studies covered by the reviews. All this excess variation or heterogeneity can make the pooling of data from the individual studies hazardous (Bridle et al. 2012). This heterogeneity may go some way to explain the inconsistent conclusions of some of the individual studies.

Until more data become available, and bearing in mind the limitations of primary studies and the reviews previously outlined, the findings obtained so far in the major comparisons

of medication and psychotherapy indicate that antidepressant medication and psychotherapy have not differed significantly in acute efficacy in the treatment of a wide range of depressed patients. Currently, the literature does not provide the robust data needed to underpin clinical recommendations in favour of drug therapy or psychological treatment. Depressed patients appear to benefit from both antidepressants and talking therapy after short-term treatment. Given the considerable clinical and methodological heterogeneity, an up-to-date systematic review and meta-analysis comparing specifically CBT, rather than psychotherapy in general, and antidepressants in particular, rather than medication in general, while focusing on a less heterogeneous population, should advance the debate incrementally.

2.3 Combination of medication and psychotherapy

Antidepressants have been shown to be efficacious in hundreds of placebo-controlled trials and represent the current standard of treatment (Hollon et al. 2005). CBT also has a considerable evidence base. Given the apparent efficacy of medication and some forms of psychotherapy, it is not surprising that the two are sometimes combined. It has been claimed that clinical management using a combination of medication and psychotherapy can retain the specific benefits of each and may facilitate the probability of a positive response over either treatment alone.

Early trials rarely documented a clear advantage for the combination treatment over either treatment alone in terms of acute symptom reduction. These studies however generally lacked sufficient power to detect statistically or clinically meaningful differences. Given the paucity of empirical evidence, recommendations relied on clinical consensus (Hollon

et al. 2005). Combination treatment was kept for patients with more chronic or complex disorders or those with an unsatisfactory response to either treatment alone.

Impact of combination therapy

A considerable proportion of patients do not respond to antidepressant medication or psychotherapy alone, prompting the investigation of combined treatment approaches. Linking psychotherapy and antidepressants is associated with the clinical assumption that two treatments are better than one. More treatment is considered better and to believe otherwise can seem counter intuitive.

The combination of medication and psychotherapy however, was viewed as controversial in the 1960s. It was initially felt that the effect of combining treatments may be inhibitory or less than the effect of either on their own. Suppression was assumed to have occurred where the combined effect came in as less powerful than the least effective treatment.

Of course, other treatment outcomes are possible. When two effective treatments are combined the results can obviously vary. There may be a positive reciprocal interaction, that is, the interaction may be as effective as the more effective of the two treatments (reciprocation type 1). Reciprocation type 2 involves a combined effect which is no greater than the less effective of the two treatments. However, the result may also be an additive effect, in which case the combined treatments interact to equal the sum of the two main effects. Another possible outcome is 'potentiation' involving a synergistic outcome. Here the combined effects interact to become greater than the sum of the two independent results. This outcome can also be termed 'enhancement'.

In practice, with recognition of the often poor response of depressed individuals to single treatment, the use of combined treatment appears to be rising, making it a common form of treatment for depression. Combined treatment is extensively used and has substantial added cost. Clarifying the efficacy of combined treatment over single treatment is important for improving care for depressed individuals.

Investigators have systematically reviewed the literature to see if the combined approach lives up to its potential. Some systematic reviewers have looked at primary studies that compared combination treatment and medication alone. Others, have reviewed studies that pitted combined treatment against psychotherapy. Both types of review are outlined below.

Combination treatment versus medication alone

In 2003, Friedman and colleagues carried out a meta-analysis to compare combined therapy and pharmacology. Their findings indicate a small improvement in efficacy for combination treatment over pharmacotherapy, and that the finding appeared consistent across studies (Friedman et al. 2004). The review authors cautiously note that adding psychotherapy to antidepressants appeared to be efficacious.

Pampallona and colleagues report that combination therapy is associated with a higher improvement rate than drug treatment alone (Pampallona et al. 2004). They considered problem-solving, interpersonal, marital and psychodynamic therapies, as well as cognitive and behavioural therapy. They highlight how the addition of psychotherapy may help keep patients in treatment. A possible 'adherence-improving' effect of combined treatment is helpful in understanding this area of research. However, targeted adherence-

enhancing approaches may be just as effective as psychological therapies. In summary, the conclusions of two previous systematic reviews in the area are broadly in agreement, generally favouring combination treatment over pharmacology.

Combination treatment versus psychotherapy

Thase and colleagues looked at 595 patients from six trials comparing medication and interpersonal therapy versus CBT (Thase et al. 1997**).** They found that patients with increased severity or chronicity had a markedly improved outcome for combined treatment as compared with psychotherapy alone. Importantly, the combined treatment embraced interpersonal therapy, not CBT. Some evidence then suggests that combined treatment is more efficacious in treating more severely and chronically depressed patients.

Cuijpers and colleagues compared psychotherapy and combination treatment employing a meta-analysis (Cuijpers et al. 2008). They concluded that combined treatment was more effective than psychological treatment. However, when subgroup analysis was used, they found a significant difference between studies that used CBT and those that used other types of psychological treatments. CBT appeared to have stronger effects than other psychological treatments and thus reduced the detected difference between combination treatment and psychotherapy. However, the overall effect size indicating the difference between psychological and combined treatment was small to moderate and they were unsure if the effect size difference was clinically significant.

Friedman and colleagues also compared combined treatment with psychotherapy alone (Table 2.2). The studies suggest almost no benefit of combined treatment compared to psychotherapy alone on symptom reduction (Friedman et al. 2004). However, we do not

know if optimal pharmacotherapy was delivered both within and across all the individual studies reviewed. Fidelity is seldom reported and is often poor (Michie, 2013). This problem with optimal prescribing is not unique to this review and may have led to an under-estimation of the effect size from antidepressants in some studies.

In summary, some previous reviews have found combination treatment to be more efficacious than psychotherapy but the advantage is much less when the comparison is specifically with CBT rather than other forms of psychotherapy. The detected advantage also tends to be quite small and the findings in favour of combination therapy are more pronounced when depression is chronic and severe.

Combination therapy tends to be associated with a higher response rate than using antidepressants alone. There is some evidence that combined treatment may be more beneficial, particularly on rates of remission, among depressed inpatients as compared to outpatients. It may be that individuals with chronic, severe depression may be less likely to respond to single treatment.

Table 2.2. Combination treatment versus monotherapy: previous reviews

Name	Included Studies	Limitations	Conclusion
Thase et al. 1997	6	Addresses psycho-therapy and pharmaco-therapy in general Combination included interpersonal therapy not CBT	Combination treatment more effective than psycho-therapy
Pampallona et al. 2004	16	Addresses pharmaco-therapy and psychological therapy in general	Combination treatment associated with higher response rate than pharmaco-therapy
Friedman et al. 2004	17	Addresses pharmaco-therapy and psychotherapy in general Fidelity not reported frequently	Combination treatment associated with improve-ment over pharmaco-therapy
Cuijpers et al. 2008	18	Addresses pharmaco-therapy and psycho-therapy in general	Combination treatment more effective than psychological therapy

Keller et al. (2000) showed that patients receiving combined treatment were more likely to enter remission than those receiving single treatment alone. However, the psychotherapy used in the Keller study, which was developed for chronic depression, may not be widely available and the implications and generalizability of their results are uncertain. There are good theoretical reasons for combined treatment being more effective than single treatment with chronic patients. These patients are more likely to

suffer functional impairment. If social difficulties persist, then without psychotherapy, relapse may be more likely. Also, severe and chronic patients may continue to experience biological dysfunction that may be particularly responsive to medication. Combined treatment may lead to change across a broader range of functioning, contributing to better outcomes for these patients.

Future directions

Medication and psychotherapy are often combined in clinical practice. However, concerns about the costs of healthcare are important. Optimum and judicious use of resources is important. It is valuable for health professionals to know the evidence pertaining to the efficacy of a combined treatment. Even a small advantage for a particular approach should not be overlooked (Friedman et al. 2004).

There is no way to control fully for therapist preferences in choosing a treatment. It is inconceivable that a clinician should have no views at all about management strategy. It is not always possible to be clinically or culturally neutral. However, one way forward is to attempt to make clinical decision making, whenever possible, more evidence-influenced. Given the considerable heterogeneity between studies, the aim here, using systematic review methodology, was to compare combination treatment with CBT rather than psychotherapy in general, and to compare combination therapy with antidepressants rather than medications in general, focusing on less heterogeneous populations of patients. Such an investigation should advance the debate regarding the relative efficacy of CBT and antidepressants.

An outstanding challenge for cognitive therapy is the translational gap between efficacy and implementation (Williams and Kuyken, 2012). Dealing adequately with issues surrounding the treatment of clinical depression requires a surge not just in 'discovery science' but also in delivery science (Collins et al. 2011).

2.4 Knowledge Translation

Evidence-based health-care should be the gold standard of practice. Some fifteen years ago, 67% of consultant psychiatrists and 74% of psychiatry higher trainees felt that effective care based on evidence was an attainable goal (Carey and Hall, 1999). EBM has been a safeguard against 'great and desperate cures' in psychiatry (McGorry, 2013). Efforts to promote evidence-based practice need to focus not only on the generation of clinical research but also on its speedy dissemination.

Previous research

Knowledge translation is a dynamic process that includes the synthesis, dissemination, exchange, and ethically-sound application of knowledge to improve health (Tricco et al. 2013). The process is also known as research utilisation, translational medicine, and implementation science. After knowledge generation and synthesis comes dissemination of the evidence, usually by publication in a recognised professional journal. This should be followed by an attempt to promote uptake of systematic review evidence more actively using various strategies. This concept of implementation science is particularly relevant to mental health research (McGorry, 2013).

An important aspect of the systematic review process is the timely adoption of the review evidence by practicing clinicians. This thesis addresses why and in what circumstances, decision makers including clinicians, adopt new information specifically from systematic reviews and thus make their practice more evidence-influenced. While many investigations have been conducted into the barriers and facilitators to the uptake of evidence in general, little is known about the specific determinants of the uptake of evidence from systematic reviews in particular.

In the past, there have been systematic reviews of the barriers to adherence to clinical practice guidelines (Cabana et al. 1999); of the barriers to the appropriate use of research evidence in policy decisions (Innvaer et al. 2002); of the barriers and facilitators to implementing shared decision-making (Gravel et al. 2006, Legere et al. 2008); of the barriers to improving the usefulness of systematic reviews for health care managers and policy makers (Lavis et al. 2005); of the barriers and incentives to optimal health care (Cochrane et al. 2007), and lastly, a review of the barriers and facilitators impacting on inter-professional education (Chickte and Khondowe, 2012). The results of this last systematic review illustrate how the nature of barriers and facilitators can charge dramatically depending on which element of evidence-based medicine is addressed. Previous reviews in this area are summarized in Table 2.3. In this thesis, the writer is concerned not with evidence uptake in general but specifically with uptake of evidence from systematic reviews.

Table 2.3. Barriers and facilitators to evidence uptake: previous reviews

Study	Focus	Studies	Limitations and results
Cabana et al. 1999	Barriers to optimal care and uptake of practice guidelines	76	Lack of a theoretical framework in primary studies. Perceived use only. 293 barriers identified.
Innvaer et al. 2002	Barriers and facilitators to research evidence uptake	24	Limited to policy makers Perceived use only. Lack of two-way communication a barrier.
Lavis et al. 2005	Barriers to usefulness of evidence	17	Limited to managers and policy makers. Highlighted a lack of value associated with evidence.
Gravel et al. 2006	Barriers to shared decision making	28	Concerned with health professionals. Highlighted the barriers of time constraints, patient characteristics, and clinical situation.
Cochrane et al. 2007	Barriers to optimal care, guideline adherence	256	Lack of a theoretical frame –work. Barriers included lack of knowledge, lack of confidence, and legal concerns.
Legere et al. . 2008	Barriers and facilitators to shared decision making	38	Concerned with health professionals. Lack of reflexivity account in primary studies. Highlighted barriers of time constraints, patient characteristics, and clinical situation.
Chickte and Khondowe, 2012	Barriers and facilitators to inter-professional education	Not known	Limited to inter-professional education. Highlights the changing nature of barriers and facilitators.

2.5 Barriers and facilitators to evidence uptake from systematic reviews

Researchers have attempted to examine the barriers to change with the long-term aim of understanding how the gaps between research and practice can be narrowed and closed (Cochrane et al. 2007).

Barriers to guideline uptake

Barriers are factors that obstruct or restrict implementation of evidence in everyday clinical practice (Cabana et al. 1999). One of the most cited conceptual frameworks regarding barriers to knowledge use in health care is the Clinical Practice Guidelines Framework for Improvement (Cabana et al. 1999). This framework was based on the literature of physician adherence to clinical practice guidelines and was structured into knowledge, attitudes, and behaviour categories.

Cabana and colleagues identified 76 published studies describing at least one barrier to adherence to clinical practice guidelines (Cabana et al. 1999). Taken together, the studies reported 293 potential barriers to physician guideline adherence. The barriers related to awareness, familiarity, agreement, self-efficacy, outcome expectancy, inertia, and also external barriers.

Some of the surveys Cabana and his colleagues included in their review examined just one barrier, others two and some others, more. The surveys addressed a rich diversity of populations and a wide variety of subjects.

Regarding barriers to adherence to specific guidelines, lack of awareness could be quite high. Lack of familiarity was also important. Lack of agreement encompassed the 'cookbook' criticism of guidelines. The lack of agreement with guidelines was as high as 90% in some cases. The guidelines were seen as not being practical or were viewed as biased, or were seen as likely to decrease clinician self-respect. Some thought that clinical practice guidelines would make the doctor-patient relationship impersonal and would decrease flexibility (Cabana et al. 1999).

The research team also found that external barriers were important. These obstacles included guideline-related, patient-related, and environmental, factors. The guidelines were sometimes perceived as inconvenient, cumbersome, and confusing (Cabana et al. 1999).

While Cabana dealt with guidelines, the barriers addressed by this writer related to factors that can limit or restrict uptake of knowledge specifically from systematic reviews and meta-analyses. The overall aim of this thesis was to develop a more comprehensive and integrated understanding of these barriers and facilitators as they modify the uptake of pre-appraised, integrative reviews.

Barriers to the usefulness of systematic reviews

Another review set out to identify ways to improve the usefulness of evidence and systematic reviews specifically for health care managers and policy makers (Lavis et al. 2005). This was not a review covering all decision makers, as occurs in the investigations conducted by this writer. Their report did however encompass improving the usefulness of systematic reviews. They drew on a previous systematic review conducted by Innvaer

and colleagues (Innvaer et al. 2002). They wished to know the optimal way to present research evidence for use in health care management and policy making. Seventeen studies met their criteria. They investigated study design, study quality, and consistency of findings.

Their systematic review identified factors such as timeliness and interactions between researchers and healthcare policy makers that appear to increase the prospects for research use among policy developers. They concluded that the future flow of systematic reviews will better inform healthcare management and policy making by involving managers and policy makers in review production and better highlighting information that is relevant for decision making.

They found that policy makers and managers did not place a high value on research evidence in general or systematic reviews in particular. Systematic reviews were never cited as the source of research evidence when research evidence was used (Lavis et al. 2005). Developing and making available more on-line, user friendly, 'front ends' for potentially relevant systematic reviews was seen as a priority. Unlike the systematic reviews conducted for this thesis, many of their findings relate to the use of evidence in general rather than evidence uptake specifically from systematic reviews.

Lavis and colleagues used a system of vote counting tempered by study quality. Both quality and quantity matter in a systematic review (Bridle et al. 2012). Lavis makes suggestions about the production and updating of systematic reviews. Their overview suggests the development of one-page, take-home messages and production of a three-page executive summary will allow assessment of relevance of systematic reviews. They

also suggest taking into account local conditions (appropriateness). They strongly advocate proactive knowledge transfer strategies.

Barriers and facilitators of evidence use

The aim of Innvaer and colleagues was to summarise the evidence from interview studies of barriers to, but also facilitators of, the use of research evidence by health policy makers (Innvaer et al. 2002). Innvaer focused exclusively on interview studies while the systematic reviews reported in this thesis encompassed surveys, interviews, focus groups and interventional, outcome investigations.

Eligible studies for the review by Innvaer and colleagues included only policy makers as participants while this writer included all possible decision makers such as doctors, nurses, researchers, patients and the public, as well as policy makers. Innvaer was concerned with uptake of evidence in general, using a limited number of databases, while this writer was focused on evidence derived from systematic reviews specifically and also used an extensive range of databases. However, similar to the research conducted by this writer, Innvaer and colleagues addressed both facilitators and barriers.

Innvaer and colleagues addressed hypothetical and perceived use of research by their included 2,041 policy makers, rather than actual use. The most commonly reported barriers to evidence uptake were absence of personal contact, lack of timely relevance, mutual mistrust, together with power and budget struggles. The most frequently reported facilitators in their 24 included studies were personal contact, relevance, and inclusion of summaries with policy recommendations. Two-way communication was the most common suggestion to improve the appropriate use of research evidence. They

summarised their results in tables and also looked at where barriers and facilitators overlapped.

Barriers and facilitators to implementing shared decision-making

Gravel and colleagues performed a systematic review of the barriers and facilitators to implementing shared decision-making in clinical practice as perceived by health professionals (Gravel et al. 2006). Shared decision-making is often an ignored step in evidence-based practice (Hoffmann et al. 2012). Using a pre-established taxonomy of barriers and facilitators to implementing clinical guidelines in practice, content analysis was performed. Gravel included 28 unique studies in the review. These encompassed 2,784 participants of whom 89% were physicians.

The three most commonly reported barriers to implementing shared decision-making were time constraints, lack of applicability due to patient characteristics, and limitations of the clinical situation. The three most often reported facilitators were provider motivation, anticipated positive impact on the clinical process, and perceived positive effect on patient outcomes. Gravel's researchers targeted health professionals while this writer included all decision makers, including policy makers. They also focused on shared decision making rather than the uptake of evidence specifically from systematic reviews, the subject of this thesis.

Barriers to optimal care

A significant gap exists between science and clinical practice. An in-depth understanding of the barriers and incentives impacting on this gap could lead to interventions that move

change towards optimal practice and thus better care (Cochrane et al. 2007). Like many researchers, Cochrane and her colleagues were concerned with understanding the barriers to optimal care in general, rather than specifically the barriers to uptake of evidence from systematic reviews, the central theme of this thesis. Their review was concerned with guideline adherence and the integration of evidence with practice. The investigators included static attributes in their analysis such as gender, age, practice maturity, and the specialities of physicians or health care providers. They assessed barriers to optimal care that were identified by responses to surveys or questionnaires, themes emerging from focus groups and interviews, or data supported by triangulated analysis from multiple sources and combinations of methodologies. They recorded the frequency of articles reporting the information extracted in order to map barrier themes found in the literature. The systematic review conducted by this writer reported the percentage of participants as well as the number of studies that identified barriers.

Cochrane and her co-investigators were interested in the methodologies employed to identify barriers to optimal care. They described the methods for collecting and analysing data. The methods that emerged were quantitative, qualitative, and mixed. The quantitative studies employed primarily survey-type data collection. The qualitative studies included either focus group or interview type data collection. Their analysis expanded previous reviews that employed primarily survey-style methods.

They confined their search to English language studies and 256 articles fulfilled their criteria. The 256 articles encompassed 34 qualitative studies, 178 surveys, and 44 mixed-model studies. The survey-based studies were cross-sectional, descriptive, self-administered, organisational, and national. Surveys were administered through mail, intranet, internet, or direct distribution.

The focus groups were discussion groups, group interviews, or structured focus groups. The interview studies were semi-structured, face-to-face, in-depth, or guided. The mixed-model studies were a combination of interviews, surveys or questionnaires, focus groups, participant observations, and document reviews. The most frequent mixed-model approach was a combination of interviews and surveys. They found a trend towards using more mixed-model research.

The 33 emerging themes were placed into 7 categories that typified the barriers. Finally, the researchers were interested in whether the categories of barrier affected the professional, the guideline, the patient or the health system (Cabana et al. 1999). The data grouping was for the purpose of reduction and interpretation. They tabulated the frequency a barrier was reported in the literature, a form of weighing of each group (Cochrane et al. 2007).

There was a lack of a theoretical framework in many of the primary studies detected but some of the questionnaires employed had a theoretical basis in the model of diffusion of innovation proposed by Rogers. This model emphasises the characteristics of the adopter, organisation, innovation, and communication (Rogers, 1995).

The analysis by Cochrane and her colleagues involved descriptive reporting of frequencies, mean scores, and simple differences between groups. The qualitative analysis conducted involved content analysis, categorical or thematic coding, and the use of constant comparison methods.

They reported the frequency of the barrier category specified in the detected articles. The frequency calculation served as an indicator of the potential strength of the barrier as an

obstacle to patient care. The barriers to optimal care they found were cognitive-behavioural, such as lack of knowledge; attitudinal, such as lack of confidence; professional, such as concern for legal issues; guideline barriers, such as lack of local applicability; and patient barriers, such as a conflicting culture embraced by the individual.

The investigators revealed the complex nature of the barriers that occur in healthcare. These barriers impact on knowledge transfer from bench to bedside. Their review provided an increased understanding of the causal nature of factors that impinge on the ability of clinicians to practice evidence-based medicine and achieve optimal care.

Barriers and facilitators to a decision-support framework

Legere and colleagues, updating a previous review, focused on the barriers and facilitators to implementing shared-decision making in clinical practice, as perceived by health professionals (Legere et al. 2008). They applied a revised version of the Clinical Practice Guideline Framework for Improvement and looked at barriers and facilitators in 41 publications, covering 38 unique studies.

They focused on the active participation of patients in shared decision making. Studies did not necessarily have as their primary objective the assessment of barriers and facilitators to shared decision making. The research group included studies that involved usable data based on the perceptions of decision makers, as occurs in the systematic reviews conducted by this writer. Using the taxonomy pioneered by Cabana and colleagues, themes were ordered according to the number of studies in which they were identified.

Quality of the included studies was assessed and content analysis was performed with the pre-established taxonomy (Cabana et al. 1999). Regarding quality, of note is that only one qualitative study explicitly provided an account of reflexivity. Ten new studies were identified in addition to the 28 of their earlier review. The updated systematic review confirmed the results of their original overview. The three most reported barriers to shared decision making were: time constraints, lack of applicability due to patient's characteristics, and the clinical situation. The three most reported facilitators were provider motivation, positive impact on the clinical process, and improved patient outcomes.

Legere advises that there is a need to standardize the reporting of barriers and facilitators for translating research into clinical practice. It is important to address both facilitators as well as barriers because one factor can be perceived as both a barrier and a facilitator. Their work tells us what factors need to be targeted in order to effectively implement shared decision-making in clinical practice.

Identification of the obstacles and enhancers impacting on evidence uptake are important. A specific barrier, if removed, may have a major effect (Collins et al. 2011). Simple diffusion of systematic reviews may not be sufficient for evidence uptake. Supplementary activities are needed to increase uptake of knowledge synthesis (Chaillet et al. 2006). Proactive knowledge transfer strategies or interventions are often required (Lavis et al. 2005).

2.6 Interventions to enhance uptake of systematic review evidence

Most of the literature in the area of facilitation research focuses on clinical practice guidelines. Woolf (1993) explored the potential impact of guidelines on patient care. Importantly, he also proposed a mechanism of action, occurring in steps, by which improved patient care can be achieved. A guideline can achieve outcomes such as improved patient health through the intermediate steps of changing practitioners' knowledge, attitudes, and behaviour (Woolf, 1993). This model of a mechanism of action was used by this writer in the systematic reviews conducted as part of this thesis.

Many parties are willing to consider guidelines to be a success if they achieve only intermediate outcomes. Guidelines are considered effective if they improve knowledge: making clinicians aware of recommendations; attitudes: getting clinicians to agree and accept the recommendations as a new standard of care; behaviour: getting clinicians to change practice patterns to conform to guidelines and improving patient health.

There is little evidence that simply distributing practice guidelines can improve clinical outcomes (Woolf, 1993). Observational studies have shown that physicians often fail to follow published recommendations. Intervention studies, however, have produced mixed results in attempting to use guidelines to change behaviour.

Woolf suggests that current evidence indicates that the publication of practice guidelines may influence knowledge and attitudes but there was inconclusive evidence that guidelines alone can change practice behaviour or patient outcomes. It seems that more than education is required. Simply distributing guidelines does not achieve significant results. He suggests that guidelines need to be coupled with feedback, reminders, training,

audits, or computer systems. Decision makers generally do not act on received information without further encouragement.

Rogers emphasized the importance of the intrinsic qualities of the actual guideline for knowledge transfer (Rogers, 1995). Grilli and Lomas (1994) validated Rogers' previous research in their review of 23 trials measuring the effectiveness of guideline dissemination. They found that guidelines that were relatively uncomplicated and could be observed or tried by the clinician tended to be more effective. Table 2.4 summarizes previous reviews of evidence in the area.

Table 2.4. Strategies to enhance evidence uptake: previous reviews

Study	Focus/Included studies	Limitations/results
Davis et al. 1995	Educational interventions to change physician performance. 99 included studies.	Exclusive focus on physicians and on educational strategies. Reminders, patient-mediated interventions, outreach visits: effective.
Oxman et al. 1995	Interventions to improve patient outcomes. 102 included studies.	An older study. Academic detailing, multiple interventions, were relatively strong strategies.
Davis and Taylor-Vaisey, 1997 .	Implementing clinical practice guidelines. Variable number of included studies addressed different interventions.	An older study. Reminder systems, academic detailing and multiple interventions were relatively strong interventions.
Bero et al. 1998 .	Strategies for the implementation of research findings. 18 included reviews.	An older study. Reminders, multi-factet-ed intervetions, interact-ive educational meetings were effective.
Grimshaw et al. 2001	Professional educational interventions. 41 included reviews.	Limited to health-care professionals. No strategy was effective in all circumstances.
Grol and Gimshaw, 2003	Interventions to change clinical practice. 54 included reviews.	Little focus on patient outcomes. Interventions that focused on barriers were more effective.
Grimshaw et al. 2004	Guideline dissemination strategies. 235 included studies.	Limited to healthcare professionals. Majority of interventions brought about modest/moderate improvement in care.
Chaillet et al. 2006	Implementing clinical practice guidelines in obstetric care. 33 included studies.	Confined to obstetric care. Generally effective strategies: reminders, academic detailing, and multifaceted approaches.
Baker et al. 2010	Tailored interventions to to address barriers to change in professional practice. 26 included studies.	Limited number of data-bases searched. Overall effectiveness of tailored interventions was modest.

Strategies affecting guideline adoption

Davis and Taylor-Vaisey wanted to recommend effective strategies for implementing clinical practice guidelines (Davis and Taylor-Vaisey, 1997). The current thesis also aims to recommend strategies that enhance uptake, specifically, of systematic reviews. Davis and Taylor-Vaisey wished to determine the impact of various factors on the adoption of guidelines. They felt that variables that affect the adoption of guidelines included the qualities of the guidelines, the characteristics of the health professional, characteristics of the practice setting, incentives, regulation, and patient factors.

They wanted to know if clinical practice guideline dissemination processes generally work. Second, they were concerned to understand if natural or non-educational factors affect the unaided adoption of guidelines. Third, they wanted to identify which specific educational interventions enhance the implementation of clinical practice guidelines.

Specific strategies to enhance adoption of guidelines fell into two categories: primary strategies involving publication and mailing of guidelines, and secondary 'interventional' strategies aimed at reinforcing the recommendations of the guidelines. They categorised the interventions as weak, moderately effective, and relatively strong (Davis and Taylor-Vaisey, 1997).

They suggest that didactic, continuing medical education and mailings were weak interventions. Moderately effective interventions were audit and feedback especially when concurrent and targeted to specific providers and delivered by peers or opinion leaders. Interventions seen as relatively strong were reminder systems, academic detailing, and employment of multiple interventions.

Educational interventions

There have been several reviews of the educational intervention literature. Some interventions attempt to improve the competence of providers by improving knowledge, skills, and attitudes. Some strategies aim to improve adoption in the practice setting by the use of reminders. Other methods look at reinforcing change through audit and feedback.

Davis and colleagues set out to review the literature relating to the effectiveness of education strategies designed to change physician performance and health-care outcomes (Davis et al. 1995). Davis and colleagues searched a limited number of databases rather than the 19 databases that were searched in the systematic reviews conducted as part of this thesis. All decision makers, not just physicians, were included in this writer's review while Davis and colleagues focused on physicians exclusively. Davis addressed continuing medical education strategies while this writer included all interventions aimed at enhancing uptake of systematic reviews.

They found 160 interventions that met their criteria. Almost two thirds of the interventions displayed an improvement in at least one major outcome measure. Some 70% demonstrated a change in physician performance and 48% of interventions aimed at health-care outcomes produced a positive effect. They felt that widely-used CME delivery methods such as conferences have little direct impact on improving professional practice. Effective change strategies included reminders, patient-mediated interventions, outreach visits, use of opinion leaders, and multifaceted activities.

Oxman and colleagues found that interventions addressing provider or patient outcome measurements, generally fall into the following categories: weak, moderate and strong interventions. The weak interventions included conferences and seminars (Oxman et al. 1995). The moderately effective interventions included audit and feedback. Again, relatively strong interventions included reminder systems, academic detailing, and multiple interventions.

Some researchers believed that formal CME failed to effect change in physician's performance (Browner et al. 1994). Nardella, Pechet, and Snyder (1995) found academic detailing or university-based educational outreach to be useful. The use of local opinion leaders was also reported to be effective (Lomas et al. 1989).

Katon described an intervention that aided the implementation of clinical practice guidelines concerning the management of depression, through the creation of patient education-materials (Katon et al. 1995). The intervention increased the number of outpatient visits and improved patients' compliance with drug therapy. Emslie showed that reminders can be effective (Emslie, Grimshaw, and Templeton, 1993).

Different types of interventions

The objective of Oxman and colleagues was to determine the effectiveness of different types of interventions in improving health professionals' performance and also health outcomes (Oxman et al.1995). They undertook a review of 102 studies of interventions to improve the delivery of healthcare services. Davis and colleagues had systematically reviewed 50 RCTs of the effectiveness of CME (Davis et al. 1992). The object of the later Oxman study was to enhance and upgrade that body of knowledge. An assessment of trial

quality was carried out. They also looked at the characteristics of the intervention including the content, format, source, recipient, setting, and timing. They also described the main outcome measure.

Oxman and colleagues focused on educational interventions and searched four databases. Interventions addressed in the primary studies included conferences, outreach visits, the use of local opinion leaders, audit and feedback, and reminder systems. Their inclusion criteria were met by 102 trials.

Dissemination-only strategies such as conferencing or mailing demonstrated little or no changes in health professionals' behaviour or health outcome when used alone. More complex interventions such as outreach visits or local opinion leaders, ranged from ineffective to highly effective, but were most often moderately effective.

They concluded that there are no magic bullets to improve the quality of health care but there are a wide range of interventions that, if used appropriately, could lead to important improvements in professional practice and patient outcomes.

Strategies for the dissemination and implementation of research findings

Bero and colleagues assert that disentangling the effects of interventions from the influence of contextual factors is difficult when interpreting the results of individual studies (Bero et al. 1998). They reviewed systematic reviews of different strategies for the dissemination and implementation of research findings in general. They did not focus specifically on systematic review evidence as is done in this thesis.

They were interested in performance change as an outcome measure while the systematic reviews conducted by this writer were concerned with multiple outcomes. They felt that the appropriateness of meta-analysis was uncertain given the broad focus and heterogeneity of the studies included in the reviews with respect to the types of interventions, targeted behaviours, and contextual factors.

They concluded that the reviews that they looked at highlighted modest improvement following an intervention. Passive dissemination was ineffective in altering practices. Computerised decision support systems have led to an improvement in the performance of doctors. Educational outreach visits have resulted in improvement in prescribing decisions. Multifaceted interventions seemed to be more effective than single interventions.

Regarding interventions to promote behaviour change among health professionals, it appears that consistently effective interventions were reminders, multifaceted interventions, and interactive educational meetings. Interventions of variable effectiveness were audit and feedback, opinion leaders, local consensus processes, and patient-mediated interventions.

Interventions changing clinical practice

Grol and Grimshaw conducted an overview of 54 reviews of interventions to change clinical practice (Grol and Grimshaw, 2003). They found that change is possible. None of the interventions was superior for all changes in all settings. There is more evidence on the professionally orientated interventions such as education, reminders, and feedback, than those aimed at the organisation or the patient (Grol and Grimshaw, 2003). Economic

assessment of performance strategies was scarce. Information on patient outcomes was also scant. Importantly, interventions targeted at specific obstacles to change seem to be more effective than interventions that are not (Grol and Grimshaw, 2003).

In a previous review, reminders had the largest effect of all interventions studied (Grimshaw et al. 2002). This finding has been replicated and computer-generated reminders do have an impact (Arditi et al. 2012). Mass media campaigns have also showed improvements in care (Grilli et al. 2000).

In conclusion, many different interventions are available and all the interventions have the potential to help with the effective transfer of evidence to practice (Grol and Grimshaw, 2003).

Guideline development, dissemination and implementation strategies

Grimshaw and colleagues undertook a systematic review of the effectiveness of guideline development, dissemination and implementation strategies. They wished to estimate the resource implications and to develop a framework for deciding when it is efficient to develop and introduce clinical guidelines (Grimshaw et al. 2004). The inclusion criteria specified randomized controlled trials, controlled clinical trials, controlled before and after trials, and interrupted time series. Medically qualified healthcare professionals were included as recipients of guidelines.

As in the systematic review conducted for this thesis, for each intervention, the number of comparisons showing a positive direction of effect and the number of comparisons

showing statistically significant effects were reported. A planned meta-analysis could not be undertaken due to the degree of heterogeneity.

The majority of interventions brought about modest-to-moderate improvements in care. No relationship was found between the number of component interventions and the effects of multi-faceted interventions. Frequently, only dissemination of educational materials and short, lunchtime educational meetings were feasible because of limited resources. They conclude that there is an imperfect evidence base to support decisions about what dissemination and implementation strategies are likely to be effective under different circumstances.

Implementing clinical practice guidelines in obstetric care

Researchers in the field of obstetric care have made significant contributions to the discipline of knowledge translation (Paterson-Brown et al. 1995, Wyatt et al. 1998, Chaillet et al. 2006). In common with this writer, Chaillet and colleagues set out to identify barriers to the uptake of a particular form of evidence (Chaillet et al. 2006). While this writer was concerned specifically with systematic reviews, Chaillet, however, focused on clinical practice guidelines. In common with this writer, Chaillet and colleagues wished to identify barriers to change and also interventions that enhance evidence uptake. They believed that identification of barriers in the field of obstetrics can allow better adaptation of effective interventions to enhance evidence uptake and so improve evidence use.

Their study differed from this writer's systematic review in that they consulted just 4 databases, were concerned with the field of obstetrics, and focused on implementation of

guidelines rather than uptake of systematic reviews. This writer, like Chaillet and colleagues, used the EPOC criteria to assess inclusion and quality of studies. Interventions were classified into three levels of effectiveness (EPOC, 2002). These levels are 'generally ineffective, mixed effects, and generally effective'.

Chaillet and colleagues found that mailing and didactic continuing medical education were ineffective interventions. Mixed-effect interventions were use of opinion leaders, audit, and continuous quality improvement strategies. Generally effective interventions were reminders, academic detailing and multifaceted interventions.

Chaillet found that the proportion of effective strategies is significantly higher among interventions that include a prospective identification of the barriers to change, compared with standard interventions. They also concluded that, in obstetric care, a multifaceted strategy is recommended to effectively change behaviour.

Tailored interventions

Baker and colleagues, updating a previous Cochrane review, set out to assess the effectiveness of interventions tailored to address identified barriers to change in professional practice (Baker et al. 2010). Tailored strategies are defined as strategies to improve professional practice that are planned taking account of prospectively identified barriers to change. Barriers to change are factors that could potentially impair the effectiveness of an intervention to improve practice (Baker et al. 2010). If the barriers to improved performance are identified and strategies then chosen and implemented to overcome them, it would appear reasonable to expect practice to improve.

Unlike this writer's systematic review of strategies to enhance uptake of systematic reviews, Baker and colleagues focused on prospectively tailored interventions to address specific barriers. They wanted to know if tailored strategies were effective in improving professional practice and healthcare outcomes. Their study reported objectively assessed professional practice or healthcare measures.

They included studies that targeted single and multiple barriers. The identification of barriers had to have been undertaken before the design and delivery of the intervention. The timing of the identification of barriers had to be clear. This current writer conducted a systematic review of interventions to improve the uptake of evidence from systematic reviews and meta-analyses. The study conducted by this writer did not specify that the included interventions had to be tailored to specific identified barriers.

Baker and colleagues undertook both a quantitative and qualitative analyses. They carried out a meta-regression to compare interventions tailored to identify barriers to change with either no intervention or an intervention not tailored to the barriers. They searched a limited number of databases, in comparison with the extensive range of sources searched by this writer.

Their review included 26 studies with twelve studies providing enough information to be included in the quantitative analysis. They found that interventions tailored to prospectively identified barriers are more likely to improve professional performance than no intervention. The overall effectiveness was modest. There was no evidence about the cost effectiveness of tailored interventions compared to other interventions.

Unlike this writer's systematic review, Baker and colleagues focused exclusively on healthcare professionals responsible for patient care rather than policy makers. Barriers were identified by various methods, including observation, focus group discussions, interviews, surveys or by analysis of the organisation or system. Their outcome measure was professional performance in a healthcare setting. Of note is that a high level of tailoring showed a greater effect size than a moderate level.

Use of local disseminators

Lastly, a more recent and important study was conducted by Kuo and colleagues who looked at the dissemination of systematic reviews in hospital settings in Taiwan (Kuo et al. 2012). They measured the 'using rate' of Cochrane reviews by a number of participating hospitals and then looked at how high-usage and low-usage hospitals differed. The high-usage hospitals tended to assign a 'disseminator' of EBM to take charge of dissemination of Cochrane reviews. The high-usage settings also often utilized a number of other methods of knowledge transfer. These included providing relevant information via e-mail, investing in early adopters, having the assistance of designated personnel, making the activity of early adopters observable, conducting workshops, and inviting experts for speeches. They suggest that disseminating the evidence using different methods simultaneously is a key element of effective knowledge translation.

Summary

All the reviews outlined above, provide valuable insights into the effectiveness of the different strategies adopted to move evidence more effectively into practice. It would appear that most interventions are effective under some conditions, but perhaps none

under all. What is clear is that we need to use active dissemination and implementation strategies. When an effective dissemination strategy is identified it can then be 'scaled up' (Collins et al. 2011). Efforts are also currently underway to identify the factors that influence the sustainability of effective knowledge translation interventions (Tricco et al. 2013).

These previous reviews highlight the importance of addressing the appropriateness of the knowledge translation intervention as well as its effectiveness. The context of the strategy is important. Local modifying factors, as they impact on the intervention, are a central consideration in selecting a strategy to improve the uptake of evidence. It is important to place interventions in the context of both barriers and facilitators that impact on systematic review evidence uptake. Relevance as well as effectiveness is central.

2.7 Combining Barriers, Facilitators and Interventions

Barriers, perceived facilitators and structured interventions can be viewed singly and in isolation from each other. However, looking at the selected intervention in the context of identified modifying factors may be advantageous. This approach brings added value in the form of relevance. This can aid not just in assessing both the potential effectiveness of uptake strategies but also the appropriateness of interventions in enhancing the uptake of evidence from systematic reviews and meta-analyses. An approach integrating both effectiveness and relevance was developed at London's Social Science Research Unit.

Evidence for Policy and Practice Information Co-ordinating Centre

The EPPI approach to looking at effectiveness in the context of appropriateness, involves developing a very broad review question and then generating separate review sub-questions (Pope et al. 2007). This approach was developed by the Evidence for Policy and Practice Information Co-ordinating (EPPI) Centre at the Institute of Education in London. The EPPI-Centre is part of the Social Science Research Unit at the University of London. They have been engaged in a programme of methodological development for systematic reviews where their focus is on the synthesis of two or more parallel systematic reviews.

The EPPI process involves asking a broad review question. Initially, the reviewer describes the different types of study to be included in the remit of the overall review question. The next step entails outlining the searching and screening process to answer the separate sub-questions, before the findings are synthesised.

With the EPPI approach, there is a building up of a mosaic of findings to produce an overall picture from the different pieces of evidence. The results of the separate syntheses are combined in a so-called 'meta-synthesis' aiming to address the review question in its entirety. Quantitative and qualitative findings are combined. The perceptions of barriers and facilitators are compared with the outcomes of the intervention studies.

This overall synthesis may be more helpful to decision makers than the presentation of each review singly. The advantage of this approach is that it uses a larger proportion of research evidence relevant to the review question. It also provides a transparent path to

evidence synthesis and to recommendations for action and to future research. The focus is broader and more relevant (Pope et al. 2007).

A framework

A model of research synthesis or an emerging framework for combining the findings of different types of studies, including those that collect qualitative data, has been described (Oliver et al. 2005). The framework helps in addressing questions that move beyond effectiveness.

Oliver and colleagues developed and extended their initial methodological explorations when undertaking a series of reviews on the barriers to, and facilitators of, young people's mental health, healthy eating and physical activity (Harden et al. 2001, Rees et al. 2001, Shephard et al. 2001). Shephard and colleagues produced a report integrating all three reviews (Shephard et al. 2002). Oliver went on to use at least two reviews as a suitable case study of research synthesis (Oliver et al. 2005).

Oliver and colleagues developed and proposed for wider use, a coherent and flexible framework, employing theoretical and methodological dimensions, for synthesizing empirical data extracted from a diversity of studies. They advanced a framework for a cross-study design synthesis. Key features included identifying a clear research question, selecting appropriate study designs for each synthesis and choosing a quality assessment and synthesis method according to the types of studies and findings to be synthesized. Lastly, Oliver and co-workers employed a theoretical framework to juxtapose the findings from each synthesis in order to facilitate a comparison. This narrative synthesis can be used to identify patterns of factors relating to the success or otherwise of interventions (Oliver et al. 2005).

For Oliver and colleagues, methodological priorities were for rigorous evaluations of the effects of interventions such as employment of a control or a comparison group. They also prioritized non-intervention studies that directly report decision makers' views. Each set of studies independently entered a quality assessment, together with a narrative and tabular synthesis. The findings from each synthesis were then juxtaposed in a cross-study synthesis.

Details of the qualitative assessments were presented in the original reports. From the studies of decision makers' views, they extracted the participant's identification of influences on their behaviour using a qualitative analysis. Oliver and colleagues then compared the findings with the populations, interventions and outcomes addressed in outcome evaluations.

Barriers and facilitators were seen as operating on three interrelated spheres: the individual, the community and wider society (Tones and Tillford, 1994). The decision-maker's views were regarded as central and were seen as a valuable resource for the development of interventions. Detailed procedures are used for gathering and making sense of the findings from diverse studies. Thematic analysis was conducted.

Oliver juxtaposed findings from the synthesis of intervention studies with the findings of the synthesis of decision maker's views. This allowed two questions to be answered: to what extent have interventions addressed the barriers identified and to what degree have the interventions built on the facilitators identified? By constant comparison of the findings from each synthesis, they looked for interventions that diminished identified barriers and built on identified facilitators, using a barriers and facilitators conceptual framework (Oliver et al. 2005).

How can systematic review uptake be improved?

The creation of systematic reviews without attention to their uptake is a sterile exercise. It wastes precious intellectual and human resources. Supplementary local activities are needed to improve the timely uptake of evidence from systematic reviews and meta-analyses by practicing clinicians and other users.

Here, this writer was concerned with views and perspectives on barriers and enablers, but also with the effectiveness of interventions to make systematic reviews more wanted. Three parallel reviews were conducted: a review of the perspectives of decision makers on barriers to uptake of evidence from systematic reviews and then a review of the views and perspectives on facilitators. Next, an effectiveness or outcome studies' review was carried out. Finally, the results of the parallel syntheses were brought together to address an overall question: how can systematic review uptake be improved?

'Meta' refers to something more organized, more comprehensive, or of a higher order. The final 'meta-synthesis' conducted as part of this thesis focuses on the extent to which the interventions evaluated could be argued either to diminish barriers identified by decision makers but also build on the previously identified facilitators. The appropriateness of the intervention can then be addressed. Following on from this, different recommendations about the intervention can be made (Pope et al. 2007). Options are to (1) recommend the intervention, (2) develop the intervention, or (3) generate a new intervention.

Delivery science is a priority (Collins et al. 2012). Transfer of knowledge is a core activity of those working on the interface between research and practice (Knotternus et al.

2013). With this in mind, the aim of the final review conducted as part of this project was to undertake a systematic mapping of research on the barriers to, and facilitators of, uptake of evidence from systematic reviews. Next, this writer set out to synthesize what is known from these studies about barriers and facilitators. Lastly, this writer proceeded to evaluate how these specific factors were addressed by the identified interventions. To this writer's knowledge, this is the first attempt to apply such methodology to the issue of systematic review uptake.

The resulting narrative synthesis provides a summary of the current state of knowledge about a pressing problem: lack of uptake of systematic reviews. An important knowledge gap is bridged: identification of the factors impacting on a significant problem. Lastly, an incremental and fresh contribution is advanced where recommendations are made for clinicians and others interested in enhancing uptake of evidence specifically from systematic reviews and meta-analyses and the databases containing them.

The next chapter outlines the methodology used in this doctoral project.

CHAPTER 3

METHODOLOGY

CONTENTS

3.1 Introduction **84**

3.2 PRISMA statement **92**

3.3 Search strategy **93**

3.4 Selecting studies and collecting data **100**

3.5 Assessing risk of bias **117**

3.6 Analysing data **124**

3.7 Reporting biases **130**

3.8 Methodology of the knowledge translation reviews **132**

This thesis deals with an extremely important and often ignored area of research: the art and science of collecting and pooling information from primary research studies in order to promote human welfare (Gough et al. 2012). The first chapter of this thesis provided a background to the project while the second chapter gave an overview of the literature, though leaving some relevant background knowledge to be integrated into the appropriate sections later. This chapter outlines the methodology used by this writer in the six disparate reviews conducted as part of this thesis. The methodology section should list all the necessary ingredients of a study (Kotz and Cals, 2013) and this section does so using the general outline and sequence of items followed by the Cochrane Handbook of Systematic Reviews of Interventions (Higgins and Green, 2008).

This chapter is integrated with the conduct of the first two systematic reviews of interventions. These reviews focus on antidepressants and CBT and the chapter outlines discrete elements from different sections of these two meta-analyses. Methodology quite specific to the remaining 4 reviews is addressed in an integrated manner in the chapters dealing with these more diverse reviews. The initial two systematic reviews are summarized and their results presented in the next chapter.

3.1 Introduction

Standards and the pursuit of excellence are central in healthcare and scientific investigation (Pimm, 2013). The first target of any search about treatment choice should be a systematic review or meta-analysis since they provide the most powerful evidence available (Oxman and Guyatt, 1988). Systematic reviews are essentially summaries of studies examining a similar research question (Doshi et al. 2013). They have potentially great value to inform policy making and clinical decision making with more accurate

evidence synthesis than those available from narrative reviews (Brugha et al. 2012). They challenge evidence that is partial and not contextualised (Gough et al. 2012).

The field of mental disorders poses particular challenges to systematic reviews because of our relatively fragile understanding of mental health outcomes and determinants, and because biologically-based gold standards measures are not available (Brugha et al. 2012). Nevertheless, systematic reviews have been used extensively to summarise treatment evidence in the fields of clinical psychology and psychiatric therapeutics (Brugha et al. 2012).

The distinction in the extent to which reviews are aggregative or configuring is useful for understanding the variation in the aims and methodology of systematic reviews (Gough and Thomas, 2012). The initial aggregative reviews conducted here are in the positivist tradition that emphasises accuracy, precision, reproducibility, reliability, and distancing from the data (Wong et al. 2013).

The basis of a systematic review is a thorough search that attempts to identify all similar and relevant studies in an area that satisfy a pre-determined set of inclusion and exclusion criteria. A systematic review of the literature is guided by formal criteria that are selected for each step in advance. Consequently, bias is identified, the results are reproducible, and the validity and trustworthiness of the systematic review can be verified. Just like clinical practice guidelines, the trustworthiness of systematic reviews is central (Ransohoff et al. 2013).

A fundamental step in a review is to identify all relevant studies (Egger et al. 2001). Systematic reviews are conducted retrospectively which makes them sensitive to potential sources of bias arising from prior knowledge of the results. Incorporating unpublished studies may be the most important obstacle to overcome in reducing bias (Egger et al. 2001).

The purpose of the pre-appraised, integrative overview is to combine all the unbiased studies that have addressed a particular problem. The review is explicit. It reports the clinical setting, follow-up, sample size, and treatment details for each included study. The systematic review attempts to reduce errors, and so strives to improve the reliability and accuracy of recommendations when compared with the traditional, narrative review or single study. Narrative reviews tend not to employ explicit measures to prevent bias. Nor do they guarantee comprehensiveness in identification of the relevant literature (Strech et al. 2013).

The purpose of the systematic review is to summarize a large, complex body of information on a subject and try to resolve conflicting reports in the literature. An attempt is made to assess the consistency of results across the literature and to identify the strengths and weaknesses of studies on the topic (Lang and Secic, 2006). The aim of a systematic review is to give an improved reflection of reality. Important advances are emphasised in real life contexts. It has to be acknowledged however, that only a small number of trial reports are analysed in up-to-date, quality systematic reviews (Heneghan and Godlee, 2013).

One of the first steps of the process of conducting a review is to define the review question.

Defining the inclusion and exclusion criteria

The primary objective of the first systematic review undertaken here was to assess the effects of cognitive-behaviour therapy (CBT) relative to antidepressant medication in depressed patients. The review sought all quality studies of a particular comparison of treatments in a particular population. The effective ingredients of the interventions were described in advance (Glasziou et al. 2010).

The types of participants, types of treatments, and types of outcomes were specified. Randomized controlled trials, clinical trials based in a hospital setting, primary care or in the community, in any country were included. There were no language restrictions.

Adults aged over 18 years of either gender with a primary diagnosis of depression were included, with this diagnosis established by criteria such as DSM-IV or ICD-10 or their predecessors. Studies specifically of children and adolescents were excluded. Reports in which individuals were in remission from depression or when an intervention was conducted as a preventive measure for depression were excluded.

All outcomes that were likely to be meaningful were considered but the primary outcomes were limited to a small number. A variety of studies was sought, but the eligibility criteria were still sufficiently narrow to ensure that a meaningful answer could be obtained when the studies are considered together (O'Connor et al. 2008). The primary outcome measure was clinical improvement in depression measured using a validated self-report or interview-based measure expressed as a continuous or dichotomous outcome.

If multiple measures were used, the Hamilton Depression Rating Scale or the Beck Depression Inventory were focused on as first choices for data extraction (Huntly et al. 2012). As a secondary outcome this writer extracted data about cost effectiveness where available. Studies were excluded from the meta-analysis when insufficient data was presented (Cuijpers et al. 2013, De Silva et al. 2013).

Explicit criteria were used for establishing the presence of depression. Both inpatient and outpatients were considered. No restriction was placed on the setting. A strategy in which eligibility criteria kept faith with the objectives of the review was adopted (O'Connor et al. 2008). A key component of a well-formulated question is to specify and clearly describe the interventions of interest and the condition against which these will be compared (Glasziou et al. 2010). The core or common features of the treatments, antidepressants and CBT, were specified. CBT was defined as an intervention based on cognitive restructuring training that also promoted behavioural change (Huntly et al. 2012).

Outcomes

Conclusions about the effects of the interventions under review were based on the outcomes chosen. Ideally, no more than three primary outcomes should be given (O'Connor et al, 2008). The main outcomes were included in the *Summary of findings* table. The aim in using the primary outcomes was to help reach a conclusion about the effects of the intervention when making a decision about treatment.

Certain study designs are more appropriate than others for particular questions (O'Connor et al. 2008). As this writer's question was about the effects of health-care interventions,

the concern was with randomised controlled trials and clinical trials.

Common sense reasoning gave rise to the two narrow-focused systematic reviews and meta-analyses rather than just one unwieldy overview that might prove difficult for readers to comprehend. There is a trend towards conducting reviews with a relatively narrow scope where an overview of the reviews might later summarize the results (O'Connor et al. 2008). The initial two systematic reviews conducted by this writer also incorporated meta-analyses. It was felt that it was desirable to be familiar with the meta-analytic process before moving on to address the diverse factors impacting on systematic review uptake.

Meta-analysis

Meta-analysis is the core methodology for reliable estimates of treatment effects (Hrobjartsson et al. 2013). The main aim in a meta-analysis is to combine the results from all the primary studies so as to deliver an estimate of the overall effect of interest (Petrie and Sabin, 2007). Combining several studies increases the chances of detecting an effect where one exists (Deeks and Higgins, 2008). A meta-analysis can improve precision, that is, the estimation of the effect can be improved because it is based on more information. The assumption of a meta-analysis is that this 'super-study' will provide a more reliable and precise overall result than any of the smaller primary studies (Bowers, 2008).

Combining the data

It must make sense to bring together the different studies when doing so. Before studies

can be combined they must satisfy the *homogeneity* criterion. Even when a set of potentially similar studies has been identified, reviewers have to be sure that they are indeed similar or homogeneous enough to be combined (Bowers, 2008). Heterogeneity needs to be investigated as many issues such as different outcome measures, participant populations, and length of follow-up can give rise to non-compatibility of the results (Kingdom, 2013). Great care is needed in interpreting a meta-analysis where there is evidence of significant heterogeneity.

Main Steps

In conducting the meta-analyses a number of steps were followed. Initially the measure for the treatment effect of interest, such as a mean difference or risk ratio, was decided on and a result was estimated for each primary study. Next statistical heterogeneity was checked for.

Having estimated an average treatment effect of interest from the different primary studies, with the associated confidence interval, interpretation of the results could then begin. It was helpful to summarize the results from each individual study in a table, detailing the sample size and the effect of interest with the related confidence interval (Higgins and Green, 2008).

Throughout each stage of a meta-analysis, evidence is prioritized (Treadwell et al. 2012). The following steps were taken by this writer in conducting the two meta-analyses outlined here:

(1) Initially this reviewer decided on the effect of interest and evaluated it for each

trial.

(2) Next statistical heterogeneity was checked for. This occurs when there is a real variation between the effects of interest from the different studies.

(3) The average effect of interest, with associate confidence interval, was investigated in the first two systematic reviews presented here and the appropriate hypothesis test on the effect was then performed.

(4) Lastly, this writer interpreted the results and presented the findings. The results from each trial were summarized in a table, detailing the sample size, effect of interest such as the risk ratio and then the related confidence interval.

After a table had been constructed, a graphical display (forest plot) was then generated of the results (Petrie and Sabin, 2005). Flow diagrams were also included. The flow of studies through various stages of the systematic review process was outlined so as to add to face validity (Egger et al. 2001).

Quality differences between individual trials need to be taken into account as the design and conduct of primary trials can vary significantly. Improper use of overviews can lead to misleading conclusions regarding treatment efficacy. Inappropriate conclusions are best avoided. However, an inappropriate lack of conclusions is not desirable either (Treadwell et al. 2012).

Six content areas are reported in the 2 initial systematic reviews undertaken here: study design, combinability, control of bias, statistical analysis, sensitivity analysis, and the

problems of applicability (Egger et al. 2001). Reporting of the systematic reviews was guided by the PRISMA statement.

3.2 PRISMA

Transparency plays an important function in enabling end users to assess a review's methodology and applicability (Treadwell et al. 2012). PRISMA is about ensuring the transparent and complete reporting of systematic reviews and meta-analyses. In 2009, Moher and his colleagues introduced PRISMA, which refers to Preferred Reporting Items for Systematic Reviews and Meta-analyses. This was an update of the QUOROM (Quality of Reporting of Meta-analyses) guidelines for reporting systematic reviews and meta-analyses. QUOROM is still used in some recently reported reviews (Choi et al. 2013).

The statement consists of a checklist and flow diagram. The 27 checklist items pertain to the content of a systematic review and meta-analysis. The flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusion. The flow diagrams outlined in this thesis by this writer have the four phases recommended by PRISMA.

Only 10% of reviews report working from a protocol and protocols were developed for the reviews reported here. The conduct and reporting of systematic reviews are, by nature, closely intertwined (Moher et al. 2009). A risk of bias assessment is essential to the good conduct of a systematic review. Both a study-level and an outcome-level risk of bias assessment were carried out. An outcome-level assessment was conducted where this

writer looked at the reliability and validity of the data for each important outcome. Quality of evidence may differ across outcomes even within the same study.

This writer assessed the risk of bias in order to gauge the extent to which an estimate of effect was correct. All decisions made about prioritizing evidence in a review should be explicitly stated in the methods section (Treadwell et al. 2012). Methods and results should be presented with the PRISMA statement in mind (De Silva et al. 2013). As stated, the PRISMA statement was used here to guide the reporting of all the reviews (Koesters et al. 2013).

3.3 The search strategy

Introduction

Medical literature doubles every ten years and can lead to information overload. Keeping track of all the available literature is not feasible. Finding the best evidence requires knowledge of the most appropriate information sources and the best ways to search them (De Brun and Pearce-Smith, 2009).

A systematic review employs explicit measures to prevent bias and to guarantee comprehensiveness in identifying and presenting relevant literature (Strech et al. 2013). Searching should be guided by the objectives and focus of the review (Wong et al. 2013). The question investigated here relates to treatment and the clinical question can best be answered by searching research literature including journal articles indexed in medical databases and other online resources.

Identification of trials

The data for systematic reviews and meta-analysis consists of accounts of research studies on identical or similar topics. It is essential to identify as many of these study reports as possible (Lang and Secic, 2006). With aggregative reviews it is important to collate as much relevant research as possible to avoid a bias from having just partial data (Gough and Thomas, 2012). Few reviews however, have a comprehensive search strategy (Anglin et al. 2013). An incomplete search can introduce serious selection bias into the review by failing to identify relevant studies (Stewart, 2013). This inadequacy of search strategies has been well noted (Lerner and Hamblen, 2013).

Sources searched depend on the research topic (Gough and Thomas, 2012). The most common databases searched in psychiatric epidemiology are MEDLINE, PsycLit, PsychINFO, EMBASE, Ovid, PubMed and CINAHL (Brugha et al. 2012). In the field of mental health, the number of databases used in systematic reviews reported in the British Journal of Psychiatry, varies. In a systematic review of self-help interventions for anxiety disorders, nine databases were searched (Lewis et al. 2012). The systematic review by Brugha searched three databases (Brugha et al. 2012). A more recent review of pharmacological interventions to improve cognitive deficits searched just 3 databases: PubMed, MEDLINE, and PsycINFO (Choi et al. 2013). A further review of outcomes of clinical depression following a stroke searched just four databases (Ayerbe et al. 2013). A systematic review and meta-analysis on the influence of smoking cessation on incidence of pneumonia in HIV utilized just two databases (Di et al. 2013). A quite recent systematic qualitative review of the ethical issues in dementia care acknowledged utilizing just Medline and Google books (Stewart, 2013).

Absence of data from unpublished studies is a potential weakness of a review (Koesters et al. 2013). Effects estimated from published studies may be inflated because of a bias towards the non-publication of small studies with null effects (Bridle et al. 2012). Accordingly, a thorough and systematic search of a wide range of databases was conducted here in order to minimise selection bias. A comprehensive search strategy, aimed at published but also grey literature, was planned and executed.

Several search strategies are better than one (Lefebvre et al. 2008). Index terms were reported in the reviews conducted here and the databases searched and the dates covered by the searches were also listed. Pharmacological companies were surveyed for information on trials, published and unpublished. Registries of potentially pertinent studies were searched also (Lang and Secic, 2006). While acknowledging that cultural norms and health-care delivery systems differ, reports from any country and in languages other than English were included.

Grey literature refers to studies not readily identified by standard bibliographic searching techniques (Lang and Secic, 2006). The term refers to print and electronic evidence published by agencies whose primary function does not lie in the field of publishing. Grey literature includes unpublished or non-indexed studies not readily available through the usual channels and not usually peer-reviewed. In this doctoral project, grey literature was especially searched for in all reviews. Consequently, literature outside the main journals was gone through such as conference abstracts and published lists of theses and dissertations.

Relevant books and chapters were identified and perused to ensure that important trials were not missed. Care was also taken to identify studies that led to multiple publications

(Lang and Secic, 2006). Studies, not reports, were the subject of this thesis. The importance of including recent or on-going studies in a review has also been emphasized (Anglin et al. 2013).

Search methods for identification of studies

Many studies investigating the treatment of depression use both randomized and non-randomized study designs (Bridle et al. 2012). A clinical trial can be defined as any study undertaken to evaluate the clinical effects of an intervention on humans or animals. The control under which such studies are undertaken varies (Po, 1998). A double-blind, randomized controlled trial is generally regarded as the gold standard.

This author aimed to identify all randomised controlled trials and clinical trials comparing antidepressant medication and CBT in treating clinical depression. Trials were eligible if there were two groups, one receiving antidepressants, the other CBT, and depression was measured before and after the intervention (Bowers, 2008). Trials were considered for the second systematic review if combination therapy (antidepressants and CBT) was compared with either treatment on its own.

The majority of non-drug interventions are inadequately described in standard publications and therefore difficult to implement in practice (Glasziou et al. 2012). Accordingly, care was taken to define the form of psychotherapy that was used, in this case specifically CBT.

Electronic bibliographic databases

Electronic databases including the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers, Cochrane Central Register of Controlled Trials, Medline (Ovid), Pubmed, Embase, PsycInfo and Web of Science were searched using a comprehensive search strategy to identify trials comparing antidepressant medication and CBT or combination therapy compared with single therapy.

Relevant and related review papers, both traditional and systematic, were checked and the reference lists inspected for published reports and citations of unpublished research. Authors of significant papers and other experts in the field were contacted, where appropriate, in order to obtain additional published and unpublished reports.

The Cochrane Library is the most important online evidence retrieval database of systematic reviews (Kuo et al. 2012). It was one of the first scientific publications to be available online (Maclehose and Hilton, 2013). So The Cochrane Library was chosen as the best place to start the search (Lefebvre et al. 2008). Within the Library, CENTRAL is the best single source of published trials for inclusion in systematic reviews (Dickerson, 2002).

Search strategy

The structure of the search strategy was based on the main concepts to be examined in the systematic review. In general databases, such as Medline, a search strategy will have three sets of terms: key words to search for the health condition of interest: depression;

the interventions to be evaluated: CBT and antidepressants; and the type of study design to be included, such as clinical and randomized controlled trials.

For the initial two systematic reviews presented here, this writer searched 14 databases from inception until December 2010. In addition, this writer also inspected the references of all selected studies for published reports, citations of unpublished reports and relevant review papers. To ensure that all relevant studies were identified, experts in the field were also contacted (Huntley et al. 2012). This extensive, main search was completed in December 2010.

The searches associated with each systematic review were conducted and completed within a specified, individual time frame. The reports of primary studies were then read, inclusion and exclusion criteria applied, data extracted and a synthesis conducted. As this process takes a considerable time, following the completion of the synthesis, a further briefer, more focused, 'updated' search was conducted for each systematic review. Brief, updated searches are usually conducted just prior to submission of the already completed systematic review for publication. The brief 'updated search' was carried out in order to detect 'studies awaiting assessment' or 'ongoing studies' (Baker et al. 2010). These primary studies could then be mentioned without being included in the completed review but could be used in updating the review. This procedure was in-keeping with the method adopted by Baker and colleagues in their important Cochrane systematic review (Baker et al. 2010). It allows the main, extensive search to be acknowledged as finishing at a specified time, as planned. It also enables the reader (and peer reviewer) to be kept current and informed of any new or ongoing studies in an 'updated search' which could then temper their appreciation of the earlier, completed main search results.

In the case of the antidepressant and CBT systematic reviews, this writer repeated limited parts of the search for the period January 2011 to April 2012 in order to identify any potentially relevant completed or on-going studies. This writer applied these same search strategies to PubMed and EMBASE, the two most productive databases in terms of reports of trials identified for inclusion in the review. Also searched were all active registers in the *meta*Register of controlled trials (http://www.controlledtrials.com/mrct/), in April 2012, for reports of relevant on-going or completed trials that could be used in an updated review.

Electronic databases

Bibliographic databases were searched from inception using a set of search terms related to depression and combined with terms related to CBT and antidepressants. The search was essentially of two parts: a primary study search and then a reference list search. The databases and reference lists searched in the first two systematic reviews are outlined in Box 3.1.

Box 3.1. The search sources for the antidepressants and CBT systematic reviews

The Cochrane Library
PubMed
Embase
PsycInfo
Theses and Dissertations: Index to Theses in Great Britain and Ireland and ProQuest Dissertations & Theses Databases
Clinical Trials Registries-Pharmaceutical databases: Bristol-Myers Squibb Clinical Trial Registry and Lilly Clinical Trial Registry-Mental Health/Neuroscience
Grey Literature
Reference List Search of Overviews
Reference List Search of Guidelines
Reference List Search of Textbooks

While a wide variety of electronic databases was utilised for primary studies, a search was also carried out for overviews and practice guidelines in order to scan their reference lists for relevant primary studies and to ensure that the proposed systematic reviews had not been conducted previously.

3.4 Selecting Studies and Collecting Data

The method of collection of data followed from the specific aims of the reviews outlined here (Treadwell et al. 2012). The methodology used was intended to generate the type of knowledge which can reasonably be expected to satisfy the aims of the thesis (Oliver, 2008).

The study selection process

Some reviewers may choose to use all included studies in an attempt to draw evidence-based conclusions, others prefer the 'best evidence' approach (Treadwell et al. 2012). Firstly, this writer examined the titles in order to remove obviously irrelevant reports. Next, abstracts of apparently relevant studies were examined. The full text of the potentially important reports was then retrieved. Articles based on the same cohort were identified and multiple reports of the same study were subsequently linked together (Ayerbe et al. 2013).

While the majority of systematic reviews give details of inclusion and exclusion criteria used to select individual studies for detailed review, much fewer give details of the method used to apply such criteria, such as the numbers of reviewers (Brugha et al. 2012). The final selection of studies for the reviews was undertaken by this writer who employed

the aid of a second author (Higgins and Deeks, 2008). The full texts of reports were examined for compliance of the studies with the eligibility criteria. Study eligibility was clarified and final decisions were made on study inclusion. Data collection was then initiated.

Implementation of the selection process

This writer screened the abstracts of all publications obtained by the search strategy, in order to exclude the obviously irrelevant articles (Huntley et al. 2012). Using the full text of the remaining papers, eligibility based on the inclusion and exclusion criteria was assessed independently by two reviewers. Disagreement about whether a study was to be included was resolved by detailed discussion and by negotiation (Higgins and Deeks, 2008, Strech et al. 2013). The reasons for any disagreements were explored and reasons for exclusion were recorded (Huntley et al. 2012). References were managed using EndnoteWeb, version 3.1, on Windows.

Full-text articles were retrieved for all studies identified as potentially relevant from the abstracts, as well as those where their relevance was unclear (Brugha et al. 2012). This writer was not blinded regarding the names of authors, journals, or institutions. A single failed eligibility criterion was sufficient for excluding a study from the systematic review.

Specific criteria for selection of studies

In an effort to obtain a more clinically homogeneous sample, several specific selection criteria were applied. To be included, the study should compare CBT with antidepressant medication, or combination therapy versus either treatment alone, and focus on the

efficacy of acute treatment. Studies were considered for inclusion in the review if they met the following inclusion criteria:

- They were randomised trials or clinical trials
- Participants had depression as diagnosed by operationalized criteria such as the International Classification of Diseases (ICD), Diagnostic and Statistical Manual, Research Diagnostic Criteria (RDC) or Feighner Criteria.
- Participants could be male or female
- Participants were aged between 18 and 65 years
- Diagnosis did not include co-morbid physical and psychiatric conditions
- Studies compared the outcomes of antidepressants versus CBT
- Compared the outcomes of either single therapy versus their combination
- The single active treatment needed to be one of the treatments of the combination
- Antidepressant medication included the tricyclics, MAOIs, and also the newer selective serotonin reuptake inhibitors and multi-action antidepressants
- CBT was based on cognitive restructuring training and behavioural change
- Measurement tools were standardized and validated, such as the Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale (HDRS)

Other outcome measures were also identified such as quality of life measures, hospital readmission, patient satisfaction, drop-out rates, side-effects and acceptability of treatment. All available studies that met criteria were included. The reason for a study not being including was stated.

The methods sections of potentially eligible reports were checked for the specifics of the treatment regimen. CBT was required to contain cognitive restructuring and behavioural testing while the eligible medications were specifically antidepressants.

Excluded studies

Studies that did not meet all the criteria but are well known and likely to be thought of as relevant by some readers were listed in an excluded studies table (Higgins and Deeks, 2008). This shows that consideration was given to these studies. The list was kept brief and does not list studies that obviously do not meet the eligibility criteria.

Studies were excluded if

- The studies employed unstructured assessment of mood
- Depression was complicated by schizophrenic illness or manic episodes
- Depression was accompanied by co-existing drug abuse or excessive alcohol use
- Depressive episodes were complicated by multiple sclerosis, cancer or other physical illness
- Antidepressants were supplemented by other strategies such as augmentation with lithium carbonate
- The psychotherapy employed was not specifically cognitive-behaviour therapy

Interpersonal therapy, general counselling, or behavioural activation were excluded as the psychotherapy under investigation was specifically CBT.

The pharmacotherapy included was antidepressants only. Medications such as lithium carbonate, sodium valproate, and carbamazepine, regarded as mood stabilisers but sometimes seen as having a role in depression prevention, were excluded. The addition of these medications as a means of augmentation of the effectiveness of antidepressants meant that such a study was not eligible. The interventions included then were specifically antidepressants and CBT.

Patients had to have clinical depression as diagnosed by operationalized criteria such as the Diagnostic and Statistical Manuel of Mental Disorder (DSM III) or the International Classification of Diseases (ICD X) in any edition, or by Feighner criteria (Feighner et al. 1972), or Research Diagnostic Criteria (Spitzer et al. 1978). Exclusion criteria encompassed specific additional psychiatric disorders. Patients diagnosed with bipolar affective disorder or organic brain syndrome, were excluded. Patients were not included if their depression was complicated by a diagnosis of intravenous drug abuse. Patients with serious concomitant physical conditions, such as metastatic disease, were also excluded. The aim was to address depression uncomplicated by other psychiatric or physical conditions. The enforcement of strict inclusion and exclusion criteria was done in order to improve 'directness' (Schunemann et al. 2008).

Data abstraction and analysis

Only 42% of the systematic reviews of observational studies in psychiatric epidemiology described the method of data abstraction (Brugha et al. 2012). Efforts were made here to identify and reduce the selective reporting of results within study reports or the selective reporting of studies themselves. Some studies will only report statistically significant results. The potential under-representation of negative studies is a major concern

(Stewart, 2013). However, the value of reporting unpublished studies, of variable quality and without peer review is also an issue (Lang and Secic, 2006).

The measure of effect size in pooled results

Meta-analyses with dichotomous outcomes may report their results as absolute risk differences, risk ratios, or odds ratios (Harris and Taylor, 2008). With continuous outcomes, a mean difference or the standardized mean difference can be used. Both risk ratios and mean differences were the measures focused on here.

Statistical methods

A meta-analysis is different to a systematic review in that each study's results are combined statistically with that of other studies in a meta-analysis (Ayerbe et al. 2013). The statistical method used in a meta-analysis can involve one of two models. The fixed-effect model assumes that there is a single, fixed effect that every study will approximate. The random-effects model assumes a distribution of effects and some degree of variation. Both models can be used and both are reported here (Deeks et al. 2008, Mitchell et al. 2012).

Few meta-analyses make no reference to heterogeneity (Fawole et al. 2012). More than 50% of a sample of systematic reviews formally tested for heterogeneity using the Q statistic, chi-squared test, and with the I^2 statistic also employed (Brugha et al. 2012). The I^2 test describes the percentage of variability among effect estimates beyond that expected by chance (Bridle et al. 2012). Significant heterogeneity is found in many reviews (Ayerbe et al. 2013). Reviews that detected significant heterogeneity make allowances for

it by employing random-effects models or by not proceeding to meta-analysis (Mitchell et al. 2012). The random-effects model is more conservative than the fixed-effect model since, by incorporating both between- and within-study variance, confidence intervals for the summary effect are wider (Bridle et al. 2012).

Several software packages can generate the summary figure such as a forest plot with pooled effect sizes and confidence intervals (Lang and Secic, 2006). RevMan is used here.

Data extraction

Full-text articles of the studies identified were obtained and inspected for trials meeting the broad and simple inclusion criteria. Qualitative and quantitative data was extracted relating to internal validity and external validity. The results of each study were summarised. For each trial, information was recorded on the study population, sample size, randomisation and blinding procedures, nature of the interventions, follow-up, statistical analysis, outcome data, discussion and conclusions (Lang and Secic, 2006).

A plan was devised in advance on what data to collect and the strategy to be employed to collect it. Different research methods can influence study outcomes by introducing different biases into results (Ayerbe et al. 2013). Basic study design characteristics, where possible, were collected here for presentation in the table of *Characteristics of included studies*. This included randomisation, trial duration, and details of participants and settings. Study aspects were collected that could affect the presence or the magnitude of an intervention effect (Higgins and Deeks, 2008). The tool suggested for this purpose and

described in the *Cochrane Handbook for Systematic Reviews of Interventions*, was used (Higgins and Green, 2008).

Participant characteristics that affect applicability are gender and age. Ethnicity and co-morbid conditions may sometimes be important (Oliver, 2008). Details of treatments were also collected, primarily for presentation in *Characteristics of included studies* table. Intervention integrity (compliance and fidelity) is significant and details of treatment integrity were looked for (Kingdom, 2013).

Outcome Measures

Psychiatry is sometimes criticised for using rating scales which are subjective and considered 'soft' outcomes. Self-report tools however can have added value over unassisted clinical judgement (Mitchell et al. 2012). Treatment in psychiatry often focuses on depression severity (Bridle et al. 2012). Reduction in disease severity, where rating scales are appropriate, is often a primary outcome in psychiatry, rather than mortality (Leucht et al. 2012).

In addition to an effect on symptom scale scores, clinical relevance can be confirmed by response and remission analysis (Koesters et al. 2013). Only those pre-specified outcomes of interest in the review were collected. Information about outcome measures believed to be important included definition (name of scale, definition of threshold), timing and unit of measurement, and the upper and lower limits of scales (Box 3.3).

Box 3.3. The Beck Depression Inventory

Rating: Self-reporting
Administration time: 5-10 minutes
Main Purpose: To assess severity of depressive symptomatology
Population: Adults and adolescents
Commentary: This is the gold standard of self-report depression rating scales. It is a screening tool and used to assess response to treatment. It assesses the patient's mood and behaviour over the previous two weeks
Scoring: The BDI consists of 21 items which assess numerous manifestations of depression. Items are scored on a 0-3 scale, yielding a score range of 0-63 where the higher scores indicate greater depression. Scores in the 0-13 range indicate minimal depression, 14-19 mild depression, 20-28 moderate depression, and 29-63 severe depression.

Reference: Beck AT, Steer, RA, Brown, GK. Manual for the BDI-II 1996. San Antonio, TX. The Psychological Corporation

Measurement using validated tools is central to reliable estimates (De Silva et al. 2013). Patients were assessed with both the 17-item Hamilton Depression Rating Scale (HDRS) and the Beck Depression Rating Inventory (BDI). To be included in the meta-analysis, usable data had to be produced. Usable data however is not always presented in primary studies (Ayerbe et al. 2013).

The advantages of the Hamilton Depression Rating Scale is that historically, it has not been associated with cognitive therapy or CBT research as has the Beck Depression Inventory (De Rubeis et al, 1999). The advantages of the Hamilton have been noted (Koesters et al. 2013). The Beck Depression Inventory and the Hamilton Depression Rating Scale (Box 3.4) were the outcome measures used here. The Hamilton Depression Rating Scale (HDRS) is also referred to as the Hamilton Rating Scale for Depression (HRSD). The Hamilton Depression Rating Scale (HDRS) will be the term used here.

Box 3.4. Hamilton Depression Rating Scale

Rating: Clinician-rated
Administration time: 20-30 minutes.
Main purpose: To assess severity of, and change in, depressive symptoms
Population: Adults
Commentary: This is the most widely used clinician-administered depression assessment scale. The original version had 17 items, pertaining to symptoms of depression experienced over the past week. Items are rated on a 0 – 2 or a 0 – 4 point scale. A later version has 21 items. For HDRS17, a score of 0-7 is generally accepted to be within the normal range. A score of 20 or higher indicates moderate severity and is usually required for entry into a clinical trial.

Reference: Hamilton, M. A rating scale for depression. J Neurosurg Psychiatry, 1960; 23:56-62.

The outcome of interest is the alleviation of depression and there may be different results for the same outcome, as occurs here, as two specific scales are used to measure the outcome of interest. An advantage of a systematic review is that both interview-based and self-report scale results can be incorporated and reported separately, as occurs in this thesis (Mitchell et al. 2012). No one measure however, is ever likely to be ideal (De Silva et al. 2013). The burden of an illness is frequently not fully captured by the available outcome measures (Knottnerus and Tugwell, 2013).

Extracting Data from Reports

In most systematic reviews, the primary source of information about each study is in published reports of studies, usually in the form of journal articles. Data extracted from all reports of a single study was recorded directly into a single data collection form. Data was managed using RevMan software (Version 5) on Windows (Huntley et al. 2012). As a high prevalence of data extraction errors has been identified in the past, more than one person should extract the data, independently (Higgins and Deeks, 2008). An explicit procedure or

decision rule was highlighted in the protocol for identifying or resolving disagreements (Higgins and Deeks, 2008).

Extracting study results and converting to the desired format

This writer was concerned with extracting study results and then converting these to the desired format, an important step in the review process. Two types of outcomes were looked at: (1) continuous and (2) dichotomous. This writer collected summary data separately for each intervention group, the CBT and the antidepressant groups for the first systematic review, and the combination group and monotherapy groups in the second systematic review. The summary data was then entered into RevMan and effect estimates, such as mean differences and risk ratios, calculated (Higgins and Deeks, 2008). This writer tabulated available results for all studies included in the systematic review, even if they could not be included in a formal meta-analysis.

Meta–analysis can be used when there is a consistent outcome measure to establish whether there is evidence of an effect; estimate the size of the effect; and investigate whether the effect is consistent across studies (Deeks et al. 2008). Measurement scale outcomes are most commonly meta-analysed as dichotomous data or continuous data depending on the way the study authors performed the original analyses. In performing a meta-analysis of continuous data either a mean difference or a standardised mean difference can be used. The standardised mean difference is used as a summary statistic when the studies assess the same outcome but measure it in a variety of ways. The results of the studies can be standardized to a uniform scale. For the standardized mean difference approach, the standard deviations are used to standardize the mean differences to a single scale, as well as in the computation of study weights. For clinical interpretation however, such an analysis

may be less helpful than dichotomizing responses and presenting proportions of patients benefiting.

The mean difference is a standard statistic that measures the absolute difference between the mean value in two groups in a clinical trial. In the mean difference approach, the standard deviations are used together with the sample sizes to compute the weight given to each study.

The analyses reported by the investigators in the clinical trials generally determine the approach that is used in a meta-analysis. Selection of summary statistics for continuous data is determined by whether the studies report the outcome using the same scales, as occurs here. The mean difference can be used as a summary statistic in meta-analysis when the outcome measures in the studies are made on the same scale, such as the BDI or HDRS, as occurs in the antidepressant and CBT systematic reviews conducted here. It is prudent not to combine outcomes that are too diverse and this decision requires clinical judgement (Deeks et al. 2008).

Occasionally data for the same outcome are presented in some studies as dichotomous data and in other studies as continuous data. Scores on depression scales may be reported as means or as percentages of patients who were depressed at some point after an intervention. In the studies populating the 2 reviews outlined here, the primary studies presented means but they also presented dichotomized data. The primary researchers dichotomized the data when conducting the primary research.

While dichotomised data is helpful, deciding on a cut-off point is problematic and information is lost when continuous data are transferred to dichotomous data (Deeks et al.

2008). In handling combinations of dichotomous and continuous data, when it is not possible to collect missing data from original researchers, it is useful to summarise the data by entering the means and standard deviations as continuous outcomes, by entering the counts as dichotomous outcomes, and by entering all of the data in text form.

The only data required for a dichotomous outcome are the numbers in each of the two outcome categories in each of the intervention groups. These are entered into RevMan as the numbers with the outcomes and the total sample sizes for the two groups. As mean scores can obscure clinically meaningful differences, data were also presented in categorical form. While researchers are concerned with measuring a decrease in symptom severity across a cohort, patients are often focused on individual treatment response and a remission that allows a return to work and resumption of previous social roles (De Silva et al. 2013).

Data extraction for continuous outcomes

For continuous data, mean differences were looked at. The studies in the two reviews conducted here, by convention, presented the same two outcome scales: BDI and the HDRS. Because of this, standardized mean differences were not required and it was not necessary to pool the different outcome scales (De Silva et al. 2013).

Reviewers are advised not to focus on change from baseline (Higgins and Deeks, 2008). Here the writer focused on final scores rather than change scores. Data was collected on paper collection forms first and then entered into RevMan.

Data analysis

The importance of these two systematic reviews lies in the attempts made to reduce heterogeneity. Excessive variation was decreased by only including CBT specifically as a treatment rather than psychotherapy in general. Diversity was also addressed by the selective use of 'antidepressants' rather than medication in general, and lastly, by including only patients suffering from primary, unipolar depression (rather than the more severe bipolar disorder) uncomplicated by other major medical or psychiatric conditions. The action taken to reduce heterogeneity in the reviews conducted as part of this thesis separates these two systematic reviews from others in the field.

Other, related reviews tended to deal with medication in general rather than antidepressants in particular, psychotherapy globally rather than CBT specifically, and include patients who could suffer from other significant co-morbid psychiatric or medical problems. To this writer's knowledge, this makes the two reviews conducted here important and innovative.

RevMan

Technology can be useful in all the basic tasks underpinning a systematic review (Tsafnat et al. 2013). RevMan is the standard systematic review software for the Cochrane Collaboration. It is used for writing protocols and full reviews, keeping a list of included and excluded studies, writing the review text and performing the statistical meta-analytic functions. It is structured and comprehensive and was released in the 1990s. RevMan works on multiple operating systems because it has been developed using the Java Swing platform. It both uses outline and content panes.

Outcomes

This writer used the mean value of the outcome measures in the experimental group and the control group. The standard deviation of the outcome measures in the experimental and control group were also used. Lastly, the number of participants on whom the outcome was measured in each intervention group, that is, the number in the experimental and control groups, was utilized.

With effect measures for dichotomous data no measure is uniformly best (Deeks et al. 2008). Odds ratios can lead to the overestimation of the benefits and harms of treatments when applied in clinical practice. Risk ratios were used here.

Box 3.5. The two steps of meta-analysis

1) A summary statistic is calculated for each study (RR or mean difference)
2) The overall treatment effect is calculated as a weighted average of these summary statistics (Deeks et al. 2008)

The only data required for a dichotomous outcome are the numbers in each of the two outcome categories (relapse versus no relapse). These data are needed for each of the intervention groups (Deeks et al. 2008). The treatment effect is expressed here as a relative effect.

The mean difference (difference in means) is a summary statistic that measures the amount by which the experimental intervention changes the outcome on average compared with the control (Deeks et al. 2008). It is used as a summary statistic in meta-analysis when outcome measurements in the primary studies are made on the same scales, as occurs here

(Box 3.5). RevMan has a number of analysis options for dichotomous data (Box 3.6) and continuous data (Box 3.7).

Box 3.6. Analysis Details Options in RevMan - dichotomous data

1) *Statistical methods available*
   Peto
   Mantel-Haenszel
   Inverse variance

2) *Analysis Model*
   Fixed-effect
   Random-effects

3) *Effect measures*
   Odds ratios
   Risk ratios
   Risk difference

Review Manager, 2008

Box 3.7 below outlines analysis options in RevMan for addressing continuous data.

Box 3. 7. Analysis Details Options in Rev Man - continuous data

1) Statistical methods available
   Inverse variance

2) Analysis Model
   Fixed-effect
   Random-effects

3) Effect measures
   Mean difference
   Standardised mean difference

Review Manager, 2008

The comparison table in RevMan reflects the fact that Cochrane intervention reviews are based on the comparison of two interventions (Box 3.8).

Box 3.8. Construction of a comparison table

Comparisons: CBT versus Antidepressants
Outcomes: Depression BDI and depression HDRS
Data: Continuous and dichotomous

Using RevMan, this writer constructed a comparison table where studies are analysed as two-way comparisons. The second level of the table consists of their outcomes: BDI and HDRS. When the comparison table had been created, then studies were added to these outcomes for use in the analysis. Once studies had been added, then data was entered for the review. Studies were entered into the analysis when they have been included in the *Included Studies* section and once a comparison table has been constructed.

Heterogeneity

A wide range of factors contribute to both clinical and methodological heterogeneity (Ayerbe et al. 2013). Since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is to be expected. Heterogeneity will always exist regardless of whether it is detectable by employing a statistical test. A test for heterogeneity is irrelevant in terms of the choice of analysis (Higgins and Altman, 2008). The choice between a fixed-effect model and a random-effects meta-analysis should never be made on the basis of a statistical test for heterogeneity (Higgins and Altman, 2008). It is best to try to quantify variation across studies and, importantly, assess the impact of heterogeneity on the meta-analysis rather than simply trying to test for its presence (Higgins and Altman, 2008).

Some methods of quantifying inconsistency across studies shift the focus away from testing whether heterogeneity exists or not. They are concerned with the impact of

heterogeneity on the analysis. Here, the I^2 statistic was used to assess the degree of true statistical heterogeneity or heterogeneity not due to chance (Lewis et al. 2012). This statistic is popular to assess heterogeneity between trials (De Silva et al. 2013). The I^2 statistic is an indicator of heterogeneity in percentages (Cuijpers et al. 2013). The *I* index is the percentage of the total variability in a set of effect sizes due to true heterogeneity. Increasing I^2 values indicate increasing heterogeneity. An $I^2$of less than 30% is taken to indicate mild heterogeneity (Deeks et al. 2008). I^2values over 30% can indicate moderate heterogeneity (Lewis et al. 2012). Sometimes, however, a figure of 40% is suggested (Bridle et al. 2012) or indeed 50% as the threshold (Koester et al. 2013). Occasionally, 80% is advanced as indicating high heterogeneity (Mitchell et al. 2012). The percentages, however, are suggested as a rough guide and using *both* a fixed- and random-effects model is advised (Deeks et al. 2008, Cuijpers et al. 2013).

Heterogeneity, of course, should not always be thought of as a burden (Knottnerus and Tugwell, 2013b). Clinical reality is heterogeneous and this insight should be integrated into clinical research (Knottnerus and Tugwell, 2013b).

3.5 Assessing the risk of bias in the included studies

Randomised controlled trials are often inadequately conducted and reported (Hrobjartsson et al. 2013). The associated biases can impact seriously on the findings and conclusion of a systematic review (Doshi et al. 2013). Systematic reviewers try to use a best evidence approach to address key questions (Treadwell et al. 2012). Quality, as well as quantity, is focused on in a systematic review (Bridle et al. 2012). Study quality and effect size typically show an inverse association. This writer wanted to avoid an underlying risk of

bias inflating the estimate of the effect sizes (Bridle et al. 2012). It is important to avoid a biased trial leading to a biased systematic review (Hrobjartsson et al. 2013).

Most Cochrane Review Groups recommend using specific trial characteristic to assess risk of bias (Hrobjartsson et al. 2013). Accordingly, an assessment of bias was carried out on each individual study using a tool recommended by the Cochrane Collaboration (Higgans and Altman, 2008, Koesters et al. 2013). The risk of bias was then summarised for each outcome across studies.

Brugha and colleagues carried out a systematic review of meta-analyses of observational studies in psychiatric epidemiology (Brugha et al. 2012). They reported that while 66% of studies made some mention of study quality, a much smaller number (19/106) formally assessed the quality of primary studies, and just 4 of more than a hundred reviews carried out a sensitivity analysis excluding studies of poor quality.

Brugha and colleagues found that many meta-analyses that they surveyed failed to mention study quality, publication bias, and confounding (Brugha et al. 2012). A recent systematic review by Collins and colleagues highlighted the hindrance that inadequate reporting in a review poses to an adequate assessment of its usefulness (Collins et al. 2013). Brugha felt however that many deficiencies found in systematic reviews are potentially remediable.

This writer assessed the quality of included studies using the Cochrane Collaboration's domain-based evaluation tool for assessing risk of bias. This consists of a number of questions that assess the applicability of the randomisation process together with the analysis of incomplete data (Koesters et al. 2013). The remaining questions cover

selective reporting and other biases (Bridle et al. 2012). The questions were answered no, yes, or unclear (Huntley et al. 2012). Randomisation, blinding and attrition are considered central (Hrobjartsson et al. 2013).

The definition of best evidence is a careful balance of risk of bias and applicability (Treadwell et al. 2012). In the systematic reviews outlined, a risk of bias table was set up for each included study where every entry addressed a specific feature of the study. The use of scales yielding a summary score is not advised and was not calculated here (Higgins and Altman, 2008, Knottnerus and Tugwell, 2013).

The quality of primary studies is of importance when interpreting the results of any meta-analysis (Lewis et al. 2012). Bias is one of several factors to be considered when judging the 'quality' of a body of evidence. The Cochrane Handbook advises a focus on risk of bias instead of quality. While bias is just one aspect of quality, the risk of bias informs the degree to which a study result should be believed (Hrobjartsson et al. 2013).

The Cochrane Collaboration's tool for assessing risk of bias

Reviewers face a variety of dilemmas when conducting a systematic review (Treadwell et al. 2012). To draw conclusions about the overall risk of bias for an outcome, it is necessary to summarize the biases. A *risk of bias summary* figure presents all of the judgements in a cross-tabulation of the studies (Bridle et al. 2012). The assessment of risk of bias is largely based on common sense (Hrobjartsson et al. 2013). The higher the number of trials assessed to be at high risk of bias, the more restrained should be the analysis and interpretation of the results.

Brugha and colleagues found that half of their included systematic reviews made no mention of bias (Brugha et al. 2012). Of those that did, few took steps to avoid bias affecting their results through the use of inclusion or exclusion criteria for the papers that populated their review. However, on a positive note, explicit discussion of confounding factors, mention of exact search terms, and specification of the exact method of data extraction, appears to be on the increase (Brugha et al. 2012). More recent meta-analyses tend to find smaller effect-sizes due to improvements in methodology (Leucht et al. 2012).

Bias has serious implications for inferences drawn or decisions made on the basis of a systematic review or meta-analysis (Brugha et al. 2012). It is not appropriate to present interpretations based on all studies, ignoring shortcomings identified during the assessment of risk of bias. This writer attempted to assess the impact of bias on the results by sticking to key bias domains in order to estimate the potential for bias to impact on the results of the meta-analysis. This writer looked at low, unclear and high risk of bias and the level of contribution of trials at different levels of bias. The aim was to estimate how much potential bias could affect the results of the meta-analysis (Treadwell et al. 2012).

Many studies combine the 'high' and 'unclear' risk of bias categories which are then compared with the 'low' risk of bias category (Higgins and Altman, 2008). This was not done here. Nor indeed were studies at low and unclear risk of bias combined in this project. Studies at low, high and unclear risk of bias were treated here as separate categories and not combined. Studies at high risk of bias should be given reduced weight in a meta-analysis, compared with studies of low risk of bias (Spiegelhalter, 2003).

Reliability between reviewers using the Cochrane Risk of Bias assessment tool has been shown to be good for most domains, except sequence generation (Hartling et al. 2013).

Sequence Generation

It is important to ensure that the same sorts of people receive each intervention if we want an unbiased study. It is advantageous to avoid selection bias, or selective enrolment in the upcoming intervention assignment. Randomisation allows the sequence to be unpredictable. Sequence generation is often inadequately addressed in published reports (Brugha et al. 2012). A simple statement such as 'we randomly allocated' is taken as insufficient here and is classified as unclear. An unpredictable sequence, together with allocation sequence concealment, should be enough to prevent selection bias.

Allocation sequence concealment

Random sequence generation is a necessary but insufficient protection against bias. Concealment of the allocation sequence is central (Higgins and Altman, 2008). This issue is important for these reviews because there may be strong beliefs among investigators and participants regarding the relative benefits and harms of the assigned interventions, such as psychotherapy and medication. Allocation concealment up to the point of assignment of the intervention and blinding after that point, address different sources of bias.

Blinding of participants, personnel and outcome assessors

Blinding happens after inclusion of participants in a study. The purpose of blinding is to reduce the risk that knowledge of which intervention was received, rather than the intervention itself, will affect outcomes and assessment of outcome. In Cochrane reviews, the focus is on participants, providers, and outcome assessors (Higgins and Altman, 2008). All these were considered here in assessing risk of bias.

Incomplete outcome data

Missing data are common and the resulting bias tends to favour the experimental intervention (Tierney, 2005). The risk of bias depends on a number of issues, including the amount and distribution across intervention groups and the reasons for outcomes being missing. Bias is also influenced by the likely difference in outcome between participants with and without data. In the reviews conducted here, if the numbers randomized into each intervention arm were not clearly reported, the risk of bias was recorded as unclear (Higgins and Altman, 2008).

Selective outcome reporting

Selective outcome reporting involves the selection of a subgroup of the original measures recorded, on the basis of the results, for inclusion in the reported study (Higgins and Altman, 2008). Outcome reporting bias was found to be highly prevalent within 37 systematic reviews of interventions for cystic fibrosis (Dwan et al. 2013).

In the systematic reviews carried out here, this writer considered if an outcome was recorded but not reported. The possibility of within-study selective outcome reporting was examined for each study (Higgins and Altman, 2008). A small number of key outcomes are routinely measured in the topic area addressed here such as the Beck Depression Inventory and the Hamilton Depression Rating Scale. This writer checked the reasons why data from these scales was not reported.

Other potential threats to validity

This heading was used as a catch-all category for other sources of bias. Some major, unanticipated, problems with specific studies can be identified during the course of a systematic review. Poor fidelity can lead to unclear or misleading conclusions (Glasziou et al. 2010). This writer looked for suboptimal delivery of interventions in the selected studies. The pre-appraised, integrative reviews carried out and described here tried to avoid null bias where interventions, medication or CBT, were insufficiently well-delivered (Kingdom, 2013). The writer also watched for inappropriate influence of financial sponsors (Kingdom, 2013).

In summary, the higher the proportion of studies assessed to be at high risk of bias, the more cautious should be the analysis and interpretation of their results (Higgins and Altman, 2008). However, the robustness of results can be assessed in a separate sensitivity analysis that excludes trials of moderate or high risk of bias (Bridle et al. 2012).

3.6 Analysing data and undertaking meta-analysis

In a systematic review, data are selected and collected from individual studies and then a decision is made on what is appropriate to analyse (Deeks et al. 2008). There are two forms of synthesis: narrative or quantitative. In a narrative analysis there is a structured summary and a discussion of the studies' characteristics and findings. This occurs as part of this doctoral project, in the later systematic reviews addressing barriers and facilitators to knowledge translation from systematic reviews and meta-analyses.

In the initial systematic reviews of treatment studies outlined here, this writer was concerned with the pair-wise comparison of interventions. The contrast between the outcomes of the two groups treated differently is known as the treatment effect. Here, the writer assembled primary studies that made one particular comparison between two treatment options in an attempt to identify the best intervention (Box 3.9).

Box 3.9. Comparisons used in the antidepressant and CBT systematic reviews

1:	CBT versus antidepressants
2:	Combination treatment versus single therapy: Combination treatment versus CBT Combination treatment versus antidepressants

Here this writer selected suitable effect measures for comparing intervention groups, taking into account the outcome data being addressed. Both continuous and dichotomous data were included here (Box 3.10). These were based on the measures of outcome used in the individual studies (Box 3.11).

Box 3.10. Data analysed in the CBT and antidepressant systematic reviews

Continuous Data: Depression scores

Dichotomous data: Relapse versus non-relapse

Sensitivity analysis was considered in order to examine whether overall findings were robust enough to potentially influential decisions or judgements that were used in the conduct of the systematic reviews.

Box 3.11. Depression rating scales used in the CBT and antidepressant systematic reviews

1. Beck Depression Scale (BDI)
2. Hamilton Depression Rating Scale (HDRS)

In the systematic reviews outlined here, this writer wished to establish whether there was evidence of an effect, the size of the effect, the direction of the effect, the uncertainty surrounding the effect size, and estimate whether the effect was consistent across studies (Deeks et al. 2008). The strength of evidence for an effect depends on the study design, the risk of bias, as well as statistical measures of uncertainty.

Box 3.12. Groups compared: CBT versus antidepressant systematic review

Experimental Intervention: CBT

Control Intervention: Antidepressants

In these two initial reviews, this writer carefully formulated the review question, specified the eligibility criteria, identified and selected the studies, critically appraised them, collected appropriate data, and decided what was appropriate to analyse. The analysis

plan followed the scientific aim of the review where this writer wished to identify the 'best' intervention: CBT or antidepressants (Box 3.12), and combination therapy or single therapy (Box 3.13).

Box 3.13. Groups compared: combination treatment versus monotherapy systematic review

Experimental Group:	Combination Therapy: (Antidepressants *and* CBT)
Control Group:	Monotherapy: (Antidepressants *or* CBT)

The unit of analysis

The number of observations in the analysis should match the number of units that were randomized. Here this writer addressed a simple parallel group design for a clinical trial where participants were individually randomized to one of two or more intervention groups. A single measurement for each outcome from each participant was collected and analysed.

There were multiple observations for the same outcome in some studies included here. The studies presented results from several periods of follow-up. This author was mindful to avoid unit-of-analysis error and selected the final, clinically important time-point in the acute treatment, usually 12 weeks.

Event

The aim was to reduce the risk of occurrence of an adverse outcome (depressive symptoms). As the focus is usually on the experimental intervention group (CBT or combination treatment), a study in which the experimental intervention reduces the occurrence of an adverse outcome (relapse) will have an odds ratio and risk ratio less than 1, and a negative risk difference. On the BDI relapse is prevented when the score drops below 9 on the scale, on the HDRS when the score is below 7 on that scale. Dichotomisation, based on these cut-off points by convention, was carried out by the primary study researchers.

Test statistic for overall effect

In all cases a test statistic for the overall difference between groups is derived as z. The null hypothesis is that there is no difference between groups (Deeks et al. 2008).

Methods of meta-analysis on RevMan

One preferred method was selected for each outcome. The method used is presented in the text of the review. For continuous data, with a mean difference as an effect measure, the software defaults to a fixed-effect inverse variance mean difference for continuous outcomes. The software defaults to the fixed-effect Mantel-Haenszel odds ratio for dichotomous outcomes.

Box 3.14. Format used to present results in the CBT and antidepressant systematic reviews

Scale	Type of Data	Scale	Type of Data
BDI:	Continuous Data	**HDRS**:	Continuous Data
	Dichotomous Data		Dichotomous Data

The above format is used to present the results (Box 3.14). The two outcome measures used here are the depression rating scales, BDI and HDRS. Results are presented first for continuous data and then dichotomous data on each scale.

Choice of methods for pooling data

Meta-analysis was considered appropriate as there were at least three similar studies in terms of patient type, setting and intervention (Huntley et al. 2012). Some reviews use just one model exclusively (De Silva et al. 2013). Here a fixed-effect analysis model but also a random-effects model (Box 3.15) were used (Lang and Secic, 2006).

Box 3.15. Analysis models used in the meta-analyses

1. **Fixed-effect**
2. **Random-effects**

The same format is used here to present results from the combination ***Combination treatment versus monotherapy*** and single therapy comparison. First this reviewer looked at the BDI, then, secondly, the Hamilton Scale (HDRS) in terms of continuous and then dichotomous data (Box 3.16).

Box 3. 16. Format Used to Present Results: Combination treatment versus monotherapy

Scale	Type of Data	Scale	Type of Data
BDI:	Continuous Data	**HDRS**:	Continuous Data
	Dichotomous Data		Dichotomous Data

Here we are concerned to compare combination treatment with single therapy: the first monotherapy looked at is CBT, the second, antidepressants. In essence, 2 comparisons are made (Box 3.17).

Box 3.17. Comparisons used in the combination treatment versus single therapy review

Combination treatment versus monotherapy:

Combination treatment versus CBT

Combination treatment versus antidepressants

Calculations were then conducted using a fixed-effect and then a random-effects model. This writer extracted the data and all data was checked for accuracy on multiple occasions and all analyses were conducted several times (Ayerbe et al. 2013).

3.7 Addressing reporting biases

In reviews assessing reporting bias, the majority of studies used funnel plots, or the fail-safe or 'file-drawer' method (Brugha et al. 2012). Of the studies that detected publication bias, few however appear to discuss the impact that this might have on their findings (Brugha et al. 2012).

Reporting biases arise when the transfer of research results is influenced by the nature and direction of the findings. There is substantial direct evidence of publication bias. Only half of abstracts presented at conferences are later published in full (Scherer, 2007). The contribution of statistically non-significant results to the march of medical science is as important as significant results. A comprehensive search for studies yielding both types of result is essential in order to reduce reporting biases (Stearne et al. 2008). The extensive searches for grey literature are documented for all reviews outlined in this project. While editors may have different views on grey literature, extensive efforts were made here to include it.

Detection of reporting bias

A funnel plot can be used to investigate possible publication bias (Ayerbe et al. 2013). A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision. A funnel plot shows graphically the distribution of effect sizes according to sample size (Dawes et al. 2005). The effect estimates are plotted on the horizontal scale, and the measure of the study size on the vertical axis. The points on this graph should look like a funnel and if they do not, then some studies may not have been found or published (Dawes et al. 2005).

Funnel plot asymmetry is equated with publication bias. The funnel plot is also seen as a generic means of displaying small study effects. There is a tendency for the intervention effects estimated in smaller studies to differ from those estimated in larger studies. Differences in methodological quality are an important potential source of funnel plot asymmetry. True heterogeneity in intervention effects may also lead to funnel plot asymmetry.

Visual interpretation of funnel plots is very subjective and its usefulness can be questioned. A test for funnel plot asymmetry formally examines whether the association between estimated intervention effects and a measure of study size is greater than might be expected by chance. The null hypothesis is that there are no small study effects. However, for various reasons, it is not possible to make definite recommendations on choice of tests for funnel plot asymmetry (Sterne et al. 2008). No test for funnel plot asymmetry was conducted here as it is best not to conduct such a test where there are a small number of trials or there is significant heterogeneity between trials (De Silva et al. 2013).

Sensitivity analysis

When review authors find evidence of small study effects, they should consider sensitivity analysis (Sterne et al. 2008). Software is used to semi-automate evidence-discovery and also synthesis (Tsafnat et al. 2013). RevMan will temporarily omit some of the studies used in an outcome from the analysis, allowing the performance of a sensitivity analysis (Review Manager, 2008). Sensitivity analysis examines how the results of the meta-analysis change under different assumptions. Lower quality studies can be excluded if enough higher quality studies are available allowing use of best

evidence (Treadwell et al. 2012). This concept of evidence prioritization is used by all systematic reviews and a sensitivity analysis was conducted as part of this doctoral project.

Summary

There is compelling evidence that publication and other reporting biases lead to over-optimistic estimations of intervention effects (Sterne et al. 2008). Because of this, comprehensive searching is vital. But this will not act as a barrier to some substantial, potential biases. For continuous outcomes, funnel plots and statistical tests for funnel plot asymmetry are valid but at least 10 studies are needed. This number was not available for the first two reviews conducted here.

3.8 Methodology of later systematic reviews

The generation-and-use cycle

Standard methods of meta-analysis are not always appropriate. Reviews vary in whether they aggregate or configure information. Diversity of approaches may add richness to systematic reviews (Gough et al. 2012). The later reviews presented as part of this thesis do not use meta-analyses. Sometimes simpler methods of representing findings from different studies, such as using median values and graphical representations, are more valuable (Brugha et al. 2012). The current chapter addressed the methodology associated with the first two systematic reviews and meta-analyses conducted as part of this doctoral project. The methods used with the systematic reviews that focus on RCTs and the methodology used in reviews that focus on other types of data are very

different. Elements of systematic review methodology associated specifically with the later systematic reviews, dealing with views and perspectives, are dealt with separately. The methodology of these reviews is presented in an integrated manner in the later, relevant chapters (Murray, 2011).

In the case of systematic reviews of outcome studies for which meta-analytic methods are not appropriate, effects may still be examined and categorized to provide a systematic assessment of the evidence available (Brugha et al. 2012). This occurs in the review of the very diverse interventions designed to enhance the uptake of evidence from systematic reviews and meta-analyses. This particular review is reported in a later part of this doctoral project.

Next chapter

This current chapter outlined the methodology used in systematic reviews. The next chapter reports specifically on the first two systematic reviews. The chapter presents tables outlining the characteristics of the included studies. It also describes data and analysis and presents a summary of findings together with the results of the first two reviews. Lastly, abstracts of the reviews are outlined followed by plain language summaries.

After knowledge generation, the relevant issue of knowledge translation is then addressed as part of the generation-and-use cycle (Gough et al. 2012). It is important that doctors, researchers, and patients benefit from knowledge generated from research (Brown, 2013). A sequential series of segregated reviews, relating to knowledge translation, are presented later, with each review further exploring aspects of a broad

research question (Gough and Thomas, 2012). These reviews provide useful information independently. Configuration rather than aggregation was predominantly used to present the findings of these later syntheses. This means that the findings of the primary studies were arranged or configured, rather than added together, in order to answer the review questions.

Finally, the series of systematic reviews addressing different aspects of review utilisation, an area within the scope of knowledge translation, are drawn together in a combined review. This final synthesis, using a mixed-methods approach, provides greater breadth and depth (Gough and Thomas, 2012). This last, mixed-knowledge review allows insight into why interventions to enhance uptake of evidence from reviews and meta-analyses are of variable effectiveness (Thomas et al. 2004).

CHAPTER 4

SYSTEMATIC REVIEWS:
CBT VERSUS ANTIDEPRESSANTS
COMBINATION TREATMENT VERSUS MONOTHERAPY

CONTENTS

4.1	Introduction	137
4.2	Results: antidepressants versus CBT systematic review	139
4.3	Sensitivity analysis: antidepressants versus CBT systematic review	157
4.4	Results: combination treatment versus monotherapy systematic review	160
4.5	Summary: CBT versus antidepressants systematic review	171
4.6	Summary of sensitivity analysis: antidepressants versus CBT review	173
4.7	Summary: combination treatment versus monotherapy systematic review	175
4.8	Author's conclusions: antidepressants versus CBT systematic review	178
4.9	Author's conclusions: combination treatment versus monotherapy review	187
4.10	Abstract	191
4.11	Plain language summary	195

The previous chapter gave an outline of the methodology employed in conducting systematic reviews and also meta-analyses. This chapter summarizes the results of the first two systematic reviews carried out comparing CBT and antidepressants. Tables are presented outlining the characteristics of the included studies, data and analysis are described, summary of findings tables are presented, and lastly, an abstract is documented together with a plain language summary.

4.1 Introduction

A requirement for earning trust in healthcare is a rigorous process of assembling, evaluating, and summarizing evidence. This requirement is satisfied by performing a systematic review (Ransohoff et al. 2013). The results section of a systematic review aims to summarize the quality and strength of a body of evidence in a clear and logical manner. And the results should be clearly reported (Brown et al. 2013). The text of a review tells the story, the tables summarise the data, while the figures illustrate (Murray, 2011).

The results section also tries explicitly to address the objectives of the review (Lang and Secic, 2006). The results are important as they guide the conclusion of the review and the conclusion should stand the test of time (Treadwell et al. 2012). Deviations from the protocol can also be specified in the results section, though no deviation from the protocols occurred in the reviews reported here.

The results section gives a summary of the results of the search strategy including how many references were retrieved from electronic databases and how many were considered as potentially eligible after screening (Higgins and Green, 2008). The date of the most recent search or update is specified. A list of the studies obtained, reviewed and excluded

is also maintained. Lastly, the studies included in the systematic review are reported (Lang and Secic, 2006).

Search methods for identification of studies

It is essential to identify as many relevant reports as possible in order to minimise selection bias (Hopewell et al. 2009). Seventeen databases were initially searched in the first two reviews outlined here. Nineteen databases were addressed in the succeeding knowledge translation systematic reviews, with their added emphasis on qualitative research and grey literature.

The search covered the full range of publication years available in each database up to December 2009 using a combination of index terms and text words derived from relevant articles previously identified. The electronic databases searched included The Cochrane Library, PubMed, Embase, PsycInfo, The Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. The grey literature search involved the Index to Theses in Great Britain and Ireland and ProQuest Dissertations & Theses Databases, Clinical Trials Registries, Conference Papers Index, Web of Science-Conference Proceedings Citation Index, the British Library, Centre for Reviews and Dissemination, National Guideline Clearinghouse, TRIP, and OpenSIGLE. Key words used included depression, antidepressants, cognitive-behaviour therapy, combination therapy and suitable synonyms.

In addition to the main search just described, later a further, briefer 'updated' search was conducted (Baker et al. 2010). This updated search, carried out at a later data following completion of the synthesis resulting from the main search, enables the reader to be kept

more current and informed of any new or ongoing studies which could temper their appreciation of the main search results. The 'updated' search was conducted in order to detect and list 'studies awaiting assessment' or 'ongoing studies'. These could then be mentioned and considered by the reader but not included in the already completed review. Baker and colleagues conducted such an 'updated search', in addition to their already completed synthesis, in their important review (Baker et al. 2010).

This writer repeated parts of the search for the period January 2010 to April 2012 in order to identify any potentially relevant, completed or on-going studies. This reviewer applied these same search strategies to PubMed and EMBASE, the two most productive databases in terms of reports of trials identified for inclusion in the review. Also searched were all active registers in the *meta*Register of controlled trials (http://www.controlledtrials.com/mrct/), in April 2012, for reports of trials to be listed under 'On-going studies' or 'Studies awaiting classification', to be available for an update of this review.

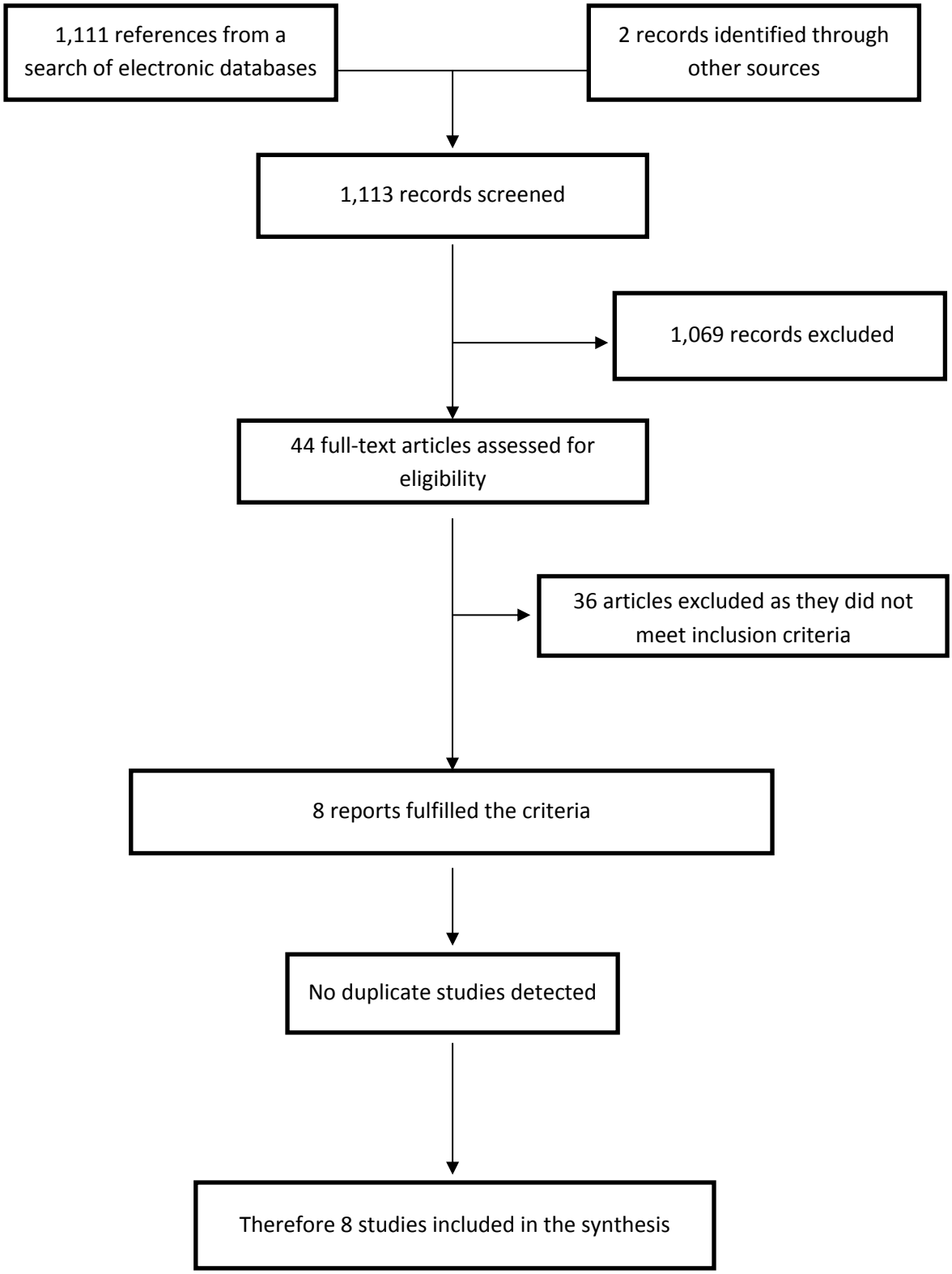
4.2 Summary of results

The search summary is divided into 4 parts: search of electronic databases for primary studies; search of reference lists of overviews for primary studies; search of reference lists of guidelines for primary studies; and lastly, a search of reference lists of textbooks for primary studies. Care was taken to identify studies that produced multiple publications so that these were not given undue weight in the analyses.

The study selection process for the systematic review comparing CBT and antidepressants is presented in Figure 4.1. The study selection process for the systematic

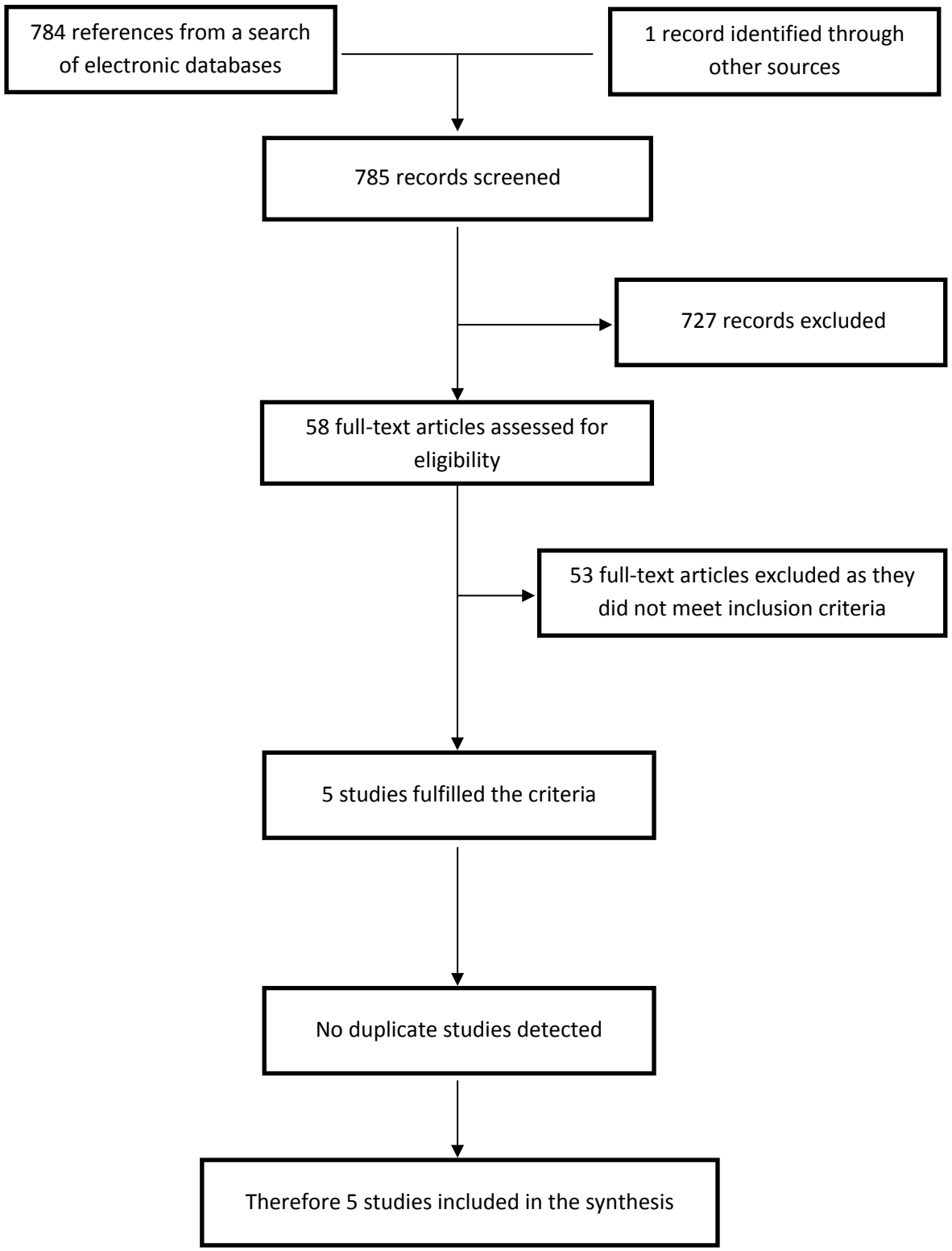
review comparing combination therapy and monotherapy is presented in Figure 4.2. The following flow diagrams document the literature retrieval process where titles, abstracts and full-text articles were reviewed (Lewis et al. 2012).

Figure 4.1 Search flow chart for the antidepressants versus CBT systematic review



All the relevant studies were retrieved by this writer and read by a second independent reviewer.

Figure 4.2 Search flow chart for the combination treatment versus monotherapy review



Appendix 1 lists excluded studies that might appear to be relevant but on closer inspection did not meet the strict inclusion criteria. In an effort to obtain a more clinically homogeneous sample several selection criteria were applied. To be included, a study had to compare CBT with antidepressant medication, or combination therapy versus either treatment alone. Studies were excluded if the focus of treatment was not on the efficacy of acute treatment. The methods sections of potentially eligible reports were checked for the specifics of the treatment regimen. The specific inclusion and exclusion criteria were detailed in the previous methodology chapter.

Tetzlaff recommends constructing a diagram documenting the process of literature retrieval including the number of citations identified during database searching, the number of citations screened, the number of articles assessed for eligibility, and lastly, the number of studies included in the review (Tetzlaff et al. 2009). In the CBT versus antidepressants systematic review, 1,113 records were identified from the search strategy (Figure 4.1). Following title screening for obvious lack of pertinence, 44 records were classified as potentially relevant. The full-text articles of these were read in order to assess their eligibility. Eight studies met the inclusion criteria.

Updated search

The *meta*Register of Controlled Trials (*m*RCT) is a platform that pools together several international trial sources. The *m*RCT provides a service to health professionals using evidence from controlled trials who want to be confident that they are aware of all of the trial evidence relevant to a particular question. It is an aid for those who want to make decisions in the light of information about relevant on-going research. The *m*RCT was initially created in response to an initiative taken in 1998 that brought together

representatives from the UK Medical Research Council, the National Health Service Executive, medical charities, pharmaceutical companies, the UK Cochrane Centre, and journals such as the British Medical Journal and The Lancet to ensure that trial information was made publicly available. Missing information is a routine barrier to knowledge transfer (Brown, 2013).

The six included registers, updated at least annually, were searched in April 2012 for studies relevant to the two systematic reviews conducted here. None of the 66 retrieved citations met inclusion criteria for either systematic review. A multi-field search of Embase in April 2012 for comparisons between CBT and antidepressants yielded 6 citations, none of which were relevant. Employing the PubMed database in April 2012, 123 citations were retrieved, none of which were pertinent. A search for reports addressing combination treatment and single therapy using Embase yielded 1 citation, but this report was not relevant. A search of PubMed for studies comparing single therapy with combination therapy yielded 123 citations, with none relevant to the focused research question posed here.

Forward citation search

In February 2014, a forward citation search was conducted using PubMed, advanced search format. This forward citation search yielded a total of 151 citations. Three of these were not detected previously and were retrieved in full text but none were eligible for inclusion. In February 2015, a further comprehensive forward citation search was carried out, including Web of Science and Scopus, and yielded 2,869 citations. The titles and abstracts of these were read, with 13 appearing relevant and full texts retrieved. Some primary studies were conducted after completion of the systematic reviews executed by

this writer and would fail to meet the strict inclusion criteria imposed by this writer's reviews, such as depression being uncomplicated by other psychiatric disorders (Huibers et al. 2014, Hollon et al. 2014), while another study was a cost effectiveness investigation (Sava et al. 2009). Just one study met this writer's strict inclusion criteria (Shamsaei et al. 2008). This and other studies are drawn on later in the Discussion section to frame the results of the systematic reviews completed and reported here.

Summary of results

Reviewers should strive to employ a comprehensive search strategy (Brugha et al. 2012). Following an extensive search conducted for the first systematic review comparing CBT and antidepressants, from a total of 1,113 citations, just 8 primary studies met the selective inclusion criteria. These studies included a total of 909 participants. Following an extensive search conducted for the second systematic review comparing combination treatment and mono-therapy, from a total of 785 citations, just 5 primary studies met the inclusion criteria. These studies included 345 participants, with different proportions of this number contributing to the different outcome measures. One study did not contribute to the meta-analysis as it did not yield usable data (Blackburn et al. 1981). It was possible to calculate post-test effect sizes in 7 studies addressing CBT versus antidepressant treatment and 4 studies addressing single versus combination therapy. The next stage of the review process involved data collection and assessment of the risk of bias.

In the CBT and antidepressant comparison, the age range was 18 to 65 years and 64% of the participants were female. All studies were published in English. Duration of treatment ranged from 10 to 16 weeks, with an average of 13.4 weeks. In the comparison between

single therapy versus combination therapy, some 79% of participants were female. Duration of treatment ranged from 18 days to 12 weeks with an average of 9.6 weeks.

Process

Two distinct processes were required to decide which studies could be included in the reviews. First, this writer linked together multiple reports of the same study because studies, not reports, were the unit of interest in the two reviews described here. The aim was to avoid the bias of including studies more than once in the meta-analysis (Tramer, 1997). The next step was to use the information available in the various reports to determine which studies were eligible for inclusion before proceeding to a risk of bias assessment for each included study.

Risk of bias

A bias appraisal process allows us to judge the value of papers with respect to their contribution to the synthesis (Lawrence et al. 2012). The Cochrane risk of bias tool was initially released in 2008 with Review Manager 5.0 (Hrobjartsson et al. 2013). The risk of bias was investigated here for both outcome measures, BDI and HDRS, using continuous and then dichotomous data.

In the CBT versus antidepressant comparison, the majority of studies reported sequence generation as adequate. No study was judged to have a low risk of bias because they had executed adequate allocation concealment.

A relatively low risk of bias through blinding was achieved in studies with the clinician-rated HDRS. Importantly, the majority of reports scored a low risk of bias from incomplete outcome data, selective outcome reporting or other sources of bias.

In the second comparison between combination treatment and single therapy, the risk of bias was again investigated. The method of sequence generation was unclear in all studies, with no study achieving a low risk of bias by executing adequate allocation concealment. Many studies had a high risk of bias from inadequate blinding. Most studies, however, achieved a low risk of bias under the headings of incomplete outcome criteria, selective outcome reporting or other sources of bias.

Having summarised the risk of bias for each outcome measure, this assessment was then used to inform the summary of findings table, outlined later (Higgins and Altman, 2008). First though, the characteristics of the included studies are described.

Characteristics of included studies

Characteristics of included studies tables present information on individual investigations. Table 4.1 shows the characteristics of included studies for the 8 studies in the systematic review comparing CBT versus antidepressants. These tables present the main findings of the reviews in a transparent form. The aim of a systematic review is to produce optimally useful information (Schunemann et al. 2008).

Table 4.1. Characteristics of studies comparing CBT and antidepressants

Study	Country	Participants entering study	Interventions	Outcome Measures
Rush et al. 1977	USA	18-65yrs 41 participants	Imipramine (75-250mg) CBT: over 12 weeks, max of 20 sessions. Inexperienced therapists.	BDI HDRS
McLean & Hakstian 1979	Canada	20-60yrs 178 participants	Amitriptyline (150mg fixed) CBT: over 10 weeks, max 12 sessions, session of 60 mins duration. On-going training provided to therapists.	BDI
Blackburn et al. 1981	Scotland	18-65 yrs 88 participants	Amitriptyline/ Clomipramine (150mg) CBT: over 12 weeks, max 15 sessions. Competent therapists.	BDI HDRS
Murphy et al. 1984	USA	18-60yrs 87 participants	Nortriptyline Blood levels: (50-150ng/mL) CBT: over 12 weeks, 50 mins duration. Competent therapists.	BDI HDRS
Elkin et al. 1989	USA	Av Age; 35yrs 250 participants	Imipramine (185mg average) CBT: over 6 weeks, 50 mins duration. Experienced therapists.	BDI HDRS
Hollon et al. 1992	USA	18-62yrs 107 participants	Imipramine (200-300mg) CBT: over 12 weeks, max of 20 sessions, 50 mins duration. Experienced therapists.	BDI HDRS

Scott & Freeman 1992	Scotland	18-65yrs 121 participants	Amitriptyline (150mg) Flexible dosing CBT: over 16 weeks, 50 mins duration. Experienced therapists.	HDRS
Murphy et al. 1995	USA	18-60yrs 37 participants	Desipramine (150-300mg) CBT: over 16 weeks, 50 mins duration. Competent therapists.	BDI HDRS

The characteristics of the 5 studies included in the systematic review comparing combination treatment and monotherapy are listed in Table 4.2, following which the summary of findings' tables are outlined.

Table 4.2. Studies included in the comparison between combination therapy and single treatment

Study	Country	Participants	Interventions	Outcome
Blackburn et al. 1981	Scotland	18-65 yrs 88 participants	Combination Treatment Vs Clomipramine/ Amitriptyline CBT: over 12 weeks, Max 15 sessions. Competent therapists.	BDI HDRS
Murphy et al. 1984	USA	18-60yrs 87 participants .	Combination treatment Vs Nortriptyline Vs CBT: over 12 weeks, session: 50 mins duration. Competent therapists.	BDI HDRS
Beck et al. 1985	USA	20-65yrs 33 participants	Combination Treatment Vs CBT: over 12 weeks, max of 20 sessions. Experienced therapists.	BDI HDRS
Bowers, 1990	USA	18-60yrs 30 participants	Combination Treatment Vs Nortriptyline CBT: over 4 weeks, 12 sessions. Experienced therapist.	BDI HDRS
Hollon et al. 1992	USA	18-62yrs 107 participants	Combination Treatment Vs Imipramine CBT: over 12 weeks, max of 20 sessions, 50 mins duration. Experienced therapists.	BDI HDRS

Summary of findings tables

The first question addressed here was whether the experimental treatment, CBT, was more or less effective than the accepted treatment for a disorder. Antidepressant medication is a

generally accepted standard treatment for depression and provides the customary comparison standard (Kingdom, 2013). The second question dealt with here addressed whether the combination treatment was more or less effective than single therapy. The summary of findings tables follow. First, a summary of findings table is presented addressing the BDI results initially and then the HDRS, using a fixed-effect analysis (Table 4.3). The quality of evidence summary assessment is taken from the systematic risk of bias inquiry already conducted.

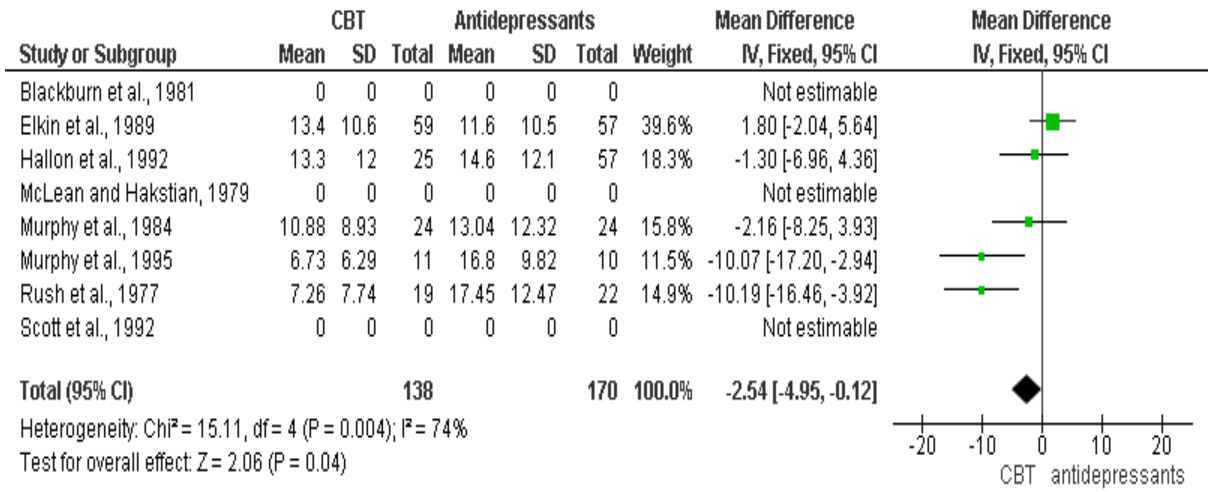
Table 4.3. Summary of Findings Table: CBT versus antidepressants, fixed-effect model

Patients: Individuals with diagnosed depression
Settings: Both inpatients and outpatients
Intervention: Cognitive-behaviour therapy
Comparison: Antidepressants

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -2.54 CI = -4.95, -0.12 P=0.04 I^2 = 74%.	308 participants 5 studies	Low	Rush study is at risk of bias. CBT superior: Stat sig diff
BDI Dichotomous data	RR = 0.77 CI = 0.63, 0.93 P = 0.008 I^2 = 63%.	383 participants 6 studies	Low	Rush study is at risk of bias. CBT superior: Highly stat sig
HDRS Continuous data	MD = -2.13 CI = -3.67, -0.59 P = 0.007 I^2 = 57%.	358 participants 6 studies	Low	Rush study is at risk of bias. CBT superior: Highly stat sig
HDRS Dichotomous data	RR = 1.01 CI = 0.83, 1.23 P = 0.90 I^2 = 34%.	309 participants 5 studies	Moderate	Rush study is not included. No Tx favoured. No stat diff.

Graphic descriptions of the above fixed-effect analyses are given below in the form of forest plots (Figures 4.3-4.6).

Figure 4.3 CBT Vs antidepressants, fixed-effect model, BDI, continuous data



Next dichotomous data is addressed employing the BDI.

Figure 4.4. CBT Vs antidepressants, fixed-effect model, BDI, dichotomous data

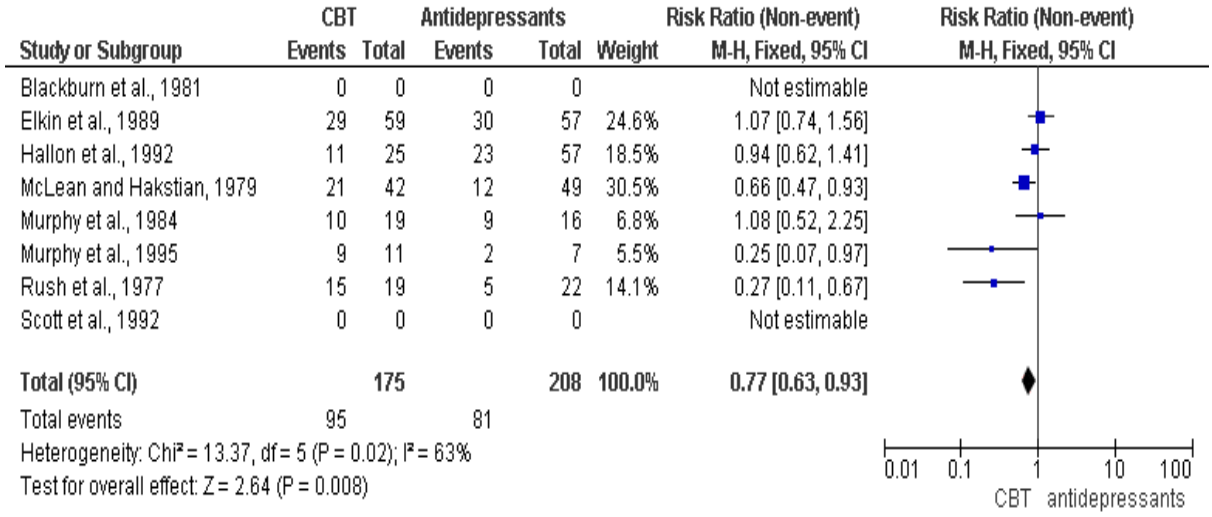
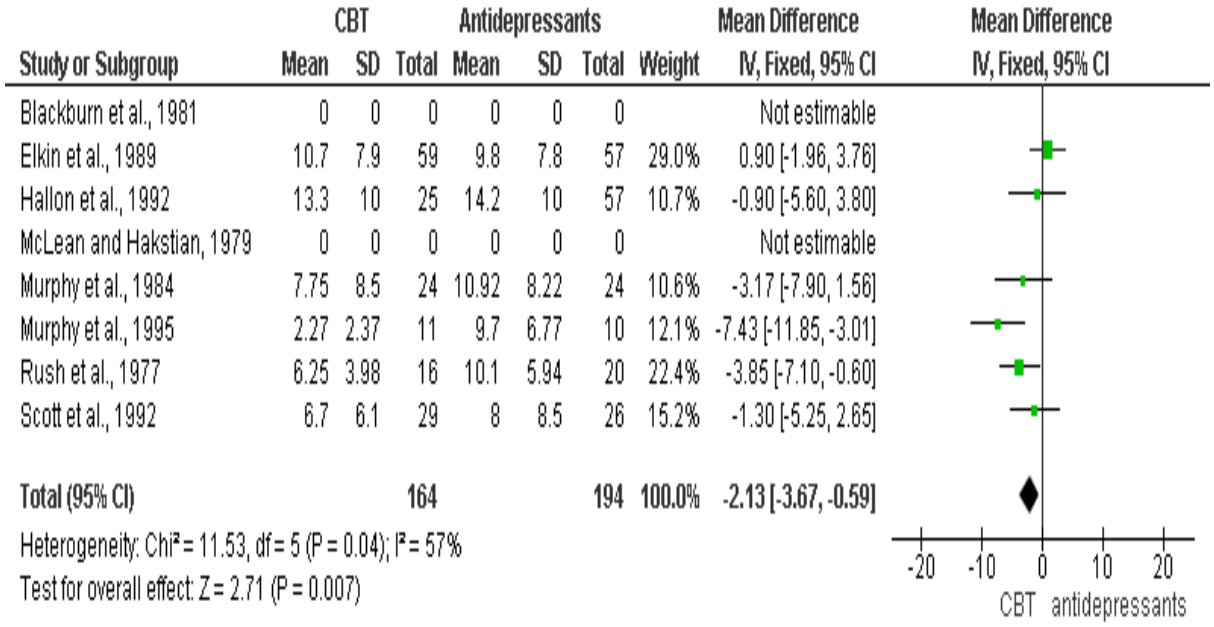
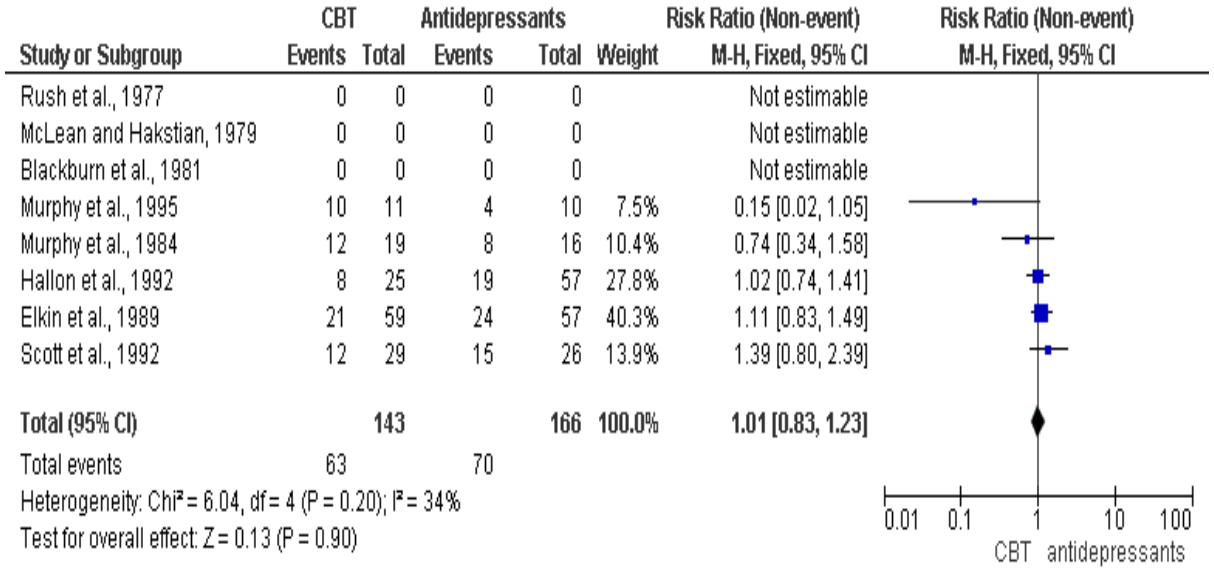


Figure 4.5 CBT Vs antidepressants, fixed-effect model, HDRS, continuous data



The HDRS analysis is graphically represented in Figures 4.5 and 4.6.

Figure 4.6 CBT Vs antidepressants, fixed-effect model, HDRS, dichotomous data



A summary of findings table using a random-effects model is now presented (Table 4.4).

Table 4.4. Summary of findings table: CBT versus antidepressants, random-effects model

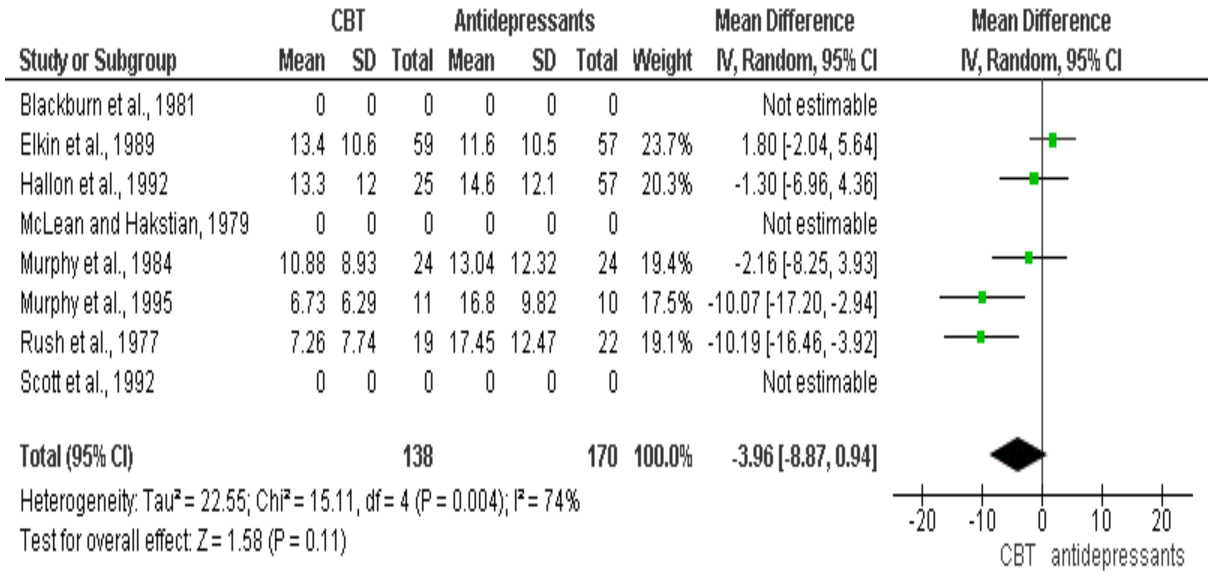
Patients: Individuals with diagnosed depression
Settings: Both inpatients and outpatients
Intervention: Cognitive-behaviour therapy
Comparison: Antidepressants

Random-effects model

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -3.96 CI = -8.87, 0.94 Z = 1.58 (P = 0.11)	308 participants 5 studies	Low	Rush study at risk of bias. CBT favoured. Not stat sig.
BDI Dichotomous data:	RR=0.73 CI =0.51, 1.06 Z = 1.65 (P = 0.10)	383 participants 6 studies	Low	Rush study at risk of bias. CBT favoured. Not stat sig.
HDRS Continuous data	MD = -2.45 CI = -4.85, -0.04 Z = 2. 00 (P = 0.05)	358 participants 6 studies	Low	Rush study at risk of bias, CBT favoured. Stat sig.
HDRS Dichotomous data	RR= 1.04 CI = 0.79, 1.36 Z = 0.26 (P = 0.80)	309 participants 5 studies	Moderate	Rush study not included. Neither Tx favoured. No stat sig diff.

The following figures graphically represent analyses using a random-effects model.

Figure 4.7 CBT versus antidepressants, BDI, random-effects model, continuous data



The analysis utilising the BDI is graphically represented first.

Figure 4.8 CBT versus antidepressants, BDI, random-effects model, dichotomous data

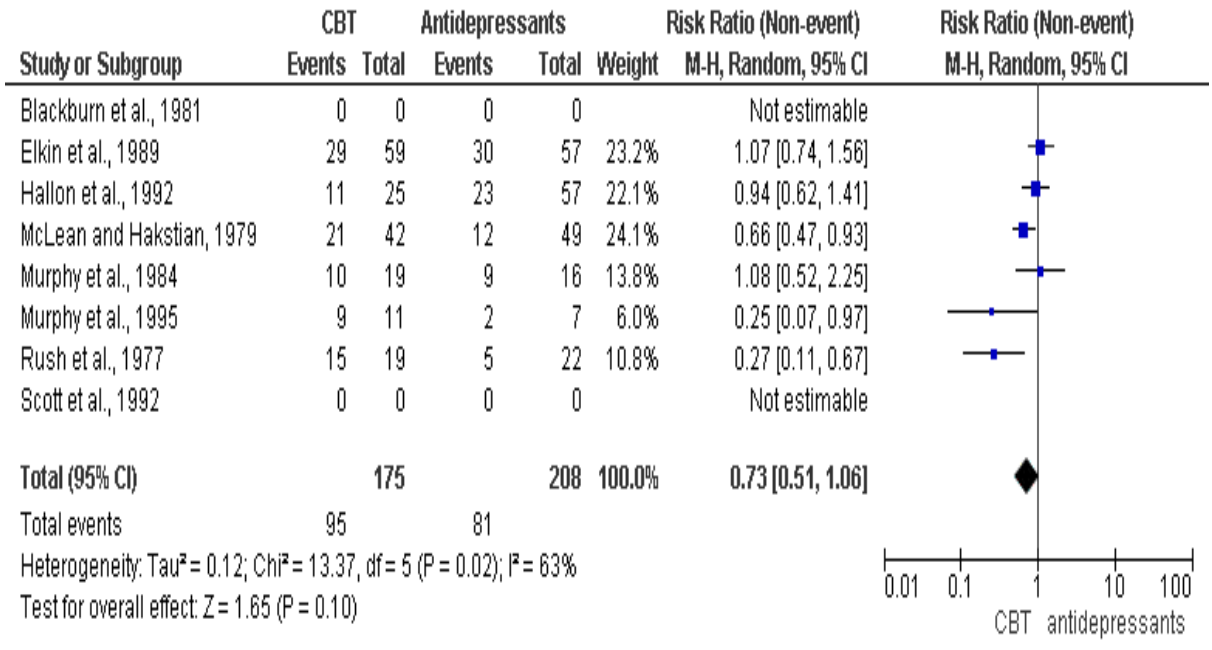
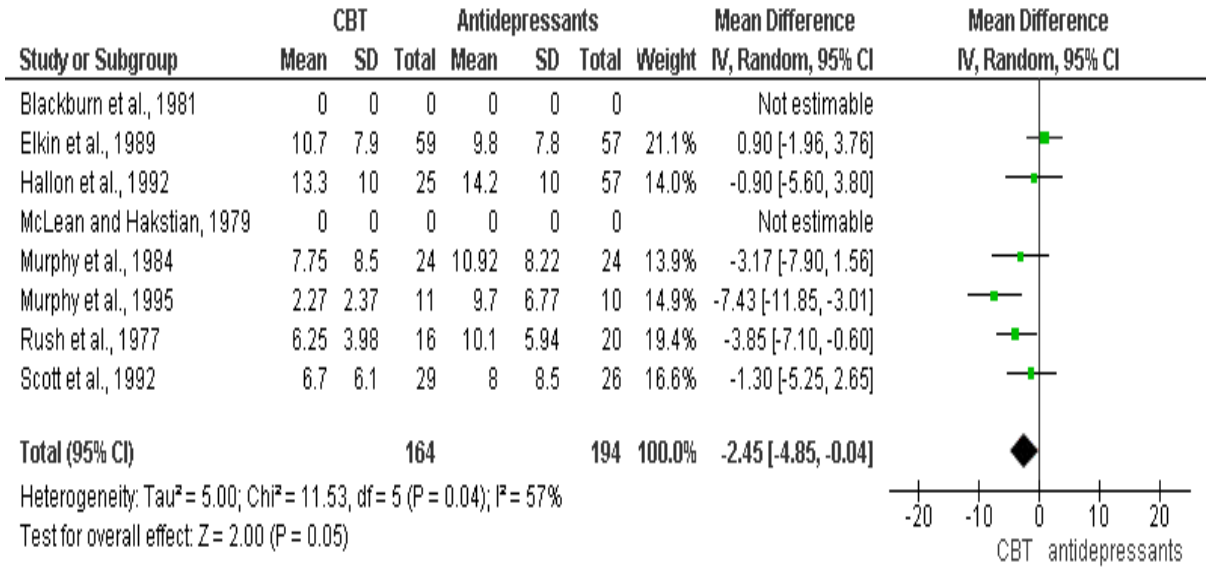
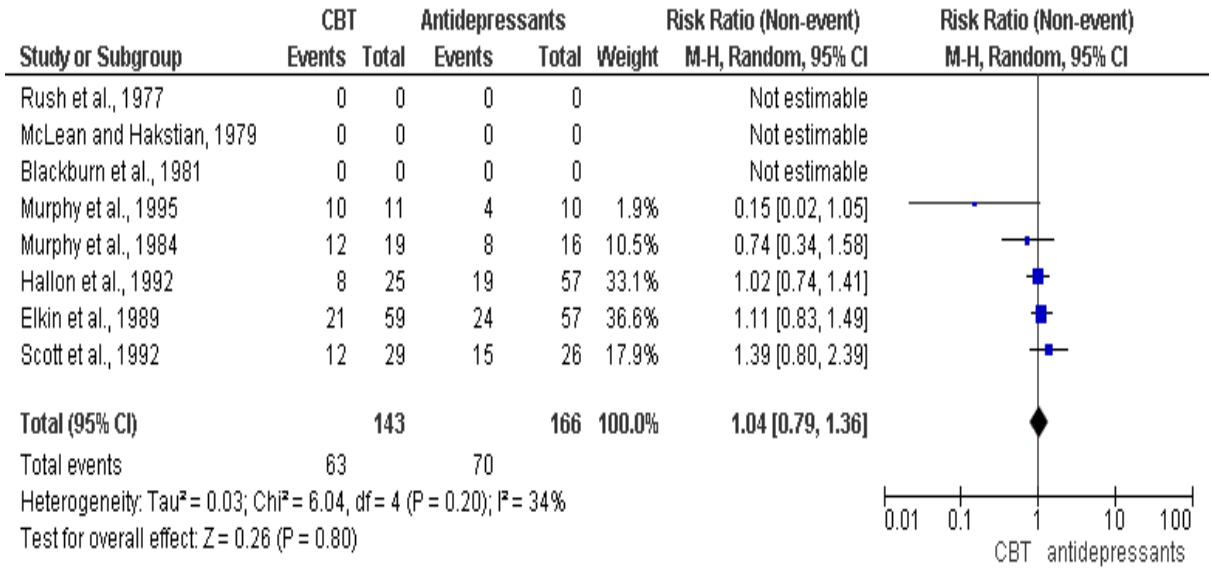


Figure 4.9 CBT versus antidepressants, HDRS, random-effects model, continuous data



Here in figures 4.9 and 4.10, the analyses utilising the HDRS are illustrated.

Figure 4.10 CBT versus antidepressants, HDRS, random-effects, dichotomous data



In summary, using a fixed-effect model, the bulk of the evidence favours CBT over antidepressants and the difference on 3 of the 4 outcome measures is statistically significant. Using a random-effects model, the evidence favours CBT on 3 outcome measures, though the difference is statistically significant on just one measure.

Because the primary studies measured the same outcome, depression, and used the same psychometric scales (BDI and HDRS), the mean difference was favoured here for analysis of continuous data.

4.3 Sensitivity analysis for CBT versus antidepressants systematic review

In sensitivity analysis informal comparisons are made between different ways of estimating the same thing (Deeks et al. 2008). We are interested in finding out if the results are robust to the decisions made in the process of obtaining them. The sensitivity analysis tells us about the degree of certainty of the results. It informs us about the degree of caution needed to interpret the findings.

With the Rush study, this reviewer was concerned about outcome characteristics, a reasonable concern to justify a sensitivity analysis (Deeks et al. 2008). This issue, suitable for sensitivity analysis, was identified during the review process due to the features of the study involved in which, before the patients receiving antidepressants were finally assessed, their treatment medication was being withdrawn or stopped (Rush et al. 1977). This has clinical implications.

Table 4.5. Summary of findings: CBT versus antidepressants, Rush study excluded

Fixed-effect Model

Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: cognitive-behaviour therapy
Comparison: antidepressants

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -1.20 CI=-3.82, 1.42 Z = 0.9 (P=0.37)	267 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
BDI Dichotomous data .	RR =0.85 CI = 0.65, 1.04 Z = 1.61 (P=0.11)	342 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
HDRS Continuous data	MD =-1.63 CI =-3.38, 0.11 Z = 1.88 (P=0.07)	358 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
HDRS Dichotomous data	RR = 1.01 CI = 0.83, 1.23 Z = 0.13 (P=0.90)	309 participants 5 studies	Moderate	Rush study not included. Neither favoured.

At the end of the Rush study, the mean BDI scores of the antidepressant group increased by 2.43 while that of the CBT group decreased by 2.17. The depression scores of the antidepressant group worsened while the scores of the CBT patient improved. Rush suggests that future studies should maintain the pharmacology patients at full dosage until the study is completed.

By excluding the Rush study, this writer wanted to assess whether the results and conclusion were affected by the decision to include it. First, a summary of findings table (Table 4.5) without the Rush study, was generated, first using a fixed-effect model (Deeks et al. 2008). CBT is favoured on 3 of the outcome measures but the difference is no longer statistically significant. Next, a summary of findings table, without the Rush study, was generated using a random-effects model (Table 4.6).

Table 4.6. Summary of findings: CBT versus antidepressants, Rush study excluded

Random-effects model

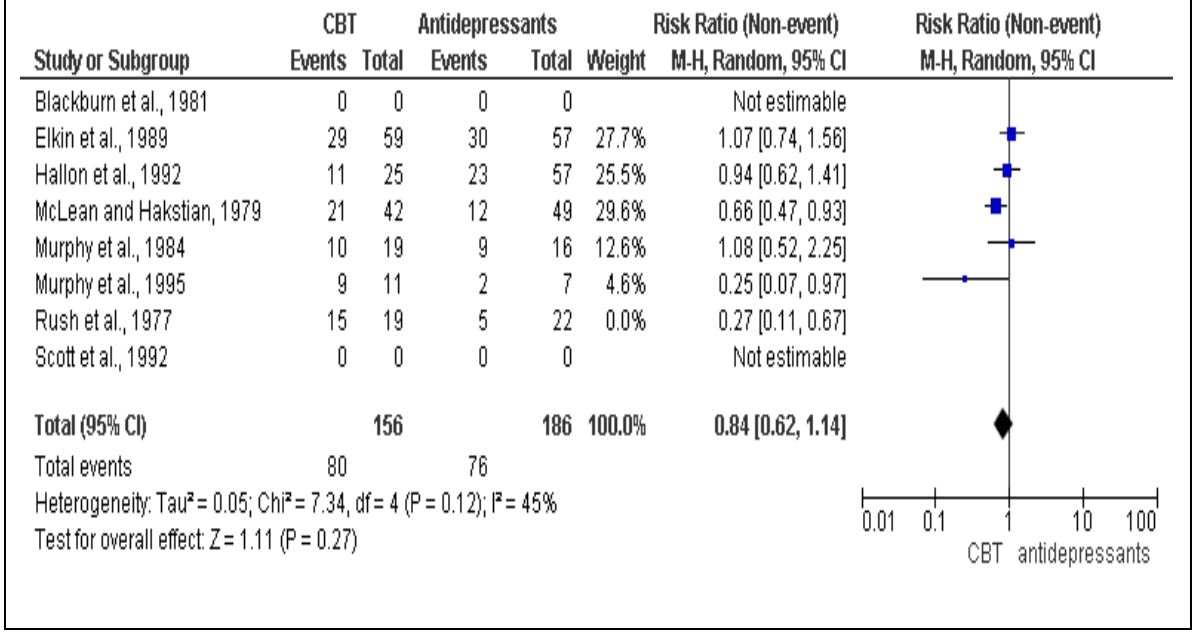
Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: cognitive-behaviour therapy
Comparison: antidepressants

Random-effects model

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -2.23 CI = -6.95, 2.30 Z = 0.99 (P=0.32)	267 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
BDI Dichotomous data	RR= 0.84 CI = 0.62, 1.14 Z = 1.11 (P=0.27)	342 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
HDRS Continuous data	MD = -2.15 CI = -5.03, 0.73 Z = 1.46 (P=0.14)	322 participants 5 studies	Moderate	Rush study excluded. CBT favoured. Not stat sig.
HDRS Dichotomous data	RR= 1.04 CI = 0.79, 1.36 Z = 0.26 (P=0.80)	309 participants 5 studies	Moderate	Rush study excluded. No treatment favoured.

Using a random-effects model, with the Rush study excluded, CBT is favoured on 3 of the outcome measures, but the difference is not statistically significant. Figure 4.11, an example forest plot drawn from the sensitivity analysis, graphically illustrates an analysis using the BDI as an outcome measure, drawing on dichotomous data, and utilising the random-effects model.

Figure 4.11 CBT versus antidepressants, BDI, random-effects model, dichotomous data, Rush study excluded



Summary of sensitivity analysis: Using a fixed-effect model and a random-effects model, with the Rush study excluded, CBT is favoured over antidepressants on 3 of the outcome measures, but the difference is no longer statistically significant.

4.4 Results of combination treatment versus monotherapy systematic review

A similar format is used here to present the results of the combination treatment versus monotherapy systematic review. As with the previous systematic review, this writer first

looked at the BDI, then the Hamilton (HDRS), in terms of continuous and then dichotomous data (Box 4.1 and Box 4.2).

Box 4.1. Format used to present results of the systematic review

Scale	Type of Data
BDI:	Continuous Data Dichotomous Data
HDRS:	Continuous Data Dichotomous Data

Here this writer was concerned to compare combination treatment with single therapy, first CBT and then antidepressants.

Box 4.2. Comparisons used for combination treatment versus single therapy systematic review

Combination treatment versus single therapy:
Combination treatment versus CBT
Combination treatment versus antidepressants

A summary of findings table was drawn up for this review addressing combination treatment and monotherapy. A fixed-effect model was employed first, then a random-effects model. Initially, combination treatment was compared with CBT and then antidepressants on the BDI and then HDRS, using a fixed-effect model. Here we address the summary results regarding two issues: (A) Combination Treatment versus CBT (Box 4.3) and (B) Combination treatment versus antidepressants using a fixed-effect model (Box 4.4).

Box 4.3. First comparison: Combination treatment versus CBT, fixed-effect model

Combination treatment versus CBT, BDI - continuous data
Combination treatment versus CBT, BDI - dichotomous data

Combination treatment versus CBT, HDRS - continuous data
Combination treatment versus CBT, HDRS - dichotomous data

Box 4.4 outlines a comparison between combination therapy with antidepressants, rather than CBT, using a fixed-effect model

.

Box 4.4 Second Comparison: Combination treatment versus antidepressants, fixed-effect model

Combination treatment versus antidepressants, BDI - continuous data
Combination treatment versus antidepressants, BDI - dichotomous data

Combination treatment versus antidepressants, HDRS - continuous data
Combination treatment versus antidepressants, HDRS - dichotomous data

---

First, this writer presents a summary of findings' table comparing combination treatment versus CBT. Two outcome measures are addressed, the BDI and HDRS, using continuous and then dichotomous data.

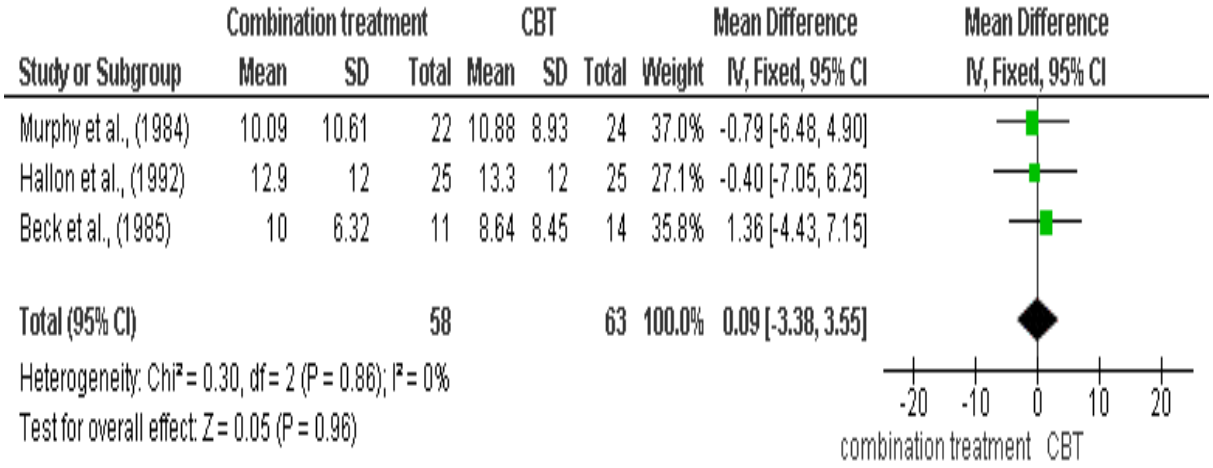
Table 4.7. Summary of findings: combined treatment compared with CBT in depression using a fixed-effect model

Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: Combination treatment
Comparison: CBT

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = 0.09 CI = -3.38, 3.55 (P = 0.96) I^2 = 0%.	121 3 studies	Moderate	Combined Tx is not superior. No significant Difference.
BDI Dichotomous data	RR =0.97 CI = 0.68, 1.39 (P =0.87) I^2 =61%.	121 3 studies	Moderate	Combination Tx is not superior. No significant Difference.
HDRS Continuous data	MD = 0.58 CI = -2.90, 1.73 (P = 0.62) I^2 = 0%.	119 3 studies	Moderate	Favours combination Tx. But no significant Difference.
HDRS Dichotomous data	RR = 0.72 CI = 0.46, 1.12 (P = 0.15) I^2 = 0%.	87 2 studies	Moderate	Favours combination Tx. But no significant Difference.

Using the fixed-effect model, there is a slight trend in favour of combination treatment over CBT, but it is not statistically significant. Figure 4.12 offers a graphic example of an analysis comparing combination treatment and CBT in terms of continuous data, with the fixed-effect model employed.

Figure 4.12 Combination treatment versus CBT, BDI, fixed-effect, continuous data



Next, again using a fixed-effect model, a comparison was made between combination treatment and, this time, antidepressants using the outcome measures BDI and HDRS, utilising continuous and then dichotomous data.

Table 4.8. Summary of findings: combined treatment compared with antidepressants in depression using a fixed-effect model

Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: Combination treatment
Comparison: Antidepressants

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -4.46 CI =-8.32,-0.60 (P=0.02) I^2 = 63%.	148 3 studies	Moderate	Combination Tx superior. Significant difference.
BDI Dichotomous data	RR = 0.58 CI = 0.38, 0.86 (P = 0.007) I^2 = 70%.	136 3 studies	Moderate	Combination Tx superior. Highly significant difference.
HDRS Continuous data	MD = -2.90 CI = -5.58,-0.22 (P=0.03) I^2 = 0%	148 3 studies	Moderate	Combination Tx superior. Significant difference.
HDRS Dichotomous data	RR = 0.59 CI =0.40, 0.86 (P = 0.007) I^2 = 9%.	136 3 studies	Moderate	CombinationTx . Highly significant difference

Here, combination treatment appeared superior to antidepressants on the two outcome measures, the BDI and HDRS, in an analysis of both continuous and dichotomous data. The difference was statistically significant in all cases and highly significant when dichotomous data is analysed using a fixed-effect model. Figure 4.13 exemplifies the results of the combination treatment versus antidepressants comparison using the BDI as the outcome measure with continuous data.

Figure 4.13 Combination versus antidepressants, BDI, fixed-effect, continuous data

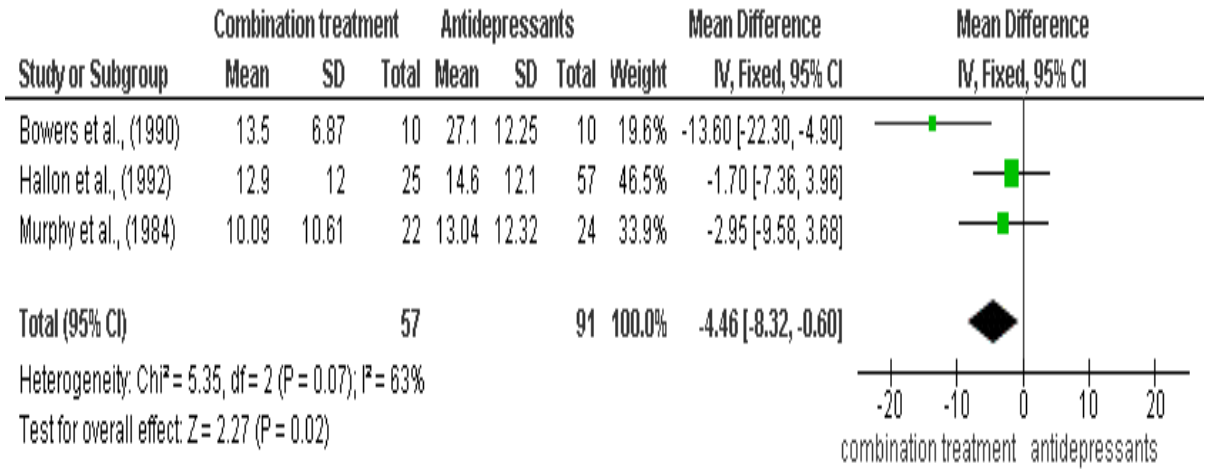
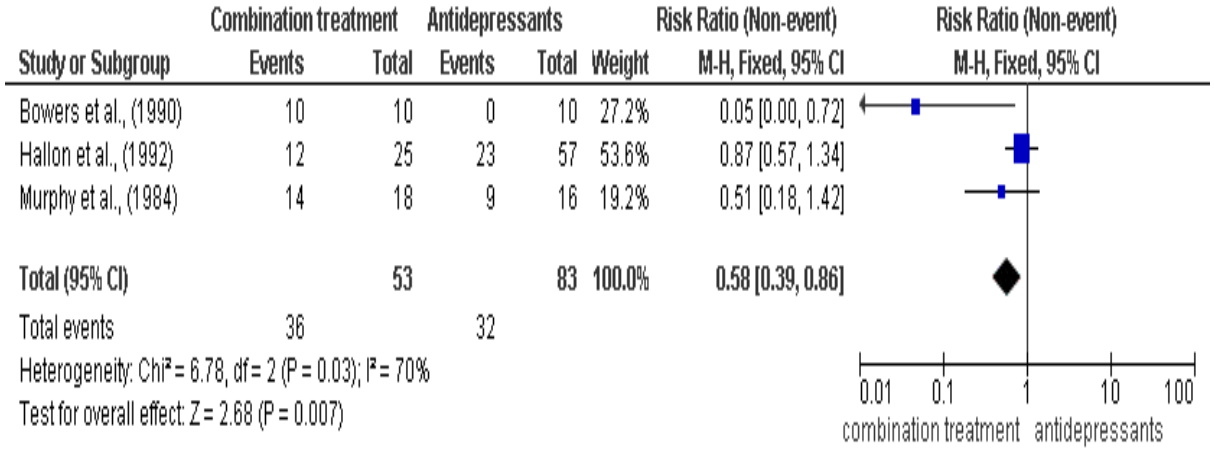


Figure 4.14 exemplifies an analysis of the combination treatment versus antidepressants comparison, using the BDI as the outcome measure, with dichotomous data.

Figure 4.14 Combination versus antidepressants, BDI, fixed-effect, dichotomous data



Next the analyses were carried out using a random-effects model.

Table 4.9. Summary of findings table: combined treatment compared with CBT in depression using a random-effects model

Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: Combination treatment
Comparison: CBT

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = 0.09 CI = -3.38, 3.55 (P = 0.96) I^2 = 0%	121 participants 3 studies	Moderate	Combination Tx not superior. No significant difference.
BDI Dichotomous data	RR = 0.98 CI = 0.53, 1.82 (P=0.95) I^2 =61%	120 3 studies	Moderate	Combination Tx not superior. No significant difference.
HDRS Continuous data	MD = -0.58 CI = -2.90, 1.73 (P=0.62) I^2 =0%	119 3 studies	Moderate	Favours Combination Tx. No significant difference.
HDRS Dichotomous data	RR = 0.72 CI = 0.46, 1.11 (P=0.13) I^2 = 0%	87 2 studies	Moderate	Favours Combination Tx. No significant difference.

Using a random-effects model, combination treatment does not appear superior to CBT on the BDI (Figures 4.15 and 4.16). The results favour combination treatment over CBT on the HDRS (Figures 4.17 and 4.18), but the difference was not statistically significant.

Figure 4.15 Combination versus CBT, BDI, random-effects model, continuous data

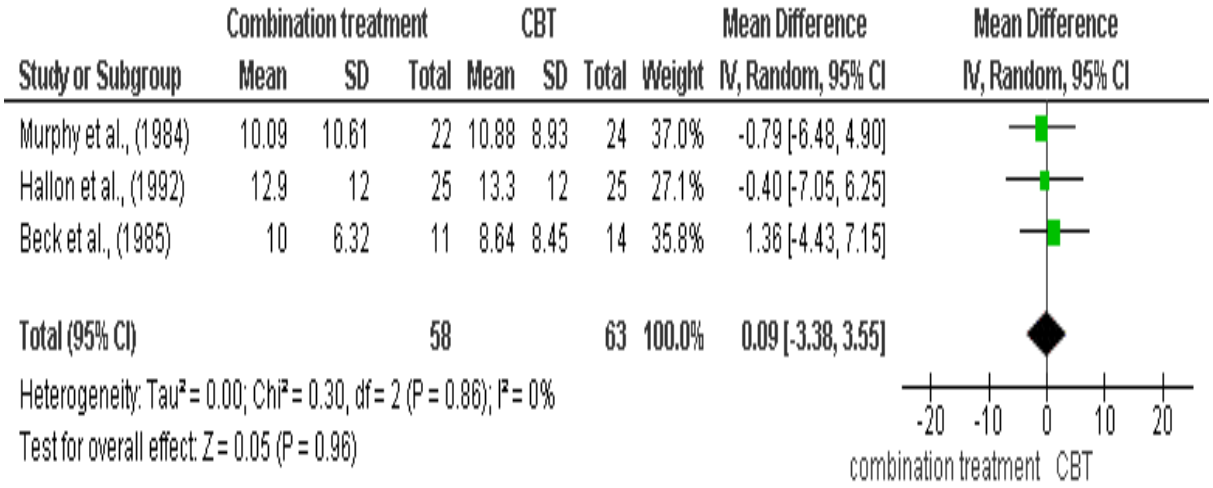
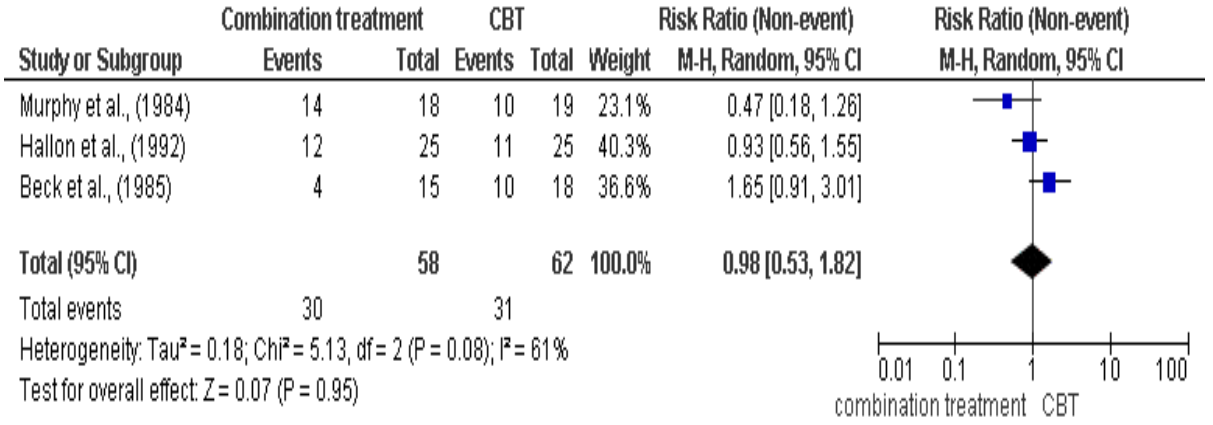
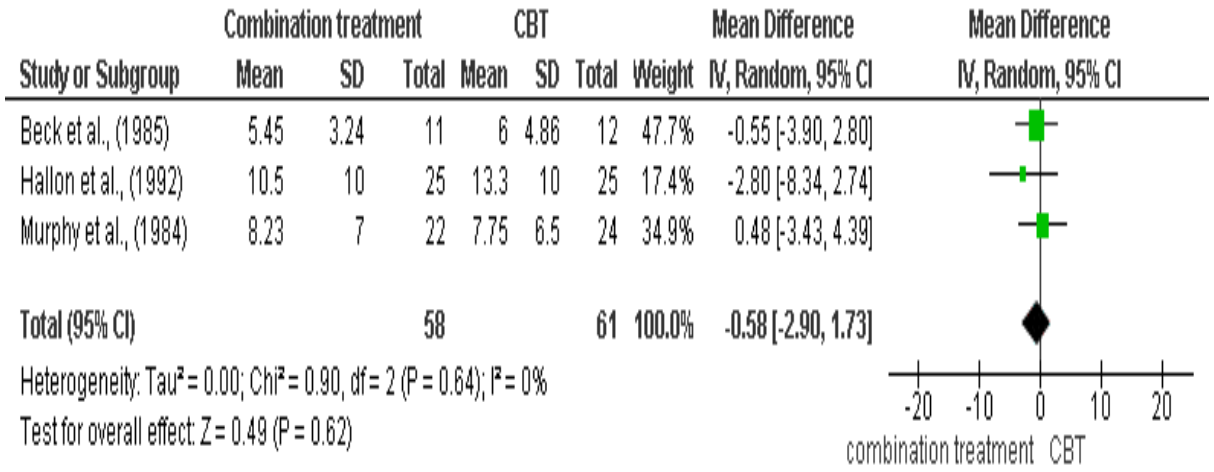


Figure 4.16 Combination versus CBT, BDI, random-effects model, dichotomous data



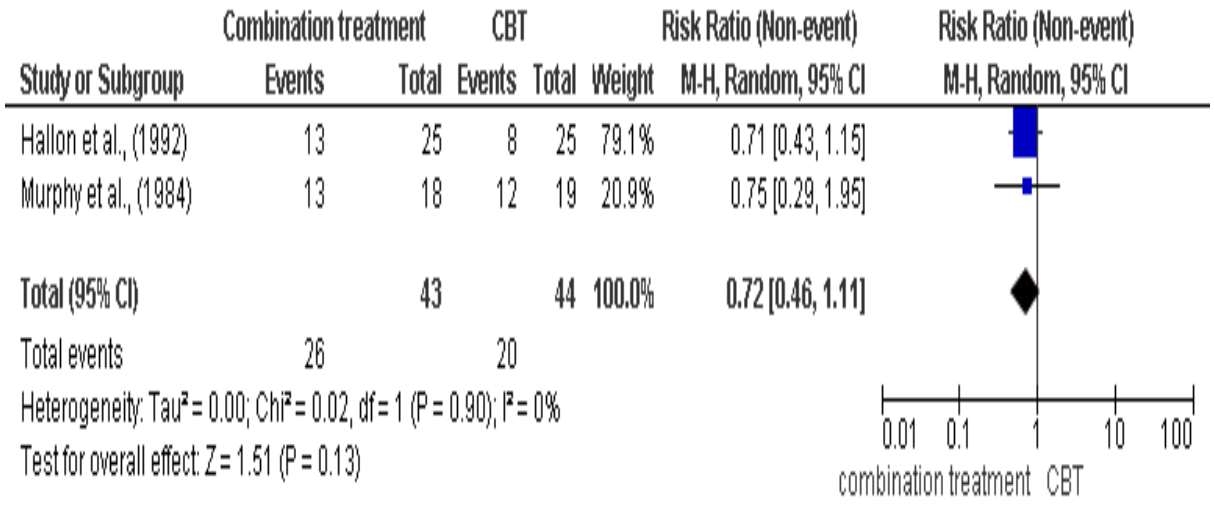
Figures 4.17 and 4.18 illustrate the results of the comparison of combination treatment versus CBT this time using the HDRS as an outcome measure, with continuous and then dichotomous data.

Figure 4.17 Combination versus CBT, HDRS, random-effects model, continuous data



Next, dichotomous data is employed.

Figure 4.18 Combination versus CBT, HDRS, random-effects, dichotomous data



Next, again using the random-effects model, combination treatment was compared this time with antidepressants.

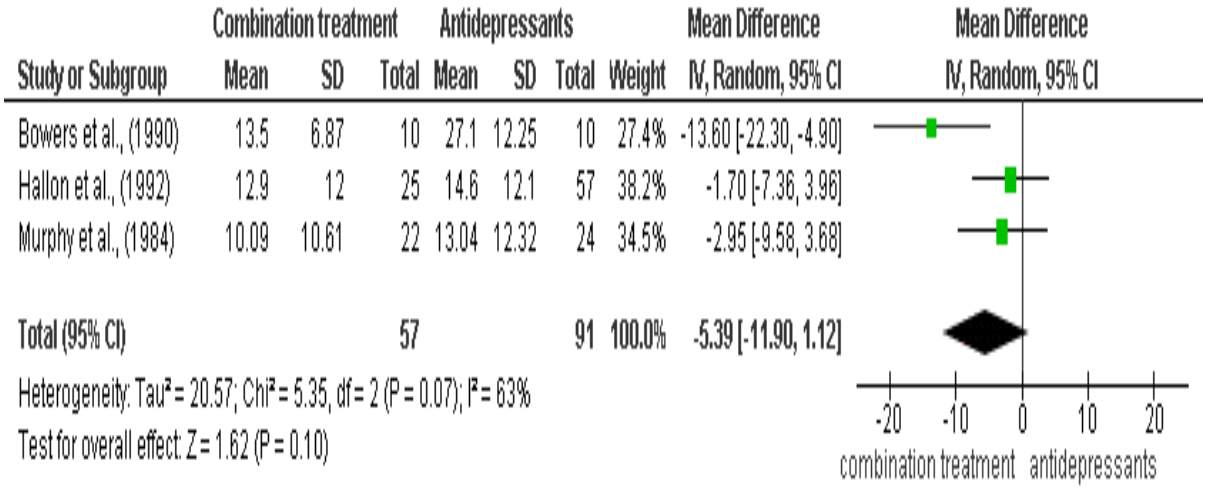
Table 4.10. Combined treatment compared with antidepressants in depression using a random-effects model

Patients: individuals with diagnosed depression
Settings: both inpatients and outpatients
Intervention: Combination treatment
Comparison: Antidepressants

Outcome	*Effect*	*Number of participants*	*Quality of evidence*	*Comments*
BDI Continuous data	MD = -5.39 CI = -11.90, 1.12 (P = 0.10)	148 3 studies	Moderate	Combination Tx favoured. Not significant.
BDI Dichotomous data	RR = 0.48 CI = 0.15, 1.54 (P = 0.22)	136 3 studies	Moderate	Combination Tx favoured. Not significant.
HDRS Continuous data	MD = -2.90 CI = -5.58, -0.2 (P=0.03)	148 3 studies	Moderate	Combination Tx superior. Statistically significant.
HDRS Dichotomous data	RR = 0.59 CI = 0.36, 0.96 (P = 0.03)	136 3 studies	Moderate	Combination Tx. superior. Statistically significant.

Using a random-effects analysis, the comparison between combination treatment and antidepressants yielded results favouring combination treatment. On the BDI, the difference was not statistically significant as illustrated for example in Figure 4.19, but on the clinician-rated HDRS, the difference was statistically significant.

Figure 4.19 Combination versus antidepressants, BDI, random-effects, continuous data



A summary of each meta-analysis is now presented.

4.5 Summary of CBT versus antidepressants systematic review

Fixed-effect model

Using a fixed-effect model, comparing CBT and antidepressants on the BDI, CBT appears more efficacious than antidepressants. The difference is statistically significant when continuous data are used from the 5 studies involving 308 participants. The difference is highly statistically significant when dichotomous data are analysed from 6 available studies involving 383 participants.

Using the fixed-effects model, comparing CBT and antidepressants on the HDRS, the difference between the two treatments is highly statistically significant when continuous data is addressed from the 6 studies involving 385 participants. When dichotomous data

was analysed, no treatment is favoured on the HDRS from 5 studies involving 309 participants.

Using a fixed-effect model, the bulk of the evidence favours CBT over antidepressants and the difference on three of the four outcome measures is statistically significant. However, it must be borne in mind that on the clinician-rated HDRS using dichotomous data, neither treatment was favoured.

Random-effects model

Using a random-effects model, comparing CBT and antidepressants on the BDI, there is a trend for CBT to appear more efficacious than antidepressants. The difference however is not statistically significant when continuous data is addressed from the 5 contributing studies involving 308 participants. Nor is the difference statistically significant when dichotomous data is analysed from the 6 available studies involving 383 participants.

Using the random-effects model, comparing CBT and antidepressants on the HDRS, the difference between the two treatments is statistically significant when continuous data is addressed from the 6 relevant studies involving 385 participants. When dichotomous outcomes are analysed, no treatment is favoured on the HDRS from the 5 available studies involving 309 participants.

Using a random-effects model, the bulk of the evidence favours CBT over antidepressants on three of the four outcome measures, though the difference is statistically significant on just one measure. So, using a random-effects model, no statistically significant advantage was found for CBT on 3 of 4 outcome measures.

4.6 Summary of sensitivity analysis

Sensitivity analysis is implicitly a best evidence synthesis (Treadwell et al. 2012). The analysis here was repeated without the Rush study, because medication was reduced or withdrawn two weeks before outcome assessment in that trial. Initially, a fixed-effect model was used.

On the BDI using continuous data from 5 studies and 265 participants, while CBT is favoured, the difference between the two treatments is not statistically significant. Using dichotomous data from 5 studies and 342 participants, while again CBT is favoured, the difference between the two treatments is not statistically significant.

On the HDRS using continuous data from 5 studies and 358 participants, while CBT is favoured, the difference between the two treatments is not statistically significant. Using dichotomous data from 5 studies and 309 participants neither treatment is favoured (and any difference between the two treatments is not statistically significant).

In summary, using a fixed-effect model, but omitting the Rush study, CBT is favoured on 3 of the outcome measures but the difference is no longer statistically significant. Next, a sensitivity analysis was carried out using a random-effects model.

On the BDI using continuous data from 5 studies, while CBT is favoured in terms of overall effect size, the difference between interventions is not statistically significant. Using dichotomous data from 5 studies, while CBT is favoured, the difference between interventions is not statistically significant.

On the HDRS using continuous data from 5 studies, while CBT is favoured, the difference between interventions is not statistically significant. On the HDRS, using dichotomous data from 5 studies, no treatment is favoured, and any minimal difference between interventions is not statistically significant.

In summary, using a random-effects model, with the Rush study excluded, CBT is favoured on 3 of the outcome measures, but the difference is not statistically significant.

In conclusion, using a fixed-effects model and a random-effects model, with the Rush study excluded, CBT is favoured over antidepressants on 3 of the outcome measures. Importantly however, the difference is not statistically significant.

Summary of results of CBT versus antidepressants systematic review

Using a fixed-effect model, the bulk of the evidence favours CBT over antidepressants and the difference on three of the four outcome measures is statistically significant. Using a random-effects model, the bulk of the evidence favours CBT over antidepressants on three of the four outcome measures, though the difference is statistically significant on just one measure. Following sensitivity analysis, CBT is favoured over antidepressants on 3 of the 4 outcome measures, but the difference is not statistically significant. While the bulk of the evidence shows a trend in favour of CBT, the advantage does not reach statistical significance on a number of important outcome measures.

None of the studies conducted a concurrent economic evaluation or assessed the acceptability of the different treatment modalities to those using and delivering the interventions.

Funnel plots

The potential for publication bias was explored here using funnel plots generated by RevMan, Version 5. These were visually examined and found to be roughly symmetrical around the mean effect line. However, the small number of studies meant that no formal test of publication bias could be carried out and it should be borne in mind that visual inspection can be of limited value (De Silva et al. 2013). Funnel plots from the CBT versus antidepressants systematic review are illustrated in appendix 2.

4.7 Summary of combination therapy versus monotherapy systematic review

Here we address the summary results regarding two comparisons: First, combination treatment versus CBT and second, combination treatment versus antidepressants. Initially, the comparisons are made using a fixed-effect model, then a random-effects model.

Combination treatment versus CBT, fixed-effect model

First, this writer compared combination treatment and CBT on the two outcome measures, the BDI and HDRS, using continuous and then dichotomous data, initially, utilising the fixed-effect model.

Using the fixed-effect model and continuous data from 3 studies comprising 121 patients, on the BDI there is little difference between the interventions (combination and CBT) and the small difference is not statistically significant. On the BDI using dichotomous data from 3 studies comprising 121 patients, there is again little difference between combination treatment and CBT and the difference is not statistically significant.

Using continuous data from the HDRS based on 119 patients from 3 studies, results favour combination treatment but the difference is not statistically significant. Using dichotomous data from 2 studies involving 87 patients, results again favour combination treatment but the difference is not statistically significant.

Combination treatment versus antidepressants, fixed-effect model

Using a fixed-effect model, a comparison was made between combination treatment and, this time, antidepressants, on the outcome measures BDI and HDRS, using continuous and then dichotomous data.

Here, combination treatment appeared more efficacious than antidepressants on the BDI using continuous data from 3 studies involving 148 patients and the difference is statistically significant. On the BDI using dichotomous data from 3 studies utilizing 136 patients, combination treatment appeared more efficacious than antidepressants and the difference is highly statistically significant.

On the HDRS, in an analysis of continuous data from 3 studies of 148 patients, combination therapy is favoured and the difference is statistically significant. The difference was highly significant when dichotomous data is analysed from 3 studies with 136 patients.

Next the same analyses were carried out using a random-effects model. First, a comparison is made between combination treatment and CBT on the BDI and HDRS analysing initially continuous and then dichotomous data on each.

Combination treatment and CBT, random-effects model

Using a random-effects model, combination treatment does not appear superior to CBT on the BDI using the continuous and dichotomous data from the same studies as outlined in the fixed-effect analysis. The results favour combination treatment over CBT on the HDRS using continuous and dichotomous data, but the difference again is not statistically significant.

Next, again using the random-effects model, combination treatment was compared, this time, with antidepressants.

Combination treatment versus antidepressants, random-effects model

Using a random-effects analysis, the comparison between combination treatment and antidepressants using continuous and dichotomous data yielded results favouring combination treatment. On the BDI, the difference was not statistically significant but on the clinician-rated HDRS, the difference was statistically significant using both continuous and dichotomous data.

In summary, using both fixed- and random-effects models, no statistically significant difference was found between combination therapy and CBT. However, combination treatment appeared significantly more effective than antidepressant medication on most outcome measures but not on all.

4.8 Author's Conclusions: CBT versus antidepressants systematic review

Use of CBT in depression depends heavily on its efficacy, cost effectiveness, and acceptability (Lewis et al. 2012). The results generated here support the on-going development and implementation of CBT as an effective treatment option for individuals diagnosed with depression. Conservatively, there is at least an equivalence of approaches.

In general, many previous reviews conclude that pharmacotherapy and psychotherapy are equally efficacious, but some however deduce that psychotherapy outperforms pharmacotherapy. Until more data become available, the findings obtained so far in the comparisons of antidepressant medication and CBT indicate that antidepressant medication cannot be considered more efficacious than CBT in the treatment of a range of depressed patients.

The first systematic review and meta-analysis presented here concurs with the conclusions of DeRubeis and colleagues that antidepressants cannot be considered more efficacious than CBT (DeRubeis et al. 1999). Their review used data from four reports, also included in this writer's systematic review, while the current review's conclusions are derived from eight studies and from a broader spectrum of depressed patients whose symptoms varied more widely in intensity. The results are also consistent with the findings of Hollon et al. (2005) who also found that medication in general cannot be considered more efficacious than psychotherapy in general.

Direct comparison data are insufficient for anything other than tentative conclusions to be drawn about the comparative efficacy of antidepressants and CBT. This writer's findings are a positive statement for one form of psychotherapy, CBT. A tentative conclusion is

that depressed patients benefit from antidepressants and CBT after short-term treatment, with some of the evidence favouring a slight advantage for CBT.

Limitations

Sometimes important methodological limitations and inconsistencies among the studies considered make it extremely difficult, at a particular moment, to justify policy action taken on the basis of evidence alone (Joly et al. 2013). The reviews conducted and presented here have many limitations. There is a reluctance in the primary studies to incorporate risk of bias assessments into conclusions (Hrobjartsson et al. 2013). However, the quality of the few studies found in this systematic review was low and sample sizes were very small, making it difficult to use this evidence to inform evidence-based policy. The reviews may not have had sufficient statistical power to detect small differences and the quality of the studies was not optimal in many cases. This may have influenced our results and distorted outcomes (Cuijpers et al. 2013). Even if a large amount of evidence is available, problems in consistency or quality may preclude a conclusion (Treadwell et al. 2012). Additional good quality RTCs are required with larger sample sizes enabling subsequent more powerful meta-analysis.

While symptom reduction is the bedrock for measuring response to treatment, daily life functioning should also be investigated. This reviewer did not address social functioning or quality of life, the ultimate goals of therapeutic intervention (De Silva et al. 2013).

Another obvious limitation is selection bias. RCTs tend to leave patients with serious co-morbidity out of their scope (Koesters et al. 2013). This limitation was compounded by a lack of data about cost-effectiveness.

Meta-analysis does not settle the question of the superiority of one technique over another. It merely provides data that might aid in the more important question concerning the relative value of the two approaches in a more broadly conceived cost/benefit analysis of the two modes of treatment of depression.

Most studies find it difficult to control for medication compliance (Choi et al. 2013). This should be an element of future research, by employing a measure of adherence (Choi et al. 2013) or through usage of interventions that have some impact on enhancing medication compliance (Haynes et al. 2008). Lastly, allegiance bias is difficult to exclude in the overall conduct of the included studies (Rush et al. 1977, Hollon et al. 1992). No study gave an account of reflexivity. Because of these limitations the results of the reviews have to be considered with caution (Cuijpers et al. 2013). This writer acknowledges reservations about the use of this phrase (Knottnerus et al. 2013).

Heterogeneity

An inherent problem with meta-analyses is excessive heterogeneity (Vasudev and Vasudev, 2013). Nevertheless, this reviewer did attempt to reduce heterogeneity by addressing CBT rather than psychotherapy in general, thus reducing the impact of a factor likely to obscure efficacy (Kisicki and Varley, 2013).

The product 'CBT' varies across studies (Kingdom, 2013). Lack of standard study design also continues to constitute a serious limitation in this area (Kisicki and Varley, 2013). Tables 4.11 and 4.12 illustrate the potential sources of heterogeneity in the two systematic reviews just outlined.

Heterogeneity may be clinical and methodological and there are many sources of heterogeneity impacting on effect sizes in the two reviews outlined. These factors include year of publication (1977 to 1995), place of publication (North America or UK), number of participants (33 to 250), age range (18 to 65 years), duration of treatment (3 to 20 weeks), severity and chronicity of depression (inpatients or less depressed outpatients), number of treatment sessions employed (12 to 20 sessions), fixed versus flexible drug dosing, use or absence of drug serum levels to ensure fidelity, and the degree of historical association of a particular research centre with either pharmacological or psychological intervention development.

The Elkin study had a large sample size (n=250) and, unusually, favoured antidepressant medication (Elkin et al. 1989). Of note is that the comparison intervention in this study, CBT, was available over a 16 week period. This investigation also had the important medication advantage of variable dosing, so central to practical clinical success. The Rush study, in contrast, had a relatively large effect size favouring CBT but had fewer participants (n=41), and provided an unusually large number of sessions, up to 20, of CBT (Rush et al. 1977). These sources of heterogeneity go some way in explaining the difference in direction and size of effect detected between these important and influential studies.

Looking at the difference in effect sizes of two other studies, this time both favouring CBT in varying degrees, Hollon and colleagues employed a relatively large sample (n=107) and detected a small effect size favouring CBT (Hollon et al 1992). The study was conducted in a centre historically associated with pharmacology and where pharmacotherapy was 'conducted aggressively' over 12 weeks. Murphy and colleagues had a larger effect size favouring CBT, but employed a much smaller sample (n=37) and

a longer duration of the psychotherapy than the Hollon study (Murphy et al. 1995). Murphy and colleagues also encompassed a more motivated group of patients, less depressed and recruited through press release.

In the combination treatment versus antidepressant review by Bowers, this short study used a small sample of more severely depressed patients (n=30) and had just one CBT therapist (Bowers, 1990). Bowers favoured combination treatment with a larger effect size than the longer, pharmacology-focused Hollon investigation (Hollon et al. 1992). Again the larger sample size populating the Hollon study is associated with a smaller effect size.

Study size emerges as a potent effect modifier in the two systematic reviews conducted by this writer. The importance of sample size as a source of heterogeneity has previously been emphasized by other investigators and the reviews presented here are consistent with this observation (Deeks et al. 2008). The number of treatment sessions of CBT is also associated with variation in effect sizes. Studies employing a longer duration of psychotherapy, 16 to 20 sessions, tend to detect a greater effect size favouring CBT (Murphy et al. 1995, Rush et al. 1977). Study size and duration of psychotherapy emerge as potent sources of heterogeneity in the reviews presented here.

Table 4.11. Potential sources of heterogeneity: antidepressants versus CBT comparison

Study Location	Clinical condition	Age	Duration of treatment	Treatment	Note
Rush et al. 1977 USA	Chronically depressed	8-65yrs 41 participants	12 weeks	Imipramine Vs CBT (centre associated with CBT).	RCT. 2 weeks prior to final assessment, meds stopped.
McLean & **Hakstian,** 1979 Canada	Individuals recruited by telephone from public	20-60yrs 178 participants	10 weeks	Amitriptyline (150mg, fixed dosage employed) Vs CBT	RCT. Therapist experience varied.
Blackburn et al. 1981 Scotland	Patients drawn from general practice and hospital outpatients	18-65 yrs 88 participants	20 weeks	Amitriptyline/ Clomipramine (150mg) Vs CBT	RCT. Duration of therapy varied.
Murphy et al. 1984 USA	Moderate to severe depression	18-60yrs 87 participants	12 weeks	Nortriptyline (Blood levels: 50-150ng/mL) Vs CBT	RCT. New and former patients. Therapists had training in CBT.
Elkin et al. 1989 USA	Outpatients with major depression	Av Age; 35yrs 250 participants	16 weeks	Imipramine (185mg average) Vs CBT	RCT. Severity of depression varied.
Hollon et al. 1992 USA	Seekers of psychiatric treatment	18-62yrs 107 participants	12 weeks	Imipramine (200-300mg) Vs CBT Pharmaco-therapy pursued aggressively	RCT. Centre linked . with pharmac-ological trials.
Scott & Freeman, 1992 Scotland .	Patients attending a GP	18-65yrs 121 participants	16 weeks	Amitriptyline (150mg, Flexible dosing employed) Vs CBT	RCT. Primary care setting. CBT provided by clinical psychologists.
Murphy et al. 1995 USA	Less depressed volunteers	18-60yrs 37 participants	16 weeks	Desipramine (150-300mg) Vs CBT	RCT. Patients recruited through press release.

Table 4.12. Potential sources of heterogeneity: combination therapy versus single treatment

Study and date	Clinical condition	Ages	Duration of treatment	Treatment	Note
Blackburn et al. 1981 Scotland	Patients drawn from general practice and hospital outpatients.	18-65yrs 88 participants	20 weeks	Amitriptyline/ Clomipramine (150mg) and CBT Vs CBT or antidepressant	RCT. Duration of therapy varied.
Murphy et al. 1984 USA . . .	Moderate to severe depression.	18-60yrs 87 participants	12 weeks	Nortriptyline (Blood levels: 50-150ng/mL) and CBT Vs CBT plus placebo	RCT. New/ former pts. Therapists had training in CBT.
Beck et al. 1985 USA	Self-referrals/ professional referrals	20-65yrs 33 participants	20 sessions over 12 weeks	Combination Tx: Amitritriptyline (75-200mg) and CBT Vs CBT	Treated at a specialist centre for CBT.
Bowers, 1990 USA .	Inpatients in psychiatric unit	18-60yrs 30 participants	12 sessions over 18 days approx	CBT and Nortriptyline (100-200mg) Vs Nortriptyline	Clinical trial. One experienced therapist conducted CBT.
Hollon et al. 1992 USA	Seekers of psychiatric treatment	18-62yrs 107 participants	12 weeks	Imipramine (200-300mg) and CBT Vs Single Tx	Centre associated with pharmac-ology.

Implications for research

The object of a systematic review is to help individuals make well-informed decisions about clinical practice and future research. An important limitation of the previous overviews in the area is the striking methodological and clinical heterogeneity in most

reviews and meta-analyses. Treatment duration varied between 4 and 79 weeks and both primary care patients and psychiatric inpatients were included. Psychotherapy encompassed interventions from social work counselling to interpersonal psychotherapy.

Not surprisingly, inter-trial homogeneity is rejected in previous overviews. Hollon and colleagues included geriatric and adult patients and encompassed dysthymia as well as major depression (Hollon et al. 2005). This clinical heterogeneity makes data pooling hazardous (Deeks et al. 2008). In the systematic reviews just presented, clinical heterogeneity was decreased by imposing strict inclusion and exclusion criteria. This writer aimed to enhance homogeneity.

The primary research question addressed the relative efficacy of antidepressants versus CBT in the acute treatment of depression. Further research needs to focus on efficacy at follow-up. Long-term studies are needed to supplement the few currently available findings. More intervention-outcome studies, rigorously designed and executed to meet the demands of evidence-based practice are necessary. Further RCTs are indicated followed by their inclusion in subsequent meta-analysis. Studies should also be conducted in clinical settings and in participants with differing degrees of depression, should include long-term outcomes, and should also address the cost effectiveness of interventions.

Implications for practice

The literature currently does not provide the robust data needed to underpin clinical recommendations in favour of antidepressants or CBT in the acute treatment of depression. All patient-important outcomes should be considered in a systematic review and it is possible to highlight different actions consistent with different patterns of values

and preferences. Different sub-groups of patient may respond differently to medication and CBT. We conclude that depressed patients benefit from both antidepressants and CBT after short-term treatment, with the bulk of the evidence favouring CBT. This should be borne in mind, while taking into account contraindications, treatment access, and patient preferences.

New Evidence

Following the forward citation search conducted in February 2015, a more recent randomized controlled trial was detected, encompassing 120 participants, compared the antidepressant, citalopram, with CBT over 8 weeks (Shamsaei et al. 2008). In common with this writer's review, Shamsaei found no significant difference between the medication and CBT, a conclusion also highlighted by Sava et al. (2009) in their RCT focusing on cost effectiveness. Unlike the findings of the systematic reviews conducted here however, Shamsaei and colleagues also found that combination therapy was more efficacious than cognitive therapy alone (Shamsaei et al. 2008). It should be noted that the patients in this trial were less depressed, were assessed on the BDI only, assessment was not blind, and the study was relatively short.

A recent trial conducted by Hollon compared a combination of cognitive therapy and antidepressant medication with antidepressants alone (Hollon et al. 2014). A total of 452 adult patients participated in this multi-centre RCT over 42 months. The outcome measure was the HDRS and depression was sometimes complicated by other psychiatric disorders. Hollon found that combined therapy enhanced the rates of recovery from depression, relative to antidepressants, a finding consistent with the findings of the systematic review conducted by this writer.

Furthermore, another meta-analysis concluded by Cuijpers and colleagues concluded that combined treatment, encompassing antidepressants and psychotherapy in general, appears to be more effective than treatment with antidepressant medication alone, another result consistent with the finding of the systematic review conducted here (Cuijpers et al. 2014).

The most recent guidance from NICE advocates a stepped-care model with a multifaceted treatment approach including medication and psychological therapies (NICE, 2010). However, the availability of individual therapy remains limited (Glover et al. 2010). Treatment access continues to be an issue in practice (Kingdom, 2013).

4.9 Author's Conclusions: Combined treatment versus monotherapy

Regarding the comparison between combination treatment and antidepressants, using a fixed-effect model, combination treatment was more efficacious than antidepressants on the outcome measures and the difference was statistically significant. Using a random-effects model, the results also favour combination treatment over antidepressants on four outcome measures and the results were statistically significant on two of these.

Regarding the comparison between combination treatment and CBT, using a fixed-effect model, there is little difference between combination treatment and CBT on the BDI and this difference is not statistically significant. On the Hamilton (HDRS), combination treatment is favoured but not significantly. Using a random-effects model, combination treatment does not appear more efficacious than CBT on the BDI. The results favour combination treatment over CBT on the HDRS, but the difference again is not statistically significant.

In summary, the bulk of the evidence favours combination treatment over antidepressants. But broadly speaking, combination treatment is not more efficacious than CBT on its own, based on the limited evidence outlined here. The results can be seen as a positive statement for CBT.

Implications for practice

CBT combined with antidepressant use is associated with a higher response rate than antidepressants alone. This finding was confirmed in a more recent study (Hollon et al, 2014). For shorter treatment, the combined therapy may be effective in some patients who would not otherwise respond to pharmacotherapy alone. For longer duration treatments, the addition of psychotherapy may induce a stronger compliance with the combined treatment.

Regarding the second comparison, if combination treatment and CBT are generally equally effective, then perhaps CBT should be offered on its own rather than a combination approach. Combined treatment may then be offered if CBT does not work.

Cuijpers and colleagues concluded from their systematic review that treatment combining psychotherapy with antidepressants appeared to be more effective than treatment with antidepressant medication alone in major depression (Cuijpers et al. 2014). Combined treatment may indeed be more efficacious than single treatment for chronic depression. Keller and colleagues showed that patients receiving combined treatment were more likely to recover than those receiving medication or psychotherapy alone (Keller et al. 2000). The effects of combined treatment may be increased for chronic depression. There are good theoretical reasons for combined treatment being more effective than single

treatment with these patients. These chronic patients are more likely to suffer functional impairment. If social difficulties persist, then without psychotherapy, relapse may be more likely. Also, severe and chronic patients may continue to experience biological dysfunction that may be particularly responsive to medication. Combined treatment may lead to change across a broader range of functioning, leading to better outcome for these patients.

Implications for research

Medication and psychotherapy are often combined in clinical practice. In the area of child and adolescent depression, Cox and colleagues found that some studies indicate that combination treatment may be more effective than medications, but not psychotherapy, (Cox et al. 2012).

We need optimum and judicious use of resources. It is valuable for health professionals to know the evidence pertaining to the efficacy of combined treatment. In research to date, there are issues of design sensitivity, ceiling effects, and non-specific placebo effects. We need adequately powered investigations of efficacy before the issue of cost effectiveness can be properly addressed.

It is important to focus on when to choose medication, psychotherapy or a combination of the two. Different patients may benefit from different treatment strategies. Combined treatment may be useful for some individuals. Further research needs to be done to find out who these patients are. Greater emphasis needs to be placed on the determination and utilisation of individual predictors of treatment response (Lewis et al. 2012).

Sufficient power is required to detect clinically or statistically meaningful differences. Studies need to have adequate power to detect the small-to-moderate treatment effects of combined treatment on outcome status. The difference may be small so it is anticipated that large samples would be required to find significant differences between combined treatment and single treatment, if it exists. Even a small advantage should not be overlooked (Friedman et al. 2006).

It is difficult to know if optimal pharmacotherapy was delivered in the studies reviewed here. There is little evidence that treatment was delivered in a consistent and standardized manner. More recent studies require stringent ratings of competency and adherence to treatment protocols.

Also, a broader outcome evaluation rather than simple control of symptoms should be adopted. More outcome measures such as patient satisfaction are required in order to complement efficacy (De Silva et al. 2013).

Research needs to clarify whether the joint therapeutic effect is additive and if the increase in response attributable to combined treatment is associated with a reduction in drop-outs. Is the genuine therapeutic effect moderate in comparison with compliance-enhancing effect? Future studies also need to address the patient's beliefs about their difficulties, in order to integrate both pharmacological and psychological care.

Conclusion

The pooled results of the trials do not support the inference that antidepressant medication is superior to CBT in acutely depressed patients. The analysis included the influential

Elkin study favouring antidepressants, upon which treatment guidelines were once based, together with data from several other comparisons of antidepressant medication and cognitive therapy.

A previous review found that across their four studies, CBT was negligibly and non-significantly more effective than antidepressant medication (DeRubeis et al. 1999). Until more data become available the findings obtained thus far in the major comparisons of antidepressant medication and CBT suggest that antidepressant medication cannot be considered superior to CBT in the acute treatment of adult, uncomplicated depression. Furthermore, combination therapy may not be more effective than CBT on its own. This review confirms the potential of CBT for effectively treating individuals diagnosed with depression and supports the on-going development of CBT.

4.10 The abstract

Structured abstracts debuted in JAMA more than 20 years ago (Bauchner et al. 2013). The format dominates the landscape of medical journals. Abstracts are stand-alone documents and no more than six key results should to be specified (Schunemann et al. 2008). After the title, the abstract is the most consulted part of a biomedical article (Beller et al. 2013). Abstracts act as a prompt to the researcher to include more complete detail, and facilitate the finding of information by the reader. The outcomes included were selected on the basis of what is more likely to help someone making a decision about whether or not to use a particular intervention. Conclusions were drawn from the findings and reflect the main results (Swales and Feak, 2009). The PRISMA statement for

abstracts checklist, used here, focuses on the truthful representation of a systematic review in an abstract (Beller et al. 2013). The combined abstract for both systematic reviews is outlined here.

Title: Cognitive-behaviour therapy, antidepressants and combination therapy for the treatment of depressed patients: a systematic review and meta-analysis

Background: The comparative effectiveness of cognitive-behaviour therapy and antidepressant medication for the acute treatment of depression is contentious.

Objective: To compare the effect of antidepressant medication versus cognitive-behaviour therapy (CBT), and the combination of the two treatments versus each on its own in adult, depressed patients.

Methods: Studies comparing CBT with antidepressants, and a combination of the two with either treatment on their own, were encompassed. Included studies addressed the efficacy of the acute treatment of clinical depression, diagnosed by operationalized criteria, uncomplicated by physical and psychiatric co-morbidity. Published and unpublished studies in any language were included. Seventeen electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials, were searched from inception to December 2009, for randomised and other clinical trials that compared CBT, antidepressants, or their combination. Risk of bias was assessed regarding randomisation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases.

Results: In the comparison between CBT and antidepressants, of 1,113 records screened, just 8 primary studies met the selective inclusion criteria. These studies included a total of 909 participants. Following an extensive search conducted for the second systematic review comparing combination treatment and mono-therapy, of 785 records screened just 5 primary studies, containing 345 participants, met the inclusion criteria.

Analysis using a fixed-effect model, in 5 studies with 308 participants employing the BDI as an outcome measure with continuous data, a statistically significant difference was found favouring CBT over antidepressants (MD = -2.54, -4.95, -0.12, P=0.04). Utilizing dichotomous data from 6 studies of 383 participants, a statistically significant difference was again found favouring CBT on the BDI (RR=0.77, 0.63, 0.93, P=0.008). Employing the HDRS with continuous data, in 6 studies with 358 participants, CBT had a statistically significantly advantage over antidepressants (MD= -2.13, -3.67, -0.59, P=0.007). Using dichotomous data from 5 studies with 309 participants, no treatment was favoured on the HDRS (RR=1.01, 0.83, 1.23, P=0.90). Using a random-effects model, CBT had a statistically significantly advantage over antidepressants on just one outcome measure, the HDRS using continuous data.

In the second systematic review involving a comparison of combination treatment and CBT, using a fixed-effect model and employing the BDI in 3 studies with 121 participants, there was no statistically significant advantage for combination treatment when continuous data was analysed (MD=0.09, -3.38, 3.55, P=0.96) or when dichotomous data was utilised. Employing the HDRS, while combination treatment was favoured, the difference was not statistically significant when continuous data was analysed in 3 studies with 119 participants (MD=0.58, -2.90, 1.73, P=0.62) or when

dichotomous data was employed. using a random effects model, no statistically significant difference was found in the comparison between combination treatment and CBT.

Again using a fixed-effect model, in the comparison between combination treatment and antidepressants using the BDI, in 3 studies with 148 participants, the combination therapy had a statistically significant advantage when continuous data was analysed (MD= -4.46, -8.32, -0.60, P=0.02) and also when dichotomous data was addressed. In the 3 studies with 148 participants utilising the HDRS, combination treatment had a statistically significant advantage when continuous data was employed (MD= -2.90, -5.58, -0.22, P=0.03) and also when dichotomous data was analysed. Employing a random effects model, a statically significant advantage was found for combination treatment over antidepressants on the HDRS, but not the BDI.

Discussion: In the first comparison, CBT versus antidepressants, the severity of depression was modestly reduced in the CBT group compared with the antidepressant group on most, but not all, outcome measures. In the second comparison, no statistically significant difference was found between combination therapy and CBT, however, combination treatment appeared significantly more effective than antidepressant medication on most, though not all, outcome measures. Meta-analysis for some outcome measures had large statistical heterogeneity. Furthermore, many studies had a substantial risk of bias due especially to lack of allocation concealment. Some studies had small sample sizes, with duration of treatment in some cases quite limited. More recent studies were lacking.

Interpretation: Antidepressants should not be considered to be superior to CBT for the acute treatment of depressed patients. Nor can combination therapy be regarded as more effective than CBT alone on the basis of the existing evidence.

Funding: No funding has received for this project from a host institution or external body.

Key words: Cognitive-behaviour therapy, antidepressants, combination therapy, depression

4.11 Plain language summary

A plain language summary is aimed at patients and other decision makers. The summary should outline the importance of the problem, the findings of the review, and comment on the limitations of the study but with no graphs or pictures (Schunemann et al. 2008).

Plain language summary

Plain language title: Talking therapy, medication and a combination of the two for depression.

Depression is very common and causes much suffering. Tablets are helpful but talking therapy is often looked for by patients. We compared antidepressants with a form of talking therapy, known as cognitive-behaviour therapy, in depressed patients. A combination of the talking therapy and antidepressants was also compared with antidepressant medication and cognitive-behaviour therapy on their own.

The main findings of the study were that cognitive-behaviour therapy alone has some advantages over antidepressant medication in individuals who are depressed but with no other major complicating problems. Also combining antidepressants with cognitive-behaviour therapy appears better than simply taking the medication alone. Combination therapy however, may not be better than simply receiving talking therapy on its own. The limitations of the review were the small number of studies available and the limited number of participants involved.

The next chapter

This current chapter described two meta-analyses addressing the relative efficacy of antidepressants and CBT. Knowledge generation however, should go hand in hand with knowledge transfer. The next chapter focuses on knowledge translation and outlines the need for a systematic review of the barriers obstructing the uptake of evidence specifically from systematic reviews, meta-analyses and the databases associated with them.

CHAPTER 5

BARRIERS TO KNOWLEDGE TRANSLATION FROM SYSTEMATIC REVIEWS

CONTENTS

5.1 Introduction 199

5.2 Problem 199

5.3 Knowledge Gap 201

5.4 Background 204

5.5 Methods 206

5.6 Results 211

5.7 Discussion 238

5.8 Conclusion 243

5.9 Abstract 244

5.1 Introduction

The previous chapter outlined two systematic reviews and meta-analyses generating evidence about the relative efficiency of antidepressants and CBT. This chapter moves on to address the important issue of knowledge translation and the factors impacting on the uptake of generated evidence.

The need for a systematic review of the obstacles inhibiting the uptake of evidence from systematic reviews, meta-analyses and the databases associated with them is outlined. The search results and the method of data extraction are then described. The data extracted from the identified primary studies are highlighted together with the taxonomy used for summarisation and tabulation. The conclusions drawn from the systematic review are outlined (Wallace et al. 2012a). Finally, this writer then presents the abstract of the review.

5.2 The Problem

Only by rigorous application of the best evidence can health systems deliver true value. What constitutes the best evidence and how best to apply it effectively to clinical practice and health policy remains a challenge (Heneghan and Godlee, 2013). Gaps between evidence and decision-making occur across many decision makers, including patients, health-care professionals, and policy makers (Wallace, 2013). The challenge of translating science into practice is common in many applied disciplines (Cook et al. 2013). Most urban and rural clinicians report that they rely on colleagues rather than

research evidence as a primary knowledge source (Curran et al. 2013). Providing evidence from clinical research is necessary but not sufficient for producing optimal clinical care delivery (Arditi et al. 2012).

The science of knowledge translation is a relatively new field. It is about the interplay between research and practice (Knottnerus et al. 2013). Knowledge translation is about the methods used for closing knowledge-to-action gaps (Straus et al. 2009a). Efforts need to be made to bridge these gaps with effective interventions, thereby improving health outcomes. Doing this is not easy and the process involves an evaluation of the multiple barriers to change (Straus et al. 2009a).

Knowledge synthesis is not a new concept. Evidence synthesis that interprets the results of individual studies within the context of global evidence should be considered the basic unit of knowledge translation (Tetzlaff et al, 2009). Systematic reviews help decision-makers deal with the rapid increase in the available research evidence (Cook et al. 2013). Synthesis should inform policy briefs, patient decision aids, and clinical practice guidelines. Knowledge synthesis should bridge the gap between research and decision making (Tetzlaff et al. 2009). Reviews of research are a vital part of the cycle of evidence generation and use (Gough et al. 2012). Good quality systematic reviews are a tool for integrating science into practice (Cook et al. 2013). Failure to optimally use results from systematic reviews in healthcare can lead to inefficiencies and reduce quality and quantity of life. Dissemination is a central part of the systematic review process.

Many factors however, may impede the uptake of evidence from systematic reviews. Despite the improvement in the conduct and reporting of systematic reviews, current

evidence suggests that they may be used infrequently by clinicians, patients, and others to make informed decisions (Tetzlaff et al. 2009). Few recommendations from practice guidelines are based on systematic reviews (Knotternus and Tugwell, 2013). It is also difficult to say whether systematic reviews ever impact on practical, on-the-ground, management practices (Cook et al. 2013). Systematic reviews are less susceptible to bias than expert opinion, so why are they used so infrequently?

Systematic reviews are sometimes felt to focus too much on methodological rigor instead of on clinical context. There are also concerns that they do not provide enough crucial information for clinicians. There is less data on the impact of the presentation of a complete systematic review on a clinician's understanding of the results or their ability to apply the results to individual patients.

A focused systematic review can be more useful than a traditional narrative review (Oxman and Guyatt, 1988). If systematic reviews are perceived in such a positive light then why is there not optimal use? There appears then to be a significant problem of knowledge translation related to the uptake of systematic reviews, as distinct from practice guidelines.

Clinical practice guidelines

Systematic reviews were the focus of this review of knowledge transfer, rather than the more commonly investigated clinical practice guidelines (Wallace et al. 2012a). Systematic reviews are different. Systematic reviews are based on primary studies while clinical practice guidelines are an amalgam of clinical experience, expert opinion, patient

preferences, and evidence. Guidelines are devised by a panel and offer recommendations based on a wide range of factors, including interpretation of evidence. Systematic reviews inform guidelines but harms, benefits, costs, feasibility issues, patient preferences, together with legal and ethical issues are also taken into account by panel members in developing guideline recommendations (Qaseem et al. 2012).

Systematic reviews are a scientific exercise aimed at generating new knowledge. They are summaries of relevant research and can help to keep us current. Pre-appraised, integrative reviews address a wide range of topics including research implementation strategies while guidelines are developed by clinicians and are intended for use in clinical practice (Dawes et al. 2005). Importantly, guidelines go beyond the best available evidence and offer specific recommendations for clinical decision making (Andrews et al. 2013).

Systematic reviews have a distinct development and purpose. Because of the considerable differences between clinical practice guidelines and systematic reviews, this writer set out to identifying the barriers to the uptake, specifically, of systematic reviews and meta-analyses, rather than of guidelines.

5.3 The Knowledge Gap

The relevance of the question being addressed here is obviously of importance to potential users of systematic reviews: doctors, psychologists, policy makers, other practitioners, patients, and the general public. Much attention is paid to enhancing the quality of systematic reviews. Little attention has been paid to the best format for presenting and transmitting the review (Tetzlaff et al. 2009). Participation in a knowledge exchange strategy depends on contextual and also individual characteristics (Curran et al.

2013). The contextualisation and the format of the presentation appear to be relevant issues. But what other factors are involved in the uptake of evidence from reviews and, importantly, how can these factors be modified?

Our lack of knowledge of the barriers to the uptake of evidence specifically from systematic reviews has important implications. It has been suggested that strategies to promote change in clinical practice are more likely to be effective if based on an analysis of barriers and facilitators specific to the context (Grol and Grimshaw, 1999). The proportion of effective strategies in evidence transfer is significantly higher with interventions that include a prospective identification of barriers to change compared with standardized interventions (Chaillet et al. 2006).

There is an important knowledge gap regarding the identity of the obstacles that inhibit the uptake of evidence from systematic reviews, meta-analyses and the databases containing them. This gap needs to be bridged and the method chosen by this writer to make this contribution involves systematic review methodology.

Many parties have a great interest in the agenda and content of clinical research, such as professionals, policy makers, insurers, research organizations, patients and the public (Knottnerus and Tugwell, 2013). The aim here is to identify the barriers to the uptake of evidence, by all decision makers, from systematic reviews, meta-analyses and the databases containing them. A related review is described in the next chapter and focuses on the identity of the facilitators or enhancers of the uptake of evidence from systematic reviews (Wallace et al. 2012b).

There has been a growth in the impact of Cochrane Reviews including their increasing inclusion in clinical guidelines (Maclehose and Hilton, 2013). However, in general, little is known about the process and factors responsible for how decision makers alter their behaviour and how physicians change their practice when they become aware of a systematic review. Physician uptake of knowledge from systematic reviews may be hindered by a variety of obstacles. By identifying these barriers it may be possible to target an intervention to the specific obstacle identified and so improve systematic review uptake by decision makers.

To this writer's knowledge, the review conducted here is the first systematic review to set out to identify the barriers to the uptake of evidence specifically from systematic reviews and meta-analyses, by all decision makers, not just policy makers or doctors.

5.4 Background

The mere existence of reviews does not ensure their dissemination and their application to routine practice and policy formulation. The uptake of evidence from systematic reviews has been inconsistent (Tetzlaff et al. 2009). Information from them may remain unused due to a perceived lack of relevance (Gartlehner and Flamm, 2013). When unsure about diagnostic and management issues, physicians routinely consult with a colleague or read a textbook (Bennett et al. 2010).

While many investigations have been conducted on the barriers to the uptake of research evidence in general, little is known specifically about the determinants of uptake of systematic review evidence in particular (Gartlehner and Flamm, 2013). In the past, there have been reviews of the barriers to adherence to clinical guidelines (Cabana et al. 1999),

of the barriers to the appropriate use of research evidence in policy decisions (Innvaer et al. 2002), of the barriers and facilitators to implementing shared decision-making (Gravel et al. 2006), of the barriers to improving the usefulness of systematic reviews for health care managers and policy makers (Lavis et al. 2005), and lastly, of the barriers and incentives to optimal health care (Cochrane et al. 2007).

Many factors contribute to the varying uptake of evidence in general (Lavis, 2006). These include financial obstacles, the volume of research evidence, and the difficulties in applying global evidence in a local clinical context (Murthy et al. 2012). Other barriers include limited time and impaired awareness of evidence sources, limited critical appraisal skills and the limited relevance of research findings (Dobbins et al. 2001a,b). Given the considerable differences between systematic reviews, primary research, and clinical practice guidelines, this writer set out specifically to identify the barriers to uptake of systematic reviews and meta-analyses rather than other sources of evidence.

What are the barriers to the uptake of evidence from systematic reviews, meta-analyses and the databases that contain them? Here this writer was concerned with all decision makers, including physicians, policy makers, patients and nursing staff. Such barrier identification can aid the development of effective strategies to improve the uptake of systematic reviews and meta-analyses by a variety of decision makers. Interventions to improve the use of systematic reviews for clinical and commissioning decision making are currently being investigated (Murthy et al. 2012).

Chapter 3 addressed the methodology associated with the first two systematic reviews and meta-analyses. As noted, specific elements of systematic review methodology associated

with reviews of perspectives and personal views are integrated in this and subsequent chapters.

5.5 Methods

Search strategy

For systematic reviews, completeness of the evidence base is crucial (Knotterus and Tugwell, 2013). Many negative trials are unpublished and there are often conflicting results between published and unpublished studies (Koesters et al. 2013). It has also been emphasized that qualitative research is poorly indexed in databases (Lawrence et al. 2012). This writer conducted a systematic review of the literature to identify barriers to evidence uptake from systematic reviews and meta-analyses. This writer searched 19 databases and used 3 search engines, for articles, not limited to the English language, drawing on the entire range of publication years covered in each database up to Dec 2010 using a combination of index terms and text words identified from previously identified, relevant articles.

The databases included The Cochrane Library, TRIP, Joanna Briggs Institute, National Guideline Clearing House, Health Evidence, PubMed (1950-2010), EMBASE (1980-2010), ERIC, CINAHL, PsycInfo, OpenSigle, Index to Theses in Great Britain and Ireland, and Conference Papers Index, Campbell Collaboration, Canadian Health Services Research Foundation, EPOC, KT+, McMaster University, Keenan Research Centre, and the New York Academy of Medicine. The search engines ALTA VISTA and Google scholar were also utilised. References from included primary studies and related review articles were scanned, experts in the field contacted, and bibliographies of

textbooks were reviewed. The following search terms were included: obstacle, barrier, impede, impair, utilisation, uptake, overview, systematic review and meta-analysis.

Following completion of the review synthesis, aspects of the search were repeated for the period December 2010 to June 2012. The aim of this 'updated search' was to identify any further relevant or on-going studies that could be used in a later update of this systematic review (Baker et al. 2010). For the updated search, this writer applied similar search strategies to PubMed and EMBASE, the two most productive bibliographic databases in terms of studies already identified for inclusion in the review.

Selection criteria

It is important to make more effective use of feedback from end-users to increase the likelihood of producing reviews that have positive effects on health outcomes (Nasser et al. 2013). Studies were included if they presented an original collection of data.

Inclusion criteria

To be included in the review, primary studies had to meet the following criteria:

- Studies were included if they addressed perceived barriers to uptake of evidence specifically from systematic reviews, meta-analyses and the databases that contained them
- These databases containing systematic reviews could include The Cochrane Library, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of

Effects, Cochrane Pregnancy and Childbirth Database, Oxford Database of Perinatal Trials, and the Reproductive Health Library

- A barrier was defined as any factor that impedes or obstructs uptake of evidence
- Barriers could negatively impact on access, awareness, familiarity, intellectual adoption, and actual use of systematic reviews
- Barriers could be reported via surveys
- Barriers could be identified via qualitative research such as interviews and focus groups
- The views of all decision makers including doctors, nurses, occupational therapists, policy makers, the public and patients were eligible
- Reports in any language were included

Exclusion criteria

Studies were excluded

- If they were intervention or outcome studies rather than studies of views and perceptions
- If they were about views and perceptions dealing exclusively with facilitating or enhancing rather than obstructing evidence uptake
- If they were exclusively about barriers to evidence uptake in general rather than encompassing uptake of systematic reviews in particular
- If they dealt exclusively with the uptake of clinical practice guidelines as systematic reviews specifically were the focus of this writer's systematic review

However, selection criteria did not specify that the inclusion of studies was restricted to those reporting, as their main purpose, the identification of obstacles specifically to systematic review uptake.

This writer focused on factors that could be altered or overcome rather than the gender or age of decision makers (Cabana et al. 1999). In many of the reports, participants specified obstacles via response to survey questions. For qualitative studies, major themes from focus groups or interviews identified the obstacles to uptake (Dobbins et al. 2001b).

Special care was taken to identify studies that appeared in multiple publications (Lang and Secic, 2006). When more than one report described a specific study and each presented the same data, the most recent publication was included for analysis. However, if more than one publication described a single investigation but each presented novel and complementary evidence then both were used.

Data collection and analysis

Reports were retrieved if it appeared likely that they contained data regarding barriers to uptake of evidence from systematic reviews. This writer reviewed all the citations, and followed up reference lists, while the retrieved full reports were assessed by at least two investigators for eligibility. Disagreements were resolved by discussion, or adjudication by a third party. Reports appearing relevant initially, but which were not, joined a list of excluded studies maintained by this writer.

Using a data collection form, data were extracted from the included studies. Information taken from each article included a description of the barriers identified, the percentage of

participants highlighting the barrier, demographics of the respondents, and the characteristics of the included study. Where possible, we estimated the percentages of respondents affected by an obstacle as the difference between 100% and the sum of the percentage with no opinion and those not affected (Cabana et al. 1999).

The creation of a taxonomy can be useful (Lawrence et al. 2012). Taxonomies facilitate the process of accumulating knowledge across heterogeneous studies (Glasziou et al. 2010). The data extraction sheet was created based on a taxonomy of barriers to implementing clinical practice guidelines (Cabana et al. 1999). The mechanism of action by which improved patient care is attained is believed to proceed through a number of stages (Woolf, 1993). Research evidence alters eventual clinical outcome through the intermediate steps of first changing clinician knowledge, then improving attitudes, and lastly, changing practitioner behaviour. This taxonomy had been used with success by other investigators. It is reported to stand up well in comparison with alternative approaches (Gravel et al. 2006).

This writer independently read individual reports and identified evidence relevant to each of the main outcomes of interest. Barriers were then grouped into themes and the obstacles ordered according to the number of studies in which they were identified. The themes were organised into groups depending on whether they impacted on knowledge, attitude, or behaviour (Cabana et al. 1999). The categories drew on an ideal mechanism of a knowledge, attitudes, and behaviour framework (Woolf, 1993).

Lack of familiarity and awareness, for instance, were listed under the *Knowledge* heading; lack of motivation was listed under *Attitudes*; patient, review and environmental factors were grouped under the *Behaviour* heading. Barriers impeding review uptake through a

cognitive component were considered obstacles affecting knowledge. If an affective component was identified then the barrier was listed as impeding attitude. A limitation or restriction on ability was regarded as a barrier affecting behaviour. Lack of familiarity included impaired ability to correctly answer questions about review content, as well as self-acknowledged lack of familiarity. Lack of awareness was viewed as the inability to adequately acknowledge systematic review existence.

In order to assess the quality of the studies, study characteristics were extracted: year of publication, country of origin, main objective of the study, the design of the study, and the characteristics of participants. In particular, the sampling strategy of the primary studies, response rate, and methodological approach, including data collection strategies, were assessed.

5.6 Results

Search yield

From 19 databases searched and three search engines utilized, there were 1,726 specific candidate articles found possibly examining barriers to uptake of evidence from systematic reviews. Some 1,659 titles were excluded after assessment of the bibliographic citation. After examination of the full text of 75 articles, 13 articles fulfilled the eligibility criteria. Fifteen primary studies were detected from the reference lists of these 75 articles. The reference lists of these 15 included studies were then checked but yielded no new eligible studies.

Therefore, a total of 28 detected reports describing 27 unique studies met the inclusion criteria (Figure 5.1). Thirteen studies that might possibly be expected to be included but are not, are outlined in appendix 3 together with the reasons for their exclusion. To be included, studies had to address perceived obstacles to uptake of evidence specifically from systematic reviews, meta-analyses and the databases that contained them.

In addition to the main search, a further, briefer 'updated' search was conducted (Baker et al. 2010). This updated search enables the reader to be kept more current and informed of any new or on-going studies detected after completion of the main synthesis. These studies could be mentioned but without being included in the completed review. A search of EMBASE and PubMed from December 2010 to June 2012, failed to detect any relevant, completed or on-going studies to be added to 'Studies awaiting classification' and 'On-going studies' tables.

The search terms used and their combination are outlined in Table 5.1.

Table 5.1 Search of PubMed and Embase for barriers to uptake of systematic reviews

PubMed was searched from December 2010 to June 2012 using the advanced search facility

Search	Query	Items found
1	systematic review AND barriers AND knowledge uptake	1
2	meta-analysis AND barriers AND knowledge uptake	1
3	systematic review AND obstacles AND knowledge uptake	1
4	meta-analysis AND obstacles AND knowledge uptake	0
5	systematic review AND barriers AND knowledge utilisation	3
6	meta-analysis AND barriers and knowledge utilisation	2
7	systematic review AND obstacles AND knowledge utilisation	0
8	meta-analysis AND obstacle AND knowledge utilisation	0
9	overview* OR review* AND impairment* AND knowledge translation	13
10	systematic review* OR meta-analys* AND barrier* AND decision making	16

37 citations were returned, none of which met inclusion criteria

Embase was searched from December 2010 to June 2012 using the advanced search facility

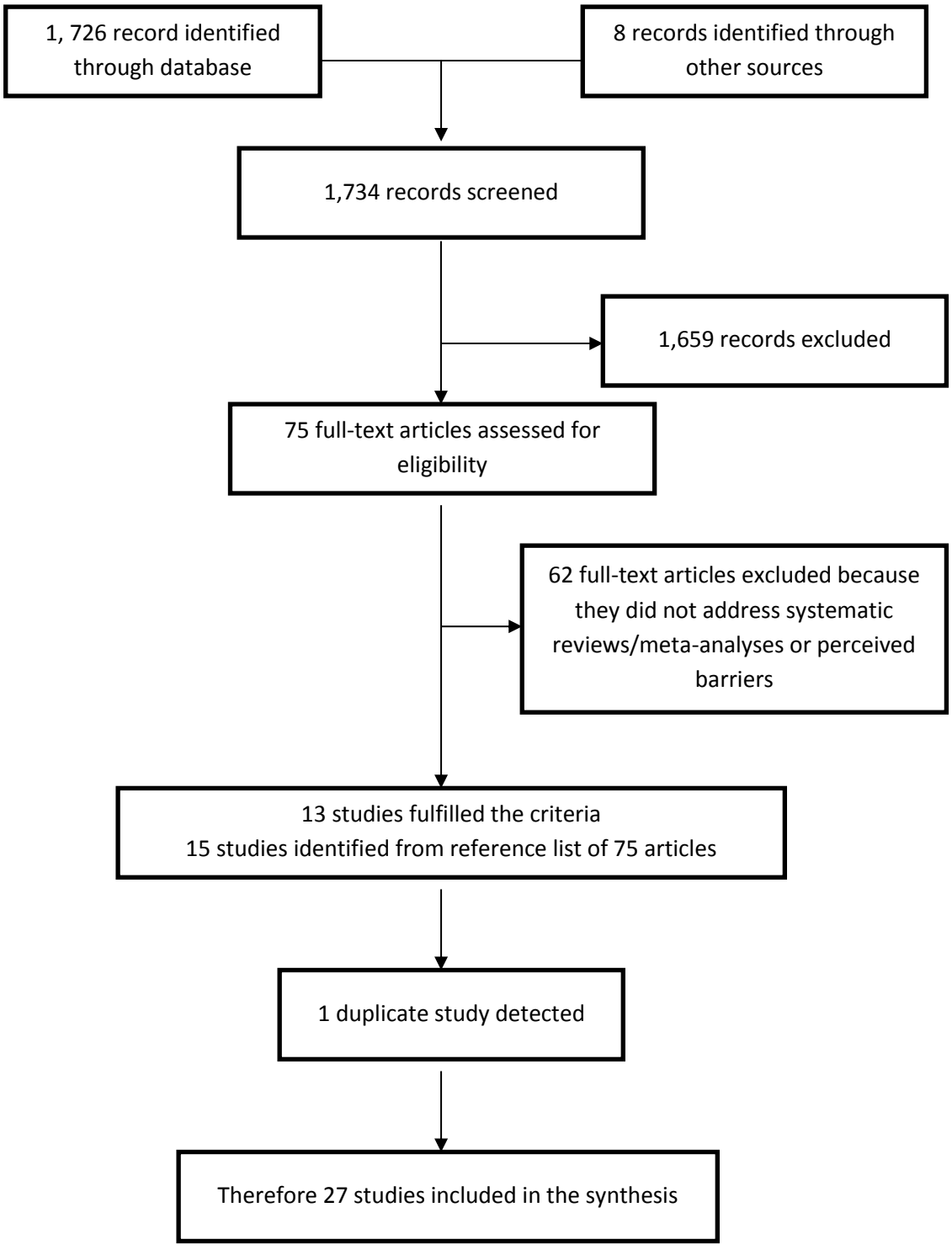
Search	Query	Items found
1	systematic review AND barriers AND knowledge uptake	14
2	meta-analysis AND barriers AND knowledge uptake	5
3	systematic review AND obstacles AND knowledge uptake	0
4	meta-analysis AND obstacles AND knowledge uptake	0
5	systematic review AND barriers AND knowledge utilisation	14
6	meta-analysis AND barriers and knowledge utilisation	0
7	systematic review AND obstacles AND knowledge utilisation	0
8	meta-analysis AND obstacle AND knowledge utilisation	0
9	overview* OR review* AND impairment* AND knowledge translation	0
10	systematic review* OR meta-analys* AND barrier* AND decision making	0

33 citations were returned, 1 full text article retrieved, no report met inclusion criteria

---

The 27 included studies encompassed 2 qualitative studies, and 25 surveys asking a total of 57 questions regarding possible barriers to uptake of evidence from systematic reviews, meta-analysis, and the databases containing them. A survey involved at least one question to a group of decisions makers about barriers to uptake of evidence from systematic reviews. Barriers were grouped into themes: 18 derived from the surveys and an additional 10 themes from the qualitative studies.

Figure 5. 1. PRISMA Flow diagram of studies through the selection process in a systematic review of barriers to the uptake of systematic reviews and meta-analyses



The studies were undertaken in the UK (n=9), Canada (n=5), Australia (n=4), USA (n=3), Ireland (n=1), Holland (n=1), New Zealand (n=1), Switzerland (n=1), India (n=1), and SE

Asia: Indonesia, Malaysia, Thailand, the Philippines (n=1). Researchers in one country, Switzerland, surveyed participants from 78 countries. Therefore, included studies reported data from decision makers in 91 countries. Of 10,218 specified participants, 64% were physicians (Table 5.2).

Table 5.2. Disciplines participating in studies of barriers to uptake of systematic reviews

Doctors:	6,549
Nurses:	1,494
Practice managers:	785
Occupational therapists:	649
Midwives:	202
Pharmacists:	178
General practice staff:	91
Surgical allied professions:	69
Policy makers:	62
Information specialists:	56
Others:	83
Total:	**10,218**

The characteristics of the included studies are given in Table 5.3. Two studies were concerned with the use of systematic review evidence for public health policy and programme management decisions. The remaining studies had a clinical practice focus concerned with investigating attitudes to evidence-based medicine. Seventeen studies (63%) were published after the year 2000.

.

Table 5.3. Characteristics of included studies in systematic review of barriers to review uptake

Year Published, Country	Objective	Design and focus	Participants	Date Conducted
Paterson -Brown et al. 1995 UK	To establish the availability of meta-analytic overviews and to find out how obstetricians keep up to date.	Telephone survey Oxford Database of Perinatal Trials	98 obstetricians	1993
Hyde et al 1995 UK	To examine use of Cochrane Pregnancy and Childbirth Database	Postal survey CPCD, Cochrane Library	274 subscribers to CPCD Included doctors	1994
Prescott et al. 1997 UK	To establish the awareness of research evidence	Self-administered, postal questionnaire survey CDSRs	800 GPs	1996
Jordans et al. 1998 Australia	To determine the proportion who report using systematic reviews	Cross-sectional telephone survey Systematic reviews	22 neonatologists obstetricians	1995
Olatunbosun et al. 1998 Canada	To examine views of EBM	Self-administered, two-page questionnaire Cochrane Library Cochrane Pregnancy and Childbirth Database	190 physicians in obstetric practice	1996
McColl et al. 1998 UK	To determine the attitude to EBM and perceived usefulness of databases	Postal questionnaire Systematic reviews Meta-analysis Cochrane Library CDSRs DARE	302 GP principals	1997
Young and Ward 1999 Australia	To determine awareness and use of the Cochrane Library and access to the Internet	Postal Questionnaire Cochrane Library	311 general practitioners	1997
Carey, et al. 1999 UK	To determine the attitudes of towards the practice of EBM	Postal questionnaire Cochrane Library	139 psychiatrists	1998

Ciliska, et al. 1999 Canada	To gain an understanding of research needs, perceptions of barriers to research utilisation, and attitudes towards systematic reviews	Telephone questionnaire survey Systematic reviews	226 decision makers in public health Included doctors	NK
McAlister et al. 1999b Canada	To assess the attitudes of general internists to EBM.	Postal Survey Cochrane Database of Systematic Reviews	294 physicians	1997
Lawrie et al. 2000 UK	To examine attitudes to evidence - based psychiatry	Survey, postal CDSRs	93 senior psychiatrists	NK
Wilson et al. 2001 UK	To identify current methods of making research evidence accessible	Postal survey Cochrane Library	1406 general practitioners	1999
Young, J and Ward, J. 2001 Australia	Examine views about EBM	Postal Survey and Semi-structured Interviews Cochrane Library	60 GPs	1999
Wilson, P. Watt, I. and Hardman, P. 2001 UK	To determine attitudes on the importance of effectiveness information	Postal questionnaire Cochrane Library	338 medical directors	1999
Kerse, N et al. 2001 NZ	Access to Internet and Cochrane Library	Cross-sectional postal and fax survey Cochrane Library	381 GPs	1999-2000
Wilson, et al. 2003 UK	To assess the awareness and use of NHSnet	Postal survey questionnaire Cochrane Library	1364 GPs: 441 nurses: 325 practice managers: 556	2001
Bennett et al. 2003 Australia	To find out about attitudes to EBP and implementation barriers	Postal questionnaire Cochrane Library	649 occupational therapists	2000

Hanson, Bhandari, Audige, and Helfet, 2004 Switzerland	To determine current understanding of study methodology and critical appraisal.	Questionnaire, self-administered Meta-analysis	532 surgeons and allied professionals from 78 countries	2002
Melnyk et al. 2004 USA	Describe major barriers and facilitators to EBP.	Limited survey CDSRs	160 nurses	2003
Dobbins, et al. 2004 Canada	To discover public health decision makers' preferences for content, format, and channels for doctors receiving research knowledge.	One-hour focus groups Systematic reviews	46 policy makers included	2002- 2003
Sur et al. 2005 USA	Investigated the attitudes of urologists toward EBM Systematic Reviews	Web-based survey Cochrane Database	714 urologists	2005
Dobbins, et al. 2007 Canada	The purpose was to identify preferences for the transfer and exchange of research knowledge.	Semi-structured interviews Systematic reviews Included a doctor	16 Policy decision-makers	2001
Poolman et al. 2007 Holland	They examined perceptions and competence in EBM	Postal survey Meta-analysis Systematic Reviews, Cochrane Library	366 orthopaedic surgeons	2005
McCaw et al. 2007 Ireland	Gain an insight into the use of Internet	Postal survey Cochrane Library	542 community pharmacists(178) GPs (364)	2005
Gavgani, and Mohan, 2008, India	Directed at exploring attitudes towards EBM	Survey method Cochrane Library CDSRs	98 physicians	2008
Martis et al. 2008 Asia	The aim was to assess current knowledge of evidence-based practice doctors	Survey, postal Reproductive Health Library, Cochrane Library	660 health care professionals included	2005

Dahn et al. 2009 USA	To investigate the attitudes of urologists to EBM	Mail survey Meta-analyses, CDSRs	889 urologists	2006

Study Quality

The included studies were limited in terms of the quality and generalizability of their results. While all but one had a well-described sampling frame (Young and Ward, 2001), just eight of the 27 studies describe selecting a random sample of participants (Table 5.4). Response rates were not mentioned in two of the 27 studies. The response rate was variable. The rate varied from 8.8% to 100% and 17 of the 27 studies describe a response rate of at least 60% . Twenty-six studies reported the number of participants investigated, with the number varying from 16 to 1,364.

The number of barriers addressed by each survey also varied. Of the 25 surveys, 8 (31%) examined only one type of barrier, and the average number of barriers examined was 1.7. None of the surveys examined 6 or more barriers and all studies relied on reported use, not actual use, of evidence.

Table 5.4. Methods and Quality of Included Studies of Barriers to Systematic Review Uptake

Study	Sample frame	Response rate	Measurement of use of evidence
Paterson -Brown et al. 1995	Purposive sample of 98 obstetricians Well-described sample	(100%) 98/98	Reported use
Hyde et al. 1995	All subscribers to CPCD Well-described sample	(71%) 274/387	Reported use
Prescott et al. 1997	Random sample of 800 GPs Well-described sample frame	(62%) 501/800	Reported use
McColl et al. 1998	Random sample of 452 GPs Well-described sample	(63%) 302/452	Reported use
Olatunbosun et al. 1998	Random sample of 190 family physicians and obstetricians Well-described sample	(76%) 148/190	Reported use
Jordans et al. 1998	Random sample of 145 Obstetricians and 104 neonatologists Well-described sample	(90%) 224/248	Reported use
Young and Ward, 1999	Random sample of 428 GPs Well-described sampling frame	(73%) 311/428	Reported use
Ciliska et al. 1999	277 who met inclusion criteria of decision makers Well-described sample	(87%) 242/277	Reported use
McAlister et al. 1999	Purposive sample of of 294 general Physicians Well-described sample	(59%) 294/521	Reported use
Carey and Hall 1999	All psychiatrists in a defined area Well-defined sample	(64%) 139/216	Reported use
Lawrie et al. 2000	All in a defined area Well-described sample	(76%) 93/123	Reported use

	but just 22/123 (17%) contributed to this review		
Wilson et al. 2001	Purposive sample of 3,087 individuals Well-described sample	(45%) 1,406/3,087	Reported use
Young, and Ward 2001	Sample of, 60 GPs Sampling frame not described	(100%) 60/60	Reported use
Wilson et al 2001	Purposive sample of 491 Medical directors Well-described sample	(69%) 338/491	Reported use
Kerse et al. 2001	Random Sample of 459 GPs Well-described sample	(83%) 381/459	Reported use
Bennett et al. 2003	Proportional random sample of 1491 occupational therapists Well-described sampling frame	(44%) 649/1491	Reported use
Wilson et al. 2003	All GPs in defined area Well-described sample	(44%) 1364/3090	Reported use
Dobbins et al. 2004	Purposeful sample Well-described sample	(77%) 46/60	Reported use
Melnyk et al. 2004	'Convenient' sample Well-described sample	(100%) 160/1600	Reported use
Hanson et al. 2004	Purposive sample of 1,064 surgeons/others Well-described sample	(50%) 532/1,064	Reported use
Sur et al. 2006	Purposive sample of 8,100 urologists Well-described sample	(8.8%) 714/8,100	Reported use
Poolman et al 2007	Purposive sample of 611 orthopaedic surgeons Well-described sample	(60%) 366/611	Reported use
McCaw et al. 2007	Sample of 1081 GPs and 522 pharmacists Well-described sample frame	(34%) 542/1603	Reported use
Dobbins et al. 2007	Purposeful sample Well-described sample	16/NK	Reported use

Gavgani And Mohan, 2008	Random sample Well-described sample	(65%) 98/150	Reported use
Martis et al. 2008	All in a defined area Well-described sample	NK	Reported use
Dahm et al. 2009	Random sample of 2000 urologists Well-described sample	(45%) 889/2000	Reported use

Characteristics of Studies

Most studies were surveys (n=25), 2 were qualitative studies with one included study using mixed methods. Data collection strategies included focus groups (n=1), individual interviews (n=1), together with mail, telephone, and web-based questionnaires (n=25). This writer found that the surveys used a heterogeneous variety of decision-making populations, based on location or speciality. They also investigated a number of resources. The surveys looked at systematic reviews, meta-analyses, The Cochrane Library, the Cochrane Database of Systematic Reviews (one of the six high-quality databases available through the Library), Database of Abstracts of Reviews of Effects, the Reproductive Health Library, also the earlier Cochrane Pregnancy and Childbirth Database and the Oxford Database of Perinatal Trials. The surveys displayed a wide range for the percentage of respondents reporting each barrier.

Identifying barriers

After classifying possible barriers into common themes, it was found that the 57 questions about obstacles to uptake of evidence from systematic reviews encompassed 28 barriers. These were grouped according to the knowledge/attitude/behaviour framework (Woolf, 1993). Barriers affecting *knowledge* could include lack of awareness, lack of familiarity

and a lack of understanding of meta-analyses. Limited awareness could impact on Cochrane reviews specifically or systematic reviews in general (Table 5.5). Lack of confidence, decreased motivation, a perceived lack of usefulness of systematic reviews and limited trust in them, were grouped under *attitudes*. Systematic review attributes, patient issues, and environmental factors have the potential to impair usage of systematic reviews. Attributes of systematic reviews such as academic terminology, and environmental factors such as limited resources or a negative organisational climate, were grouped under the *behaviour* heading.

The tables that follow, adopted from Cabana et al. (1999), outline the studies and the percentage of respondents reporting specific barriers in various surveys. The barriers are grouped under the knowledge, attitude and behaviour headings advocated by Woolf (1993) and utilised by Cabana and colleagues

Knowledge barriers and the studies citing them

Lack of awareness: Eleven studies measured lack of awareness as a possible barrier. Sample size ranged from 248 to 8,100 (median, 475) and the response rate ranged from 8.8% to 100% (median, 66%). The percentage of respondents reporting lack of awareness as a barrier was as high as 82% (DARE: McColl et al. 1998) and as low as 1% (Cochrane Library: Wilson et al. 2001a) with a median of 55%. In 9 (82%) of the 11 studies, at least 10% of the respondents cited lack of awareness as a barrier (Table 5.5).

.

Table 5.5. Lack of awareness and the studies citing this barrier	
Lack of awareness of systematic reviews	Jordans et al. (1997) **17/224 (7.5%)** Ciliska et al. (1999) **104/242 (43%)**
Lack of awareness of CDSR	McColl et al. (1998) **169/284 (60%)** Prescott et al. (1999) **328/501 (65%)** Sur et al. (2004) **385/714 (54%)** Dahm et al. (2007) **675/889 (73%)**
Lack of awareness of Cochrane Library	Young and Ward (1999) **231/311 (74%)** Kerse et al. (2001) 2**03/381 (55%)** Wilson et al. (2001a) **2/338 (1%)** Wilson et al. (2004**) 229/1364 (21%)** Martis et al. (2008) **353/660 (53%)**
Unawareness of Database of Abstracts of Reviews of Effects	McColl et al. (1998) **231/283 (82%)**
Had not heard about Reproductive Health Library	Martis et al. (2008) **483/660 (73%)**

Tables summarise while figures illustrate. Figure 5.2, a column chart, on the following page illustrates the percentage of respondents reporting lack of awareness of The Cochrane Library as a barrier across studies over time.

.

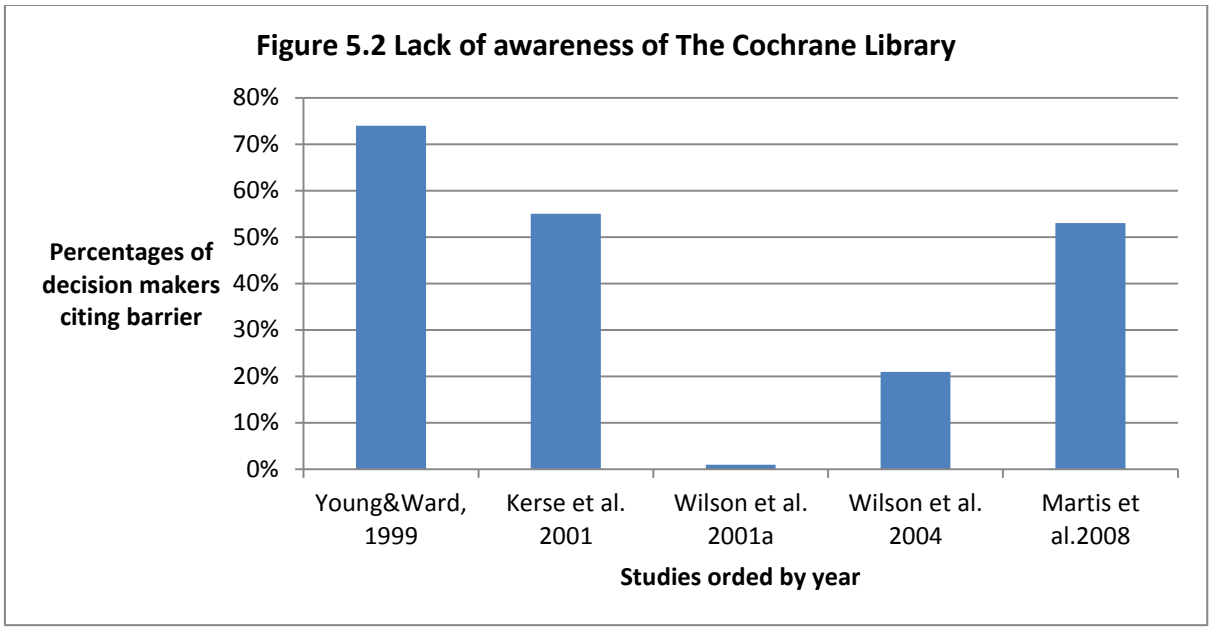
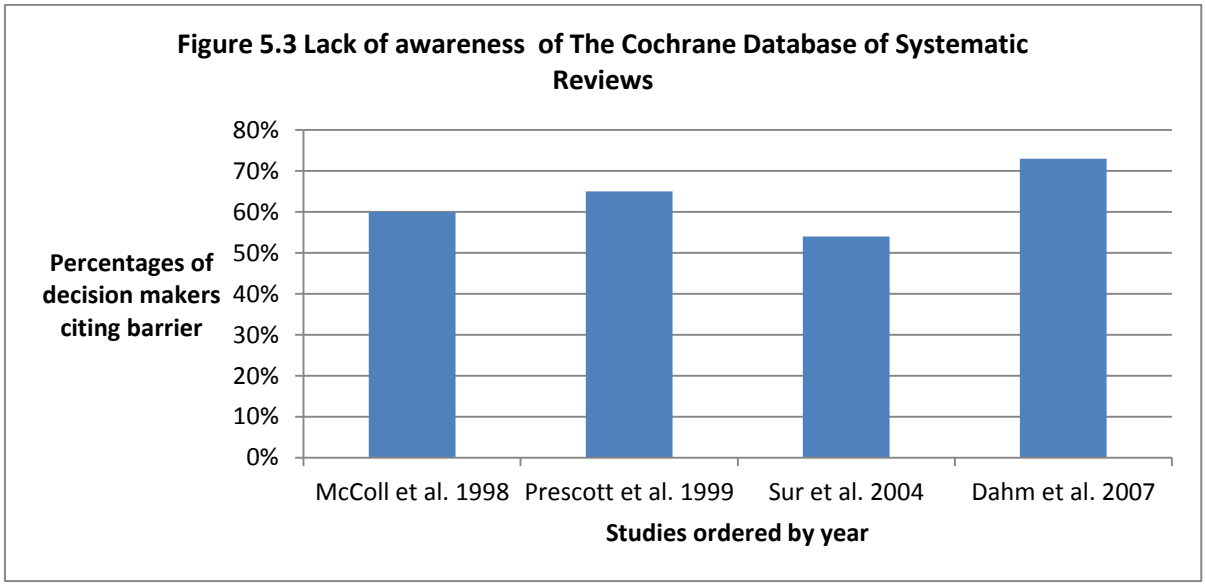


Figure 5.3 below, a column chart, illustrates the percentage of respondents reporting lack of awareness of The Cochrane Database of Systematic Reviews (CDSR) over time.



Lack of familiarity: Seven surveys measured lack of familiarity as a possible barrier. Sample size ranged from 60 to 8,100 (median, 531) and the response rate ranged from 8.8% to 100% (median, 63%). The percentage of respondents suggesting lack of familiarity as a barrier was as high as 98% (DARE: McColl et al. 1998) and as low as

19% (systematic reviews: McColl et al 1998) with a median of 70%. In 7 (100%) of the 7 surveys, at least 10% of the respondents cited lack of familiarity as a barrier (Table 5.6).

Table 5.6. Lack of familiarity and the studies citing this as a barrier

Lack of **full** understanding of systematic reviews: Unable to explain to others	McColl et al. (1998) **223/288 (77%)** Young and Ward (2001) **49/60 (81%)** Poolman et al. (2007) **134/359 (38%)**
Lack of understanding of systematic review	McColl et al. (1998) **55/288 (19%)**
Lack of understanding of meta-analysis	McColl et al (1998) **63/291 (22%)**
Lack of **full** understanding of meta-analysis: Unable to explain meta-analysis to others	McColl et al. (1998) **195/291 (67%)** Young and Ward (2001) **51/60 (85%)** Sur et al. (2004) **368/714 (51%)** Dahm et al. (2007) **578/889 (65%)** Poolman et al. (2007) **144/362 (40%)**
Lack of ability to define CDSRs	Gavgani & Moran (2008) **70/98 (72%)**
Not read the Database of Abstracts of Reviews of Effectiveness:	McColl et al. (1998) **276/283 (98%)**
Not read CDSR	McColl et al. (1998) **269/284 (95%)**
Not able to define Oxford Database of Perinatal Trials	Paterson-Brown et al. (1995) **70/98 (71%)**

Figure 5.4 illustrates how the percentage of respondents citing lack of familiarity with systematic reviews as a barrier in each study varied over time.

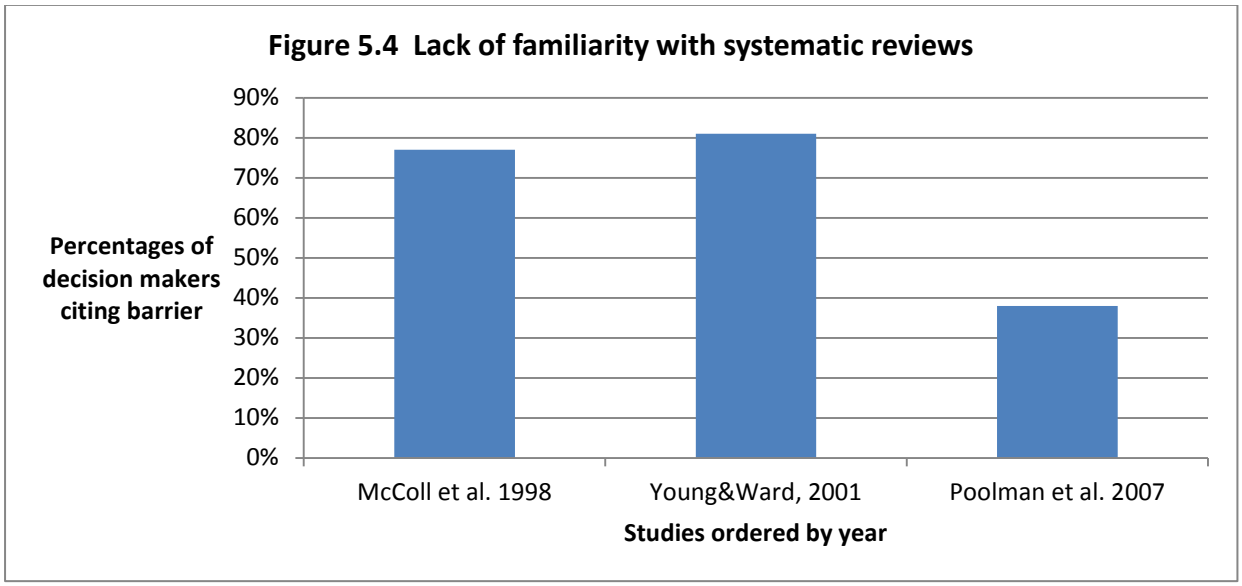
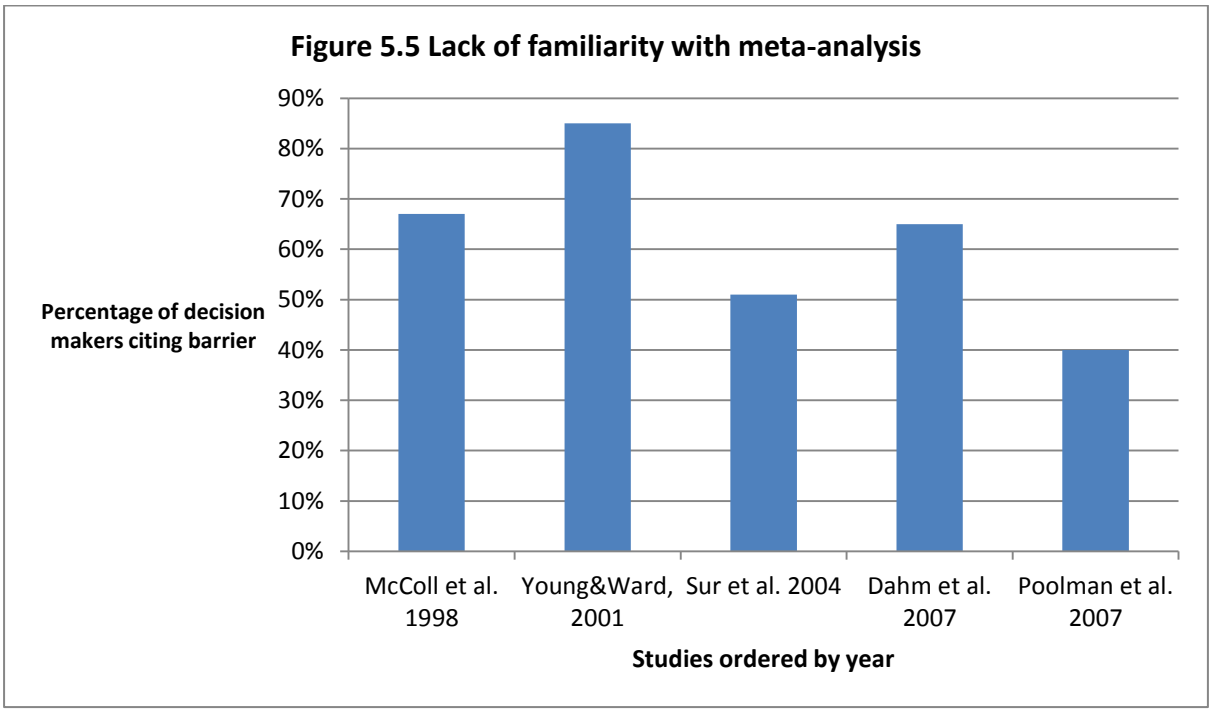


Figure 5.5 below illustrates how lack of familiarity as a perceived barrier to uptake of meta-analysis appears to be generally decreasing over time.



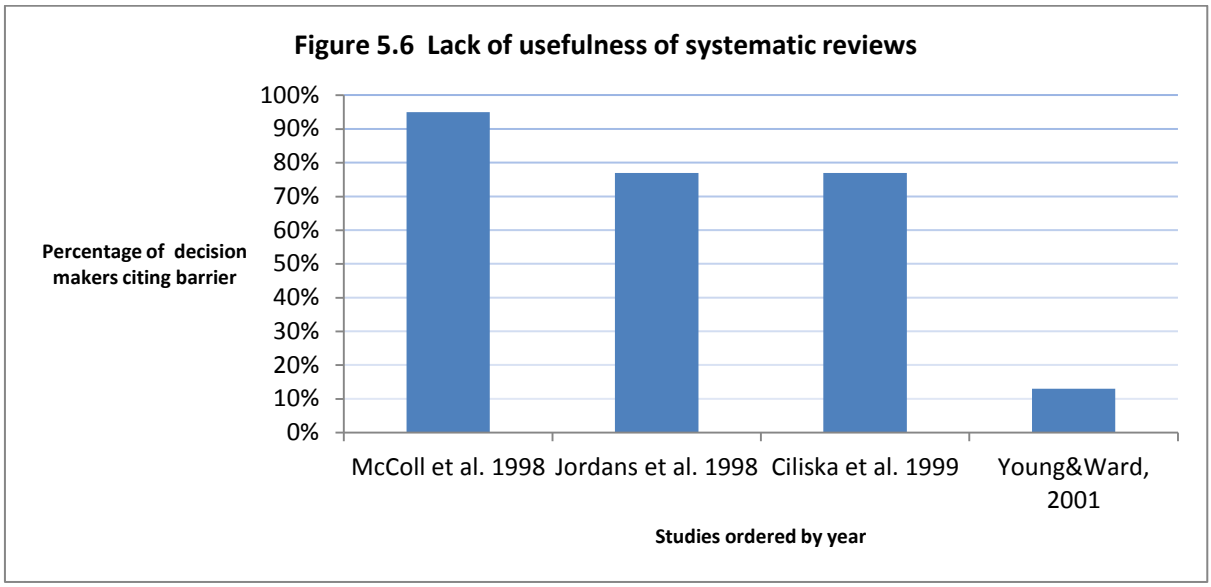
Attitude barriers and the studies citing them

*Lack of usefulness***:** Seven surveys measured lack of perceived usefulness as a possible barrier. Sample size ranged from 60 to 491 (median, 350), and the response rate ranged from 63% to 100% (median, 87%). The sample size and response rate were not reported in 1 of the studies (Martis et al. 2008). The percentage of respondents identifying lack of usefulness as a barrier was as high as 95% (systematic reviews, McColl et al. 1998) and as low as 7% (Cochrane Library, Wilson et al. 2001a) with a median of 16.5%. In all of the seven surveys, at least 10% of the respondents cited lack of usefulness as an issue (Table 5.7).

Table 5.7. Lack of usefulness and the studies citing this barrier

Lack of usefulness of systematic reviews .	McColl et al. (1998) **286/302 (95%)** Jordans et al. (1998) **170/225 (77%)** Ciliska et al. (1999) **186/242 (76.8%)** Young and Ward (2001) **8/60 (13%)**
Cochrane Library (CL) not useful .	Young and Ward (2001) **8/60 (13%)** Martis et al. (2008) **57/140 (40%)** Gavgani&Mohan (2008) **69/98 (71%)**
Found RHL only useful sometimes	Martis et al. (2008) **30/70 (43%)**
Cochrane Library (CL) not useful to inform clinical decision making	Wilson et al. (2001a) **22/169 (13%)**
CL not useful to inform policy making	Wilson et al. (2001a) **19/169 (11%)**
CL not useful to guide research	Wilson et al. (2001a) **28/169 (17%)**
CL not useful to find references	Wilson et al. (2001a) **27/169 (16%)**
CL not useful to find evidence for clinical guidelines	Wilson et al. (2001a) 1**2/169 (7%)**
CL not useful to provide standards for clinical audit	Wilson et al. (2001a) **19/169 (11%)**

Figure 5.6 illustrates how the perceived lack of usefulness of systematic reviews has decreased over time.



Lack of motivation: Four studies measured lack of motivation as a possible barrier. Sample size ranged from 98 to 8,100 (median, 1,305). The percentage of respondents identifying this barrier was as high as 10% (Oxford Database of Perinatal Trials, Paterson-Brown et al. 1995) and as low as 2% (Meta-analysis, Sur et al. 2006) with a median of 3.6%. In none of the surveys did more than 10% of respondents report lack of motivation as a barrier (Table 5.8).

Table 5.8. Lack of motivation and the studies citing this barrier

No wish to understand meta-analysis	Sur et al. (2006) **11/714** (**2%**) Poolman et al. (2007) **10/362 (2.8%)** Dahm et al (2009) **45/889 (5%)**
Don't need Oxford Database Perinatal Trials	Paterson-Brown et al. (1995) **10/98 (10%)**

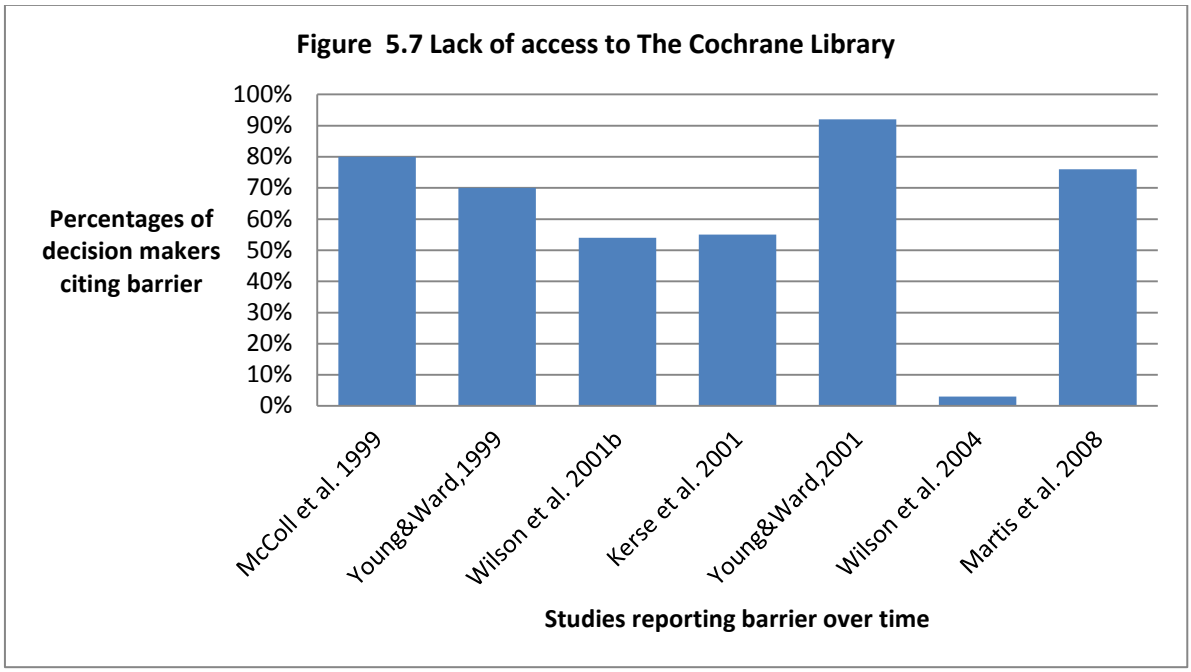
Behavioural barriers and the studies citing them

Lack of access: Eleven surveys measured lack of access as a possible barrier (Table 5.9). Sample size ranged from 60 to 3,087 (median, 440), and the response rate ranged from 44% to 100% (median, 71%). The sample size and response rate were not reported in one study (Martis et al. 2008). The percentage of respondents identifying lack of access as a barrier was as high as 95% (Wilson et al. 2001b, lack of easy access to Cochrane Library) and as low as 3% (Wilson et al. 2003, lack of access to Cochrane Library), with a median of 55%. In 10 (91%) of the 11 surveys, at least 10% of the respondents cited lack of access as a barrier (5.7).

Table 5.9. Lack of access and the studies citing this as a barrier

Lack of access to systematic reviews	Jordans et al. (1997) **49/224 (21%)**
Lack of access to relevant meta-analysis	Paterson-Brown et al.(1993) **36/98 (36.7%)**
Lack of access to Cochrane Library	McColl et al (1999) **242/302 (80%)** Young and Ward (1999) **218/311 (70%)** Wilson et al. (2001b) **766/1406(54%)** Young and Ward (2001) **55/60 (92%)** Kerse et al. (2001) **203/381(55%)** Wilson et al. (2004) **41/1364** (**3%)** Martis et al. (2008) **504/660 (76%)**
Lack of easy access to Cochrane Library	Wilson et al. (2001b) **1337/1406 (95%)** Wilson et al. (2001a) **110/338 (33%)**
Lack of access to Cochrane Library at surgery	Carey and Hall, (1999) **107/139 (77%)**
No availability of the Oxford Database of Perinatal Trials:	Paterson-Brown et al. (1995) **71/98 (72%)**
Did not have access to RHL	Martis et al. (2008) **94/177 (53%)**

Figure 5.7 illustrates the percentage of respondents reporting lack of access to The Cochrane Library as it varies over time, with the difference between two large studies (Wilson et al. 2001b, Wilson et al. 2004) indicating that lack of access is decreasing as a perceived barrier over time.



External barriers: Five studies investigated 10 external barriers to overview uptake. The external barriers investigated were environment related in 5 studies and overview related in one study, with no patient related barriers cited. More than 10% of respondents cited lack of resources, lack of policy climate (Ciliska et al. 1999), lack of workshop attendance (Martis et al. 2008), and lack of training in Cochrane Library use (Wilson et al. 2001a, Wilson et al. 2004) as possible environmental barriers, though not lack of time (Wilson et al. 2001a). More than 10% of respondents cited the limited range of topics covered (Wilson et al. 2001a) as a possible overview uptake barrier (Table 5.10).

Table 5.10. Environmental barriers and the studies citing them	
LACK OF POLICY CLIMATE	Ciliska et al. (1999) 1**69/242 (70%)**
LACK OF RESOURCES	Ciliska et al. (1999) **188/242 (78%)**
LACK OF TIME Time required to use and search for information	Wilson et al. (2001a) **6/127 (5%)**
LACK OF TRAINING Cochrane Library workshop non-attendance	Martis et al. (2008) 3**11/660 (70%)**
Lack of training to use the Cochrane Library	Wilson et al. (2001a) **135/169 (80%)** Wilson et al. (2004) **1250/1364 (92%)**
Had not attended a workshop on RHL	Martis et al. (2008) **42/70 (60%)**
REVIEW FACTORS A limited range of topics and clinical areas covered	Wilson et al. (2001a) **44/127 (35%)**
Narrow focus on RCTs and meta-analysis	Wilson et al. (2001a) **11/127 (9%)**
Not regularly updated enough	Wilson et al. (2001a) **9/127 (7%)**
Poorly promoted /marketed	Wilson et al. (2001a) **8/127 (6%)**

Lack of use: Fourteen surveys looked at lack of actual use of overviews as a potential barrier to their uptake (Table 5.11). Sample size ranged from 150 to 8,100 (median, 490) and the response rate ranged from 8.8% to 100% (median, 63%). The percentage of respondents reporting lack of use was as high as 99% (DARE, McColl et al. 1999) and as low as 18% (Cochrane Library, Martis et al. 2008) with a median of 78%. In all 14 of the surveys, at least 10% of the respondents did not use overviews or the databases containing them.

Table 5.11. Lack of use and the studies citing this barrier

Lack of use of systematic reviews	Jordans et al. (1998) **98/224 (44%)**
Lack of use of CDSR	Prescott et al. (1999) **456/501 (91%)** McColl et al. (1999) **273/284 (96%)** Melynk et al. (2004) **110/160 (69%)** Sur et al. (2004) **532/ 714 (75%)** Dahm et al. (2007) **817/889** (**92%)**
Lack of use of CDSR on a regular basis	McAlister et al. (1999) **279/294 (95%)** Sur et al. (2004) **65/714 (93%)**
Lack of use of Cochrane Library Lack of regular use	Young and Ward (1999) **287/311 (92%)** Kerse et al. (2001) **309/381 (83%)** Wilson et al. (2001a) **169/338** (**50%)** Wilson et al. (2003) **1063/1364 (78%)** Poolman et al. (2007) **128/367 (35%)** Gavgani & Mohan, (2008) **35/98 (36%)**
Lack of easy use of Cochrane library	Wilson et al. (2001a) **46/169 (27%)**
With access to The Cochrane Library had never used it did not use it more than once a week	 Martis et al. (2008) **28/156 (18%)** Martis et al (2008*)* **144/156 (92%)**
Aware of but never used The Cochrane library	Wilson et al. (2001) 1**04/338 (31%)**
Of those who subscribed, that did not use Cochrane Pregnancy and Childbirth Database	Hyde et al. (1995) **38/274 (14%)**
Not used in clinical decision making-DARE:	McColl et al. (1999) **281/283 (99%)**

Figure 5.8 illustrates the variation in the percentages of respondents citing lack of usage of the CDSR as a barrier over time.

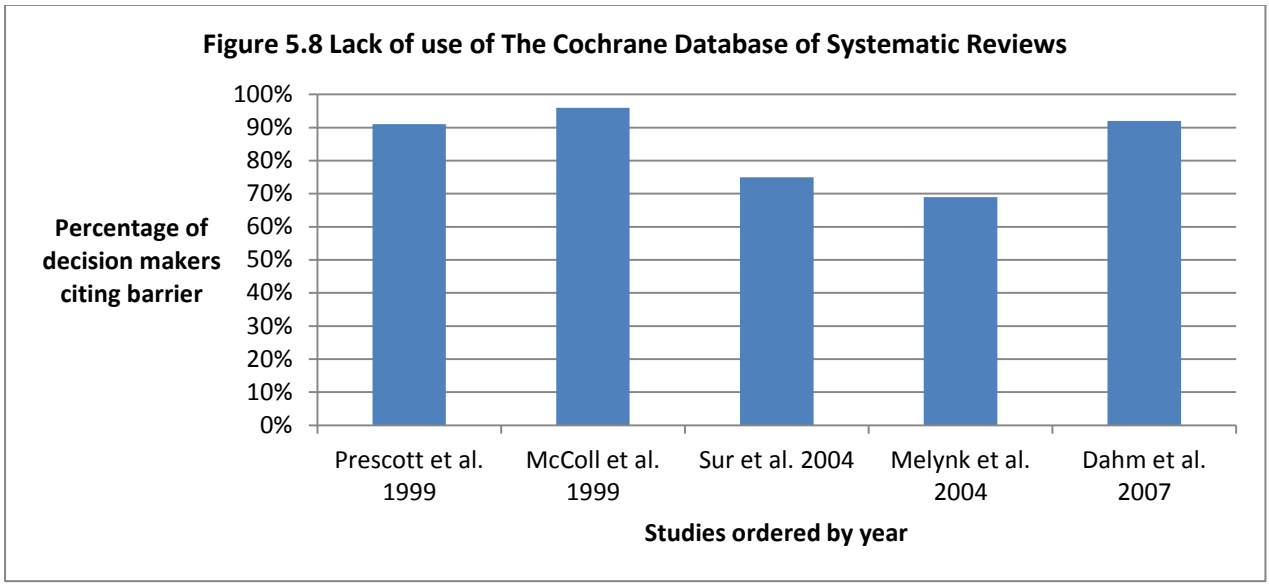
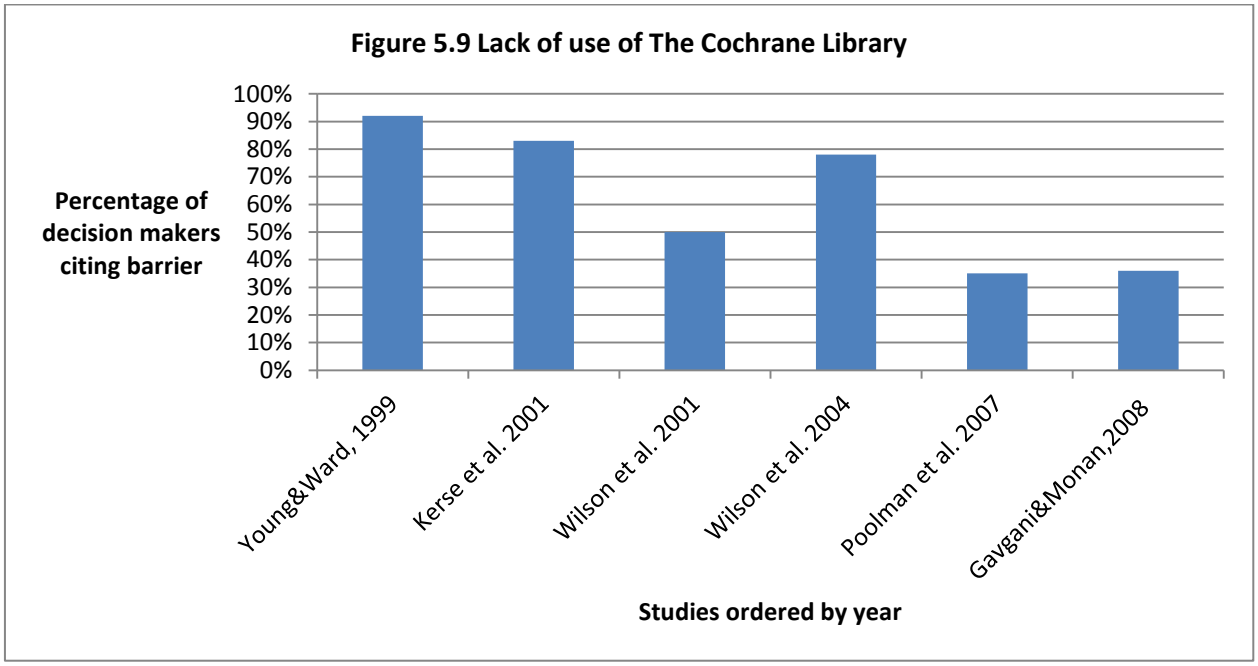


Figure 5.9 illustrates how reported lack of use of The Cochrane Library has gradually decreased as a perceived barrier, according to the different studies over time.



In summary**,** a total of 63 questions were asked about varied, potential obstacles to uptake of evidence from systematic, meta-analysis and their databases in the 25 surveys. A summary of the number of detected barriers investigated by each study is given in Table 5.12.

Table 5.12. Number of detected barriers investigated by each study to uptake of evidence from systematic reviews, meta-analyses, and the databases containing them

Surveys	Number of barriers addressed by each study
Wilson et al. (2001)	4: lack of access, awareness, use, and training
Paterson-Brown et al. (1995)	2: lack of access, awareness
Hanson et al. (2004)	2: lack of trust, training
Poolman et al. (2007)	2: lack of understanding, use
Sur et al. (2006)	3: Lack of awareness, use, and understanding
Dahm et al. (2009)	3: Lack of awareness, use, and understanding,
McAlister et al. (1999)	1: Lack of use
Wilson et al. (2001)	1: Lack of access
Ward and Young (2001)	3: Lack of access, understanding, usefulness,
McCaw et al. (2007)	1: Lack of use
Kerse et al. (2001)	3: Lack of access, awareness, use
McColl et al. (1998)	3: Lack of awareness, access, and understanding
Bennett et al. (2001)	1: Lack of confidence
Young and Ward (1999)	3: Lack of awareness, access, use
Paterson-Brown (1993)	3: Lack of awareness, availability, and need
Prescott et al. (1999)	2. Lack of use, awareness
Jordan et al. (1999)	3: Lack of use, awareness, access
Ciliska et al. (1999)	4: Lack of awareness, use, policy climate, resources
Olatunbosun et al. (1998)	1: Lack of access
Melnyk et al. (2004)	1: Lack of use
Gavgani et al. (2008)	2: Lack of use, usefulness
Wilson et al. (2003)	4: Lack of access, awareness, use, and training
Carey and Hall, (1999)	1: Lack of access
Lawrie et al. (2000)	1: Inability to search
Hyde et al. (1995)	1: Inability to search
Martis et al. (2008)	5: Lack of access, awareness, use, usefulness, training,
Qualitative studies:	
Dobbins et al. (2004)	2: Lack of access, training
Dobbins et al. (2007)	4: Lack of relevance, implications, implementation strategies, understanding of the information needs of the target audience.
Wilson et al. (2001)	6. Limited range, access, focus, use, up-datedness, promotion and time

The barriers addressed in the surveys were grouped under the headings of knowledge, attitude, and behaviour (Table 5.13).

Table 5.13. Barrier Category and Barrier Descriptive Findings

Barrier category	Barrier Descriptive
Knowledge barriers	Eleven studies measured lack of awareness as a possible barrier. The percentage of respondents reporting lack of awareness as a barrier was as high as 82% and as low as 1%, with a median of 55%. Seven surveys measured lack of familiarity as a possible barrier. The percentage of respondents suggesting lack of familiarity as a barrier was as high as 98 and as low as 19%, with a median of 70%.
Attitudinal barriers	Seven surveys measured lack of perceived usefulness as a possible barrier. The percentage of respondents identifying lack of usefulness as a barrier was as high as 95% and as low as 7%, with a median of 16.5%. Four studies measured lack of motivation as a possible barrier. The percentage of respondents identifying this barrier was as high as 10% and as low as 2% with a median of 3.6%.
Behaviour barriers	Eleven surveys measured lack of access as a possible barrier. The percentage of respondents identifying lack of access as a barrier was as high as 95% and as low as 3%, with a median of 55%. Five studies investigated 10 external barriers to review uptake. More than 10% of respondents cited lack of resources, lack of positive policy climate, lack of workshop attendance, and lack of training as possible environmental barriers. Fourteen surveys looked at lack of use of systematic reviews. The percentage of respondents reporting lack of use was as high as 99% and as low as 18% with a median of 78%.

Particular barriers and the studies addressing them have been outlined. Appendix 4, adopted from Cabana et al. (1999), adopts a slightly different approach and, emphasising the evidence source, lists the studies investigating barriers to the uptake, specifically, of systematic reviews, then meta-analyses, followed by the Cochrane Database of Systematic Reviews, The Cochrane Library, DARE, Cochrane Pregnancy and Childbirth Database, and the Oxford Database of Perinatal Trials. The number of respondents reporting the barrier is also listed.

Qualitative studies

Two qualitative studies cited six important barriers to evidence uptake from systematic reviews (Dobbins et al. 2004, Dobbins et al. 2007). They emphasised lack of accessibility. They also cited a lack of training in the purpose and methodology of systematic reviews as a barrier to uptake. Content issues such as lack of relevance, lack of implications for practice, and limited implementation strategies were also cited. A deficient understanding of the information needs of the target audience of systematic reviews was also raised as a major barrier.

One study had a qualitative element exploring the perceived weaknesses of The Cochrane Library (Wilson et al. 2001a). Participants suggested as barriers the limited range of topics covered by reviews, poor access, the narrow focus on RCTs and meta-analysis, difficulty of use, lack of regular update, poor promotion, and the time required to use and search the related database.

5.7 Discussion

The results section of a systematic review attempts a qualitative description of principal findings (Bauchner et al. 2013). This review identified a number of factors that if addressed would improve the uptake of evidence from systematic reviews (Lawrence et al. 2012). While access is improving, The Cochrane Library is still not free in all countries and lack of access is still seen as a significant barrier. Access, of course, impacts on awareness and familiarity. While The Cochrane Library has achieved widespread awareness, in the majority of the studies more than 10% of participants still

cited lack of awareness of systematic reviews, or the databases that contain them, as a barrier.

Casual awareness does not guarantee familiarity with systematic reviews. Lack of familiarity was more common than lack of awareness (McColl et al. 1998). Furthermore, at least 10% of the respondents in each study, cited the lack of usefulness of systematic reviews as a significant obstacle.

A negative attitude and a lack of knowledge may inhibit the uptake of systematic reviews. However, factors related to the review itself, the patient, or wider environmental barriers may also impair uptake. Limited relevance and a paucity of implications for practice were seen as barriers, together with the limited range of topics covered (Wilson et al. 2001a). More than 10% of respondents cited lack of a receptive policy climate (Ciliska et al. 1999) and lack of training in database searching (Wilson et al. 2003), as possible environmental barriers.

Good quality surveys, using a random sample, with a well-described sampling frame, a good response rate, and addressing more than one barrier, all emphasize the lack of actual use of systematic reviews as a formidable barrier. The remaining studies tend to highlight lack of access, awareness and familiarity as obstacles to systematic review uptake. More everyday usage of systematic reviews should improve attitudes to this form of evidence. However, there were indications that this was not happening.

Surprisingly, lack of time and motivation did not emerge as major barriers to systematic reviews uptake.

Limitations

Systematic reviews often cover only a small fraction of the geographical and taxonomic breath they initially aimed to address (Cook et al. 2013). Many reviews avail of seven or fewer databases (Lawrence et al. 2012). The extensive and systematic literature search using 19 databases, with a special emphasis on grey and qualitative literature, is one of the strengths of this systematic review. Explicit inclusion criteria and a transparent approach to collecting data were also utilised. The limitations of our systematic review largely reflect the shortcomings and age of the reports reviewed.

All the 27 included studies, except the two qualitative studies, were surveys using closed-ended questions. This meant that the obstacles addressed were dependent very much on investigator preference. A fear of being outside a consensus for instance, was not specifically investigated as a barrier. Use of a different taxonomy may have altered our findings. But the taxonomy selected and used here compares well to other taxonomies (Espeland et al. 2003).

Because much of the research in the knowledge translation field is poorly indexed in electronic databases and spread over many disciplines, relevant studies may have been overlooked. Searching the reference lists of related studies yielded additional reports that were not found in the original searches.

Another potential defect is the use of participant self-ratings. The individual studies depended on the decision maker's perceptions and views. Actual clinical practice was not assessed. Whether an obstacle is real or perceived may affect the strategy required to address the identified barrier.

Some of the included studies were limited with respect to sampling and generalizability. Some surveys were small and used non-random samples confined to specific groups. This limits the extent to which the findings can be generalised. A well-described sampling frame and a good response rate improve our confidence in a study's results. A low response rate in some of the surveys increases the potential for selection bias. The external validity of the studies can be questioned as a poor response rate increases the impact of non-responder bias in the survey results (Dahm et al. 2009). However, by including a wide range of decision makers in the systematic review, this increases our appreciation of how differences in health-care systems can impact on review uptake.

Implications

This analysis offers a list of reasons for understanding why decision makers may be disinclined to use systematic reviews. A number of the barriers already cited by Cabana and colleagues to guideline adherence were identified, though in our study, time constraints, limited motivation and patient related factors were not highlighted. The results of this review have a number of implications for systematic review uptake in particular and evidence uptake in general.

Despite the high regard in which systematic reviews and The Cochrane Library are held, there are a variety of barriers to systematic review uptake. These include lack of access, lack of awareness, lack of familiarity, lack of perceived usefulness, limited actual use in practice and finally, a number of external barriers to do with systematic review content, presentation, and also wider organisational factors.

In terms of future research, few studies appear to have considered the full variety of barriers that must be overcome to achieve enhanced uptake. The average number of barriers examined was 1.7. By not investigating a full variety of barriers, strategies to improve use are less likely to address all the important factors inhibiting systematic review uptake and, as a result, are less likely to be successful (Cabana et al. 1999). Interventions designed to change practice should be based on an accurate assessment of the factors that support targeted health outcomes (Grol et al. 1999). The accuracy of this assessment is directly related to the future impact of the intervention (Bloom et al. 2005). If we accept this finding, then it is vital to identify the factors that influence the uptake of evidence from systematic reviews in order to help develop targeted interventions to enhance information uptake from this important resource (Cochrane et al. 2007). Future research needs to address a fuller range of impediments to evidence uptake. Practical difficulties encountered in using systematic reviews should be observed and documented by researchers through 'user testing' of this source of evidence by participants (Rosenbaum et al. 2008).

Access to The Cochrane Library is critical in order to advance evidence-based healthcare. Connectivity seems to have increased but access and use of databases needs to be improved. Even different professionals working in the same clinical setting can have different levels of access to the same database, an issue deserving of further investigation (Wilson et al. 2003).

If most of those who have access to the database then go on to actually use The Cochrane Library, access may be an important issue to be investigated further. Good quality evidence suggests that lack of use is an important barrier. Strategies to assist those least

likely to use Cochrane databases may help the move towards evidence-based practice (Kerse et al. 2001).

5.8 Conclusion

Much work has been done on the barriers to uptake of evidence from clinical practice guidelines (Cabana et al. 1999). The barriers that Cabana and colleagues commonly identified to guideline adherence were lack of awareness, limited familiarity, lack of belief in a good outcome after adopting the guideline, and the inertia of previous practice including lack of motivation.

Lack of time and motivation to use integrative, quality reviews did not emerge as major obstacles to systematic review uptake in our study. However, in common with research on the uptake of evidence in general, lack of access and limited awareness continue to be significant perceived barriers to systematic review uptake. Importantly, there is strong evidence to indicate that lack of practical use of systematic reviews continues to present a major challenge to evidence uptake. To become familiar with an innovation, it must be used. For systematic reviews, this is not happening often enough.

It is important to understand and overcome these potential barriers (Lawrence et al. 2012). Strategies to improve uptake of reviews should emphasize the usefulness of reviews for research and clinical practice. They should also provide a practical opportunity to use and become familiar with systematic reviews and the databases containing them, preferably in an organizational climate that values research.

To this writer's knowledge, this study represents the first systematic review of a diverse group of decision makers, of the barriers to the uptake of evidence from systematic reviews, meta-analyses and their related databases. The results presented here have immediate and practical relevance for clinicians and organisations that are trying to improve access to the best available evidence and enhance its use in routine practice. These findings provide a sound basis on which to plan future interventions to enhance the uptake of evidence from systematic reviews and meta-analyses among physicians and other decision makers, leading to improved quality of care for the individual patient.

5.9 ABSTRACT

Title

Barriers to the uptake of systematic reviews and meta-analyses: a systematic review of decision makers' perceptions.

Objective

To identify the barriers to the uptake of research evidence from systematic reviews and meta-analyses by all decision makers.

Methods

Inclusion criteria: Studies were included if they addressed perceived barriers to uptake of evidence specifically from systematic reviews, meta-analyses and the databases that

contained them. Barriers could be reported via surveys or through qualitative research such as interviews and focus groups. The views of all decision makers were eligible and reports in any language were included.

Information sources: Nineteen databases were searched including PubMed, Embase and The Cochrane Library, covering the full range of publication years from inception to December 2010, utilising three search engines. Reference lists of primary studies and related reviews were also consulted.

Risk of bias assessment: One investigator screened titles to identify candidate articles then two reviewers independently assessed the quality and the relevance of retrieved reports. In order to assess the quality of the studies, the sampling strategy of the primary studies, response rate, and methodological approach, including data collection methods, were assessed.

Data extraction: The methods of included studies and the extracted data were summarised in tables and then analysed. Using a pre-established taxonomy, the barriers were organized into a framework according to their effect on knowledge, attitudes, or behaviour.

Results

Included studies: Of 1,726 articles initially identified, 27 unique published studies were selected describing at least 1 barrier to the uptake of evidence from systematic reviews. These studies included a total of 25 surveys and 2 qualitative studies. Of the specified participants (n=10,218), the majority were physicians (64%).

Synthesis of results: The most commonly investigated barriers were lack of use (14/25), lack of awareness (11/25), lack of access (11/25), lack of familiarity (7/25), lack of usefulness (7/25), lack of motivation (4/25), and external barriers (5/25). Good quality studies, employing a random sample, a well-described sampling frame, a good response rate, and addressing more than one barrier, all implicate the lack of actual use of systematic reviews as a major barrier.

Discussion

Strengths and limitations of the evidence: The 27 included studies, except the two qualitative studies, were surveys using closed-ended questions, dependent on investigator preference. Much of the research in the knowledge translation field is poorly indexed in electronic databases so relevant studies may have been overlooked. The extensive and systematic literature search using 19 databases, with a special emphasis on grey and qualitative literature, is one of the strengths of this systematic review.

Interpretation

This systematic review reveals that strategies to improve uptake of evidence from reviews and meta-analyses will need to overcome a wide variety of obstacles. This review describes the reasons why knowledge users, especially physicians, do not call on systematic reviews. This study can inform future approaches to enhancing systematic review uptake and also suggests potential avenues for future investigation.

Funding

No internal or external funding was involved in the conduct of this research.

The next chapter outlines the conduct of a systematic review that identified the perceived or 'natural' facilitators to the uptake of evidence from systematic reviews and meta-analyses. This is followed by a chapter containing the systematic review that identified interventions, based on outcome studies, associated with enhanced systematic review uptake.

CHAPTER 6

FACILITATORS TO KNOWLEDGE TRANSLATION FROM SYSTEMATIC REVIEWS

CONTENTS

6.1	**Introduction**	**250**
6.2	**Background**	**251**
6.3	**Methods**	**251**
6.4	**Results**	**260**
6.5	**Discussion**	**275**
6.6	**Conclusions**	**280**
6.7	**Abstract**	**281**

IDENTIFICATION OF FACILITATORS TO SYSTEMATIC REVIEW UPTAKE

6.1 Introduction

In this chapter, the facilitators to uptake of evidence from systematic reviews are identified. In the previous chapter, a systematic review of the barriers to uptake was carried out while in the next and seventh chapter, outcome studies or interventions that enhance uptake of systematic reviews are identified.

Systematic reviews should be able to increase the likelihood that they will be used. When attempting to improve the uptake of systematic reviews, similar to attempts to implement clinical practice guidelines, it is important to identify specific facilitators to change, using theoretical frameworks of behaviour change. It is then possible to develop strategies that build on these facilitators. Facilitators of optimum practice in general have already been addressed in previous research. Here, this writer set out to identify the facilitators specifically to uptake of evidence from systematic reviews, meta-analyses and the databases that contain them (Wallace et al. 2012b). This writer focused on all decision makers including physicians. Such identification of uptake enhancers can help developers of systematic reviews, health-care services researchers, and clinicians design effective interventions to improve uptake of research evidence from systematic reviews and meta-analyses. Such an identification of facilitators of uptake constitutes an important, incremental contribution in bridging a significant knowledge gap.

6.2 Background

A large gap exists between science and clinical practice. The disparity is striking. Interventions designed to change practice should be based on an accurate assessment of barriers and facilitators (Cochrane et al. 2007). The accuracy of this assessment is directly related to the future effectiveness of the intervention (Bloom et al. 2005). So it is important to identify the facilitators to the uptake of evidence from systematic reviews. Accordingly, this writer set out to review studies that attempted to identify the facilitators to the uptake of evidence from systematic reviews as perceived by a variety of decision makers. The protocol is maintained by the author (Wallace et al. 2012b).

6.3 Methods

Search strategy

Billions of dollars are spent on research that is difficult to find (Maclehose and Hilton, 2013). An important feature of the systematic reviews conducted here is the extensive search strategies employed. A systematic review of the literature was conducted in order to identify facilitators to evidence uptake from systematic reviews, with grey literature and translation research specifically covered. In total, nineteen databases were searched and three search engines were utilised (Box 6.1).

Box 6.1. Search engines used

Google

Google scholar

Alta Vista

A search for previous overviews on the same or related topics was carried out (Box 6.2). The aim was to ascertain if a systematic review had already addressed the research question. Having established that the question had not been looked at previously through systematic review methodology, the second aim was to scrutinise the reference lists of related reviews for relevant primary studies.

Box 6.2. Eleven Databases Searched for Overviews

1) Cochrane Library
2) DARE and HTA. http://www.york.ac.uk/inst/cdr/crddatabases.htm
3) TRIP. http://www.tripdatabase.com/index.html
4) National Guideline Clearing House. http://www.guideline.gov/
5) NICE
6) Campbell Collaboration. http://www.cambellcollaboration.org/frontend.aspx
7) PubMed
8) Embase
9) PsycInfo
10) Health Evidence. http://www.health-evidence.ca/
11) Joanna Briggs Institute. http://www.joannabriggs.edu.au/about/home.php

The resources outlined in Box 6.3 were searched for primary studies.

Box 6.3. Resources searched for primary studies

Cochrane Library

PubMed

Embase

PsycInfo

CINAHL

Theses and Dissertations: Index to Theses in Great Britain and Ireland and ProQuest

Dissertations & Theses Databases

Reference Lists of Overviews

Reference Lists of Guidelines

Grey Literature

Some research is never published by commercial publishers (Maclehose and Hilton, 2013). A specific search using a number of databases was also conducted for grey literature (Box 6.4). Grey literature is information not under the jurisdiction of commercial publishers. It is especially important to those involved in knowledge translation. In general, grey literature publications are non-conventional, fugitive, and sometimes 'ephemeral' publications (Alberani, 1990). Due to the nature of grey literature, librarians have had difficulty acquiring and making accessible this form of evidence.

Box 6.4. Grey literature search

Conference Papers Index

Web of Science- Conference Proceedings Citation Index accessed via Web of Science

British Library

Centre for Reviews and Dissemination

National Guideline Clearinghouse

TRIP database for evidence-based medicine

The Irish Health Service Executive Database

OpenSIGLE: System for Information in Grey Literature in Europe

Index to Theses in Great Britain and Ireland

ProQuest Dissertations & Theses

Knowledge translation

This writer was concerned with how to improve the uptake of research evidence from systematic reviews by potential users, so as to facilitate evidence-based practice. Searching for material related to knowledge translation (KT) can be difficult. KT is a relatively new field that interrelates with several existing disciplines. One resource that consolidates much information that is useful to KT practitioners and researchers is TRIP. Other useful resources are listed in (Box 6.5).

Box 6.5. Databases encompassing KT and qualitative studies

Google scholar

CINAHL

Atlantic Health Promotion Research Centre KT Library, Dalhousie University.
http://www.ahprc.dal.ca/kt/library.cfm

Canadian Health Services Research Foundation.
http://www.chsrf.ca/knowledge_transfer/index_e.php

Cochrane Effective Practice and Organisation of Care Group, University of Ottawa.
http://www.epoc.cochrane.org/en/index.html

KT+, McMaster University. http://plus.mcmaster.ca/kt/Default.aspx

Keenan Research Centre - Research Programs Joint Program in Knowledge Translation.
http://www.stmichaelshospital.com/research/ktliterature.php

New York Academy of Medicine (http://www.nyam.org/library/pages/grey_literature_report

---

The search of 19 databases covered the full range of publication years to December 2010 and 3 search engines were used to search for articles, published in any language and with any publication status. A combination of index terms and text words derived from relevant articles previously identified was used. References from included studies and related review articles were scanned, experts in the field contacted, and bibliographies of textbooks were reviewed. The following index terms and text words derived from relevant articles were included: facilitator, incentive, improve, enhance, disseminate, utilisation, uptake, systematic review and meta-analysis. Individuals contacted and textbooks searched are listed in Table 6.1 and Table 6.2.

Table 6.1. Individuals contacted in the course of the search

Professor Russell Gruen, russell.gruen@menzies.ed.au

Prof Marilyn Oermann, moermann@email.unc.edu

Andrew Booth, a.booth@sheffield.ac.uk

Professor Maureen Dobbins, dobbinsm@mcmaster.ca

Huw-Denis Davies, hd@st-andrews.ac.uk

Bernadette Melnyk, bernadette.melnyk@asu.edu

Table 6.2. Textbook bibliographies searched for studies of facilitators of review uptake

Dawes M, Davies P, Gray A, Mant J, Seers K, Snowball R. 2005 Evidence-based practice. London, Elsevier Churchill Livingstone

Straus S, Tetroe J, Graham ID. 2009 Knowledge translation in health care: moving from evidence to practice. Chichester, Wiley-Blackwell

---

In addition to the main search, a briefer 'updated' search was also conducted (Baker et al. 2010). This updated search enables the reader to be kept informed of any new or ongoing studies. This writer repeated the search for the period January 2011 to February 2012, using MEDLINE and EMBASE. Any papers identified by the searches conducted in February 2012, considered likely to be eligible would be listed under 'On-going studies' or 'Studies awaiting classification'. These would then be mentioned but not fully included in the completed review.

Selection criteria

Finding ways to engage the perspectives of all decision makers is important (Knottnerus and Tugwell, 2013). Studies containing interviews, focus groups and surveys with all decision makers were eligible here. This writer did not restrict the search to the inclusion of studies reporting as their main objective the assessment of facilitators to systematic review uptake. Studies were included if they addressed perceived facilitators to uptake of evidence specifically from systematic reviews, meta-analyses and the databases associated with them.

A facilitator was defined as any factor that enhances, improves or predicts uptake of evidence from systematic reviews. Respondents could indicate facilitators via response to survey questions or from themes emerging from focus groups or interviews. Care was also taken to identify studies that produced multiple publications.

Inclusion criteria

To be included in the review, primary studies had to meet the following criteria:

- Studies addressing perceived facilitators to the uptake of evidence specifically from systematic reviews, meta-analyses and the databases that contained them.
- Databases could include The Cochrane Library, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Pregnancy and Childbirth Database, Oxford Database of Perinatal Trials, and the Reproductive Health Library.
- A facilitator was defined as any factor that increases or enhances uptake of evidence

- Facilitators could impact positively on knowledge, attitudes, and behaviour
- Facilitators could be reported via surveys or qualitative research
- The views of all decision makers including doctors, nurses, managers, occupational therapists, policy makers, the public and patients were eligible
- Reports in any language were included

Studies were excluded if

- They were intervention or outcome studies focusing on increasing evidence uptake
- They were about views and perceptions dealing exclusively with obstructing rather than enhancing evidence uptake
- They were exclusively about facilitators to evidence uptake in general but not including systematic reviews uptake
- They dealt exclusively with the uptake of clinical practice guidelines rather than systematic reviews

This writer reviewed all the citations and followed up reference lists, while the retrieved full articles were assessed by at least two reviewers for inclusion in the systematic review. Disagreements were resolved by discussion or adjudication by a third party.

This writer extracted data from the included studies using a data collection form based on a taxonomy of barriers to implementing clinical practice guidelines in actual practice (Cabana et al. 1999, Gravel et al. 2006). The data collection form used is outlined in Table 6.3.

Table 6.3. Data Collection Sheet adopted for systematic review of review uptake facilitators

Source
Study Name
Report Name
Citation and contact details

Eligibility
Confirm eligibility
Reason for exclusion

Methods
Objective
Study design
Sample frame
Sample strategy
Response Rate
Measurement of use of evidence
Description of methods

Participants
Total number
Setting
Age
Gender
Country

Results
Facilitators identified by each study

Miscellaneous
Funding source
Key conclusions
Comments from study authors

Adopted from Cochrane Handbook of Systematic Reviews of Interventions, 2008, Editors: Higgins J, Green S. Chichester, John Wiley and Sons

---

During the review process, facilitators were aggregated into themes and ordered according to the number of studies in which they were identified. The theoretical underpinning was derived from a model that describes an ideal, general mechanism of the

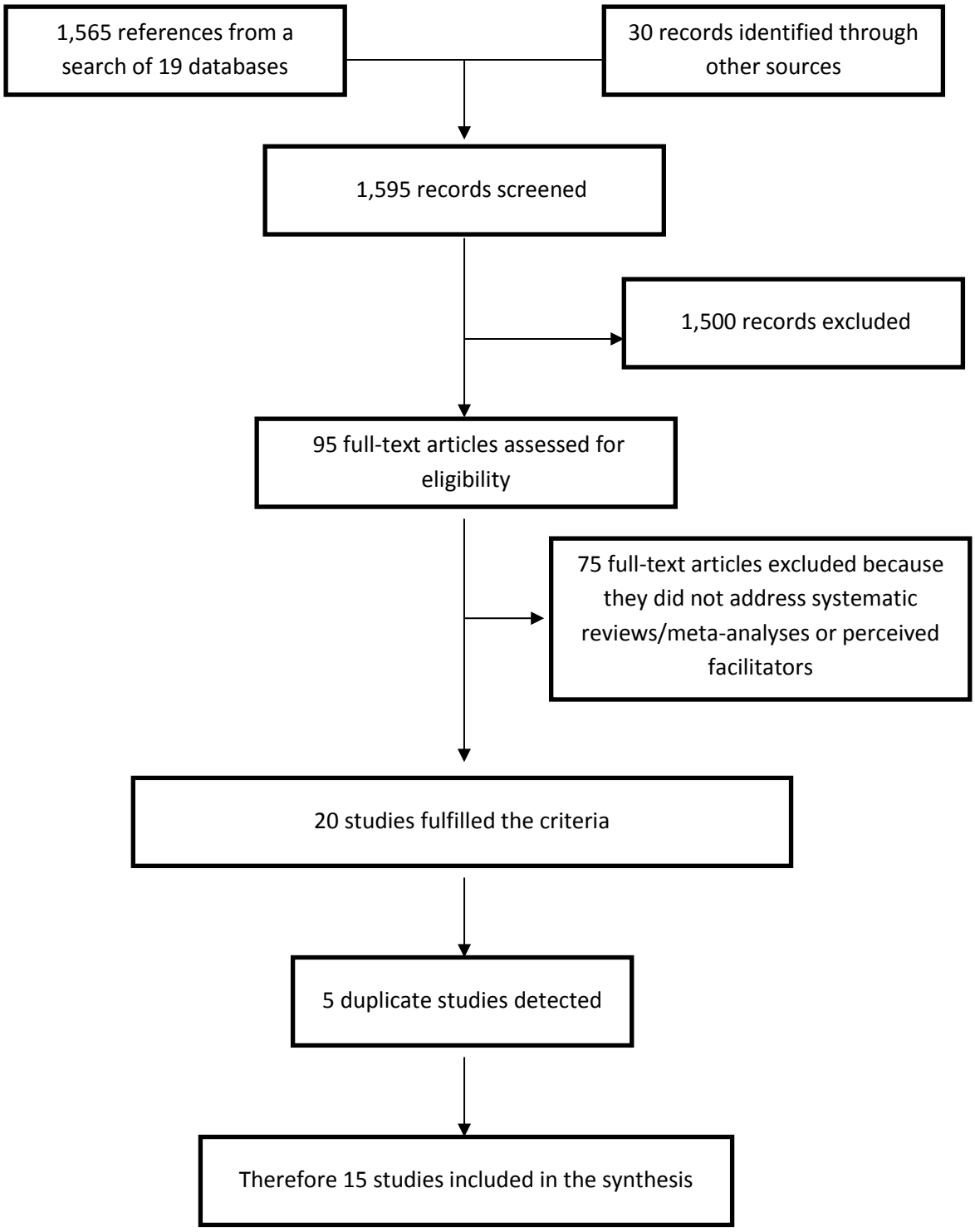
knowledge, attitudes, behaviour framework (Cabana et al. 1999). The extracted data were summarised and tabulated.

6.4 Results

Search yield

A search of 19 databases using Google's search engine, and two other search engines, yielded 1,564 references. The flow diagram outlines the search process (Figure 6.1).

Figure 6.1 Search flow chart showing selection of studies for the facilitators systematic review



Thirty reports were identified from other sources. The number of records screened was 1,595, and 1,500 reports were excluded as not meeting inclusion criteria. The remaining 95 articles were checked in full-text for eligibility and 75 were excluded because they did not address perceived facilitators, systematic reviews, meta-analyses or the databases associated with them. Five duplicates, separate reports of the same study, were removed and reported in Table 6.4 at the end of this chapter. Fifteen unique studies met inclusion criteria (Table 6.5).

Table 6.5. Included studies in the systematic review of facilitators of systematic review uptake

Fahey T, Griffiths S, Peters TJ. Evidence-based purchasing: understanding results of clinical trials and systematic reviews. BMJ. 1995. Nov 4; 311(7014):1229.

Hyde C. Who uses the Cochrane pregnancy and childbirth database? BMJ. 1995; 310:1140-1.

Paterson-Brown S, Fisk M, Wyatt J. Uptake of meta-analytical overviews of effective care in English obstetric units. Br J Obstet Gynaecol. 1995. April; 102(4):297-301.

Jordans C, Hawe P, Irwig L, Hendeson-Smart D, Ryan M, Donoghue D, Gabb R, Fraser I. Use of systematic reviews of randomized trials by Australian neonatologists and obstetricians. MJA. 1998. 168: 267-270.

McColl A, Smith H, White P, Field J. General practitioner's perceptions of the route to evidence-based medicine: a questionnaire survey. BMJ. 1998; 316:361-365.

Ciliska D, Hayward S, Dobbins M, Brunton G, Underwood J. Transferring public-health nursing research to health-system planning: assessing the relevance and accessibility of systematic reviews. Can J of Nurs Res. 1999;31(1):23-36.

Young J, Ward J. General practitioner's use of evidence databases. MJA 1999; 170:56-58.

Dobbins M, Cockerill R, Barnsley J, Ciliska D. Factors affecting the utilization of systematic reviews. Int J of Tech Ass in Health Care. 2001; 17(4):467-478.

Young J and Ward J. Evidence-based medicine in general practice: beliefs and barriers among Australian GPs. J Eval Clin Pract. 2001; 7(2):201-210.

Dobbins M, DeCorby K, Twiddy T. A knowledge transfer strategy for public health decision makers. Worldviews Evid Based Nurs. 2004; 1(2):120-128.

Dobbins M, Thomas H, O'Brien MA, Duggan M. Use of systematic reviews in the development of new provincial public health policies in Ontario. Int J of Tech Ass in Health Care. 2004; 20(4):399-404.

Lavis J, Davies H, Oxman A, Denis JL, Golden-Biddle K, Ferlie E. Toward systematic reviews that inform health care management. J of Health Services Research & Policy. 2005; Vol 10 Suppl 1:35–48.

Dobbins M, Jack S, Thomas H, Kothari A. Public health decision-makers' informational needs and preferences for receiving information. Worldviews Evid Based Nurs. 2007;4(3):156-163.

Martis R, Ho J, Crowther C. Survey of knowledge and perception on the access to evidence-based practice and clinical practice change among maternal and infant health practitioners in South East Asia. BMC Pregnancy Childbirth. 2008; 8:34.

Yousefi-Nooraie R, Rashidadehian A, Nedjat S, Majdzdeh R, Mortaz-Hedjri S, Etemadi A and Salmasian H. Promoting development and use of systematic reviews in a developing country. J Eval in Clinl Prac. 2009; 15:1029-1034.

A further 13 studies were identified that might have been expected to be included in the review but, on close assessment, did not meet the inclusion criteria. These are shown in appendix 5. The brief updated search conducted in February 2012 did not yield any on-going or new study to be used to update this review.

Study characteristics

Of the investigations addressed here, 5 studies were from Canada, 4 from the UK, 3 from Australia with 1 from Iran, and 1 from South-east Asia (Indonesia, Malaysia, Thailand and the Philippines). One study covered both Canada and UK. In total, fifteen studies involved participants from eight countries on four continents.

From a total of 2,495 participants, at least 1,343 (53.8%) were doctors, and 641 (25.7%) were nurses or midwives (Table 6.6).

Table 6.6. Summary of participants

GPs: 711
'Doctors': 132
Obstetricians: 304
Neonatologists: 4
Paediatricians: 36
Medical trainees: 156
Nurses and midwives: 641
Members of regional health authorities: 182
Local health board members: 14
Epidemiologists: 4
Researchers, health care managers, health care policy makers, programme directors, and support staff: 301

The number of participants in each individual study and their associated discipline is given in Table 6.7.

Table 6.7. Number of participants in each study and their discipline

Hyde et al. (1995)
Midwives: 83, Doctors: 81, Information specialists: 56
Fahey et al. (1995)
Executive and non-executive members of UK regional health authorities: 182
Patterson-Brown et al. (1995)
Obstetricians: 98
McColl et al. (1998)
GPs: 302
Jordans et al. (1998)
Neonatologists: 98, Obstetricians: 126
Young and Ward, (1999)
GPs: 311
Ciliska et al. (1999)
Nurses: 162, Doctors: 50, Others: 29
Dobbins et al. (2001)
Medical officers of health, programme directors, and programme managers: 141
Young and Ward, (2001)
GPs: 98.
Dobbins et al. (2004)
Programme managers: 12, Directors: 8, Epidemiologists: 4, Medical officers of health: 4
Provincial consultants: 9, Local health board members; 14
Dobbins et al. (2004)
Medical officers of health: 7, Public health managers: 14, Directors: 11, Health promotion managers and health policymaker: 14
Dobbins et al. (2007)
Nurses: 15, Physicians: 1
Lavis et al. (2007)
Health care managers: 10, Healthcare policy makers: 19
Martis et al. (2008)
Obstetrics and gynaecology: 80, Neonatologists: 4, Paediatricians: 36, Medical trainees: 156
Nurses: 263, Midwives: 119
Yousefi-Nooraie et al. (2009)
Researchers, health policy makers, research policy makers and support staff: 131.

Some 8 of the 15 studies (53%) were published after the year 2000. Regarding methodology, 10 studies were exclusively surveys, 3 were exclusively qualitative studies and 2 were mixed studies including both surveys and qualitative research.

Of the 12 studies reporting surveys, there were 6 postal, 5 telephone and 1 on-line survey. The 3 qualitative studies were made up of 2 focus group studies and 1 semi-structured

interview. Two studies were mixed and combined surveys together with semi-structured interviews and participant observations. The characteristics of each study are in Table 6.8.

Table 6.8. Characteristics of included studies in the systematic review of uptake facilitators

Year Published, Country	*Objective*	*Design*	*Participants*	*Date Conducted*
Fahey et al. 1995 UK	To assess if the way in which results of a RCT and systematic reviews are presented influences health policy decisions	Postal questionnaire	n =182 Members of a health authority including doctors	Not stated
Paterson -Brown et al 1995 UK	To establish the availability of meta-analyses and to find out how obstetricians keep up-to-date	Telephone survey	n = 98 Obstetricians	1993
Hyde et al. 1995 UK	To examine use of Cochrane Pregnancy and Childbirth Database	Postal survey	n = 274 Subscribers to database (CPCD) Include doctors	1994
Jordans et al. 1998 Australia	To determine the proportion who report using systematic reviews	Cross-sectional telephone survey obstetricians	n = 224 Neonatologists	1995
McColl et al. 1998 UK	To determine the attitude to EBM and perceived usefulness of databases	Postal questionnaire	n = 302 GP principals Included doctors	1997
Ciliska et al. 1999 Canada	To gain an understanding of research needs, perceptions of barriers to research utilisation, and attitudes towards systematic reviews	Telephone questionnaire survey	n= 226 Decision makers in public health, included doctors	Not stated
Young &Ward 1999 Australia	To determine awareness and use of the Cochrane Library and access to the Internet	Postal Questionnaire	n =311 GPs	1997

Dobbins et al. 2001 Canada	To determine the extent to which public health decision makers use 5 systematic reviews	Telephone survey	n = 141 Decision makers, included doctors	1998
Young, J and Ward, J. 2001 Australia	To examine views about EBM	Postal survey and semi-structured interviews	n = 60 GPs	1999
Dobbins et al. 2004 Canada	To discover public health decision makers' preferences for content, format, and channels for receiving research knowledge	One-hour focus groups	n = 46 Policy makers, included doctors	2002- 2003
Dobbins et al. 2004 Canada	To determine if systematic reviews were used in policy making	Telephone survey	n = 51 included doctors	2000
Lavis et al. 2005 UK and Canada	To look at how to adopt systematic reviews to better inform health care management and policy making	Semi-structured interviews, face-to-face and telephone	n = 29 Health care managers, and policy makers	Not stated
Dobbins et al. 2007 Canada	The purpose was to identify preferences for the transfer and exchange of research knowledge	Semi-structured interviews,	n = 16 Decision-makers, included a doctor	2001
Martis et al 2008 Asia	The aim was to assess current knowledge of evidence-based practice	Online survey	n = 660 Health care, professionals, including doctors	2005
Yousefi-Nooraie et al. 2009 Iran	To assess views on how development & usage of evidence from systematic reviews can be promoted in a country with limited resources	Self-administered questionnaire	n = 131 Researchers, decision makers, research policy makers. Doctors included: not known	Not stated

The included studies used a heterogeneous variety of decision-making populations, based on location or speciality. The studies looked at systematic reviews, meta-analyses, The Cochrane Library, and the Reproductive Health Library. A description of each category of facilitator and the studies that investigated these facilitators are included in Table 6.9.

Table 6.9. The detected facilitators addressed by each primary study

Study	Facilitators
Hyde et al. 1995	Installing a disk in a common area Improves knowledge, persuades others, guides research
Fahey et al. 1995	Method used to summarize results, such as RRR
Paterson -Brown et al. 1995	Essential for education, revision of childcare protocols, medico-legally Saves much time
McColl et al, 1998	Formal training in searching
Jordans et al. 1998	Familiarity with computers, with authoring a research paper Professional conferences, being full-time, being a recent graduate
Ciliska et al. 1999	Usefulness to overcome barriers of time, cost, timeliness Preferred method of delivery: full-paper, Internet, diskette format Component of systematic review that receives most attention: The Conclusion and Discussion and Results receive most attention
Dobbins et al. 1999	Mode of delivery: electronic delivery was preferred Credibility and reliability of presentation with recognisable logos Content should be current, transparent, contextualized, and timely Customizability: abstract, full document, summary, delivery mode Training: in the definition, significance, and appraisal of systematic reviews.
Young and Ward, 1999	Peer contact can promote evidence uptake from systematic reviews
Dobbins et al. 2001 .	Position in organisation predicts use of systematic reviews Expectation of use of a systematic review in the future Perception of overcoming of limited critical appraisal skills Perception that the reviews are easy to use
Young and Ward, 2001	Useful to support EBM

Dobbins et al. 2004	An executive summary followed by the conclusion Ease of use Relevance to policy decisions Importance in comparison to other sources of information
Lavis et al. 2005	Information on benefits, harms, cost, 'uncertainty', disadvantaged groups Using a 1:3:25 format is preferred over current approaches
Dobbins et al. 2007	Save time Improves confidence Executive summary, key findings, implementation outcomes Summaries e-mailed directly
Martis et al. 2008	Training in the use of RHL and The Cochrane Library
Yousefi-Nooraie et al. 2009	Priority and support for systematic reviews

Quality of studies

The studies were limited in terms of the quality and generalizability of their results. Response rates were mentioned in 12 of the 15 studies. The response rate was variable. The rate in these 12 studies varied from 67% to 100%. All included studies reported the number of participants (range: 16 to 660).

While all 15 studies had a well-described sampling frame, just 2 studies describe selecting a random sample of participants. The assessment of the use and determinants of use of evidence was mostly descriptive. All studies measured perception or hypothetical use rather than actual use of research evidence. No study gave an account of reflexivity.

Type of Facilitators

A wide range of individual facilitators were identified. The individual perceived enhancers of evidence uptake from systematic reviews are outlined using the knowledge,

attitude and behaviour taxonomy. The tables were adapted from the study by Legere and colleagues (Legere et al. 2008). The individual facilitators falling under the *knowledge* heading are given in Table 6.10 below.

Table 6.10. Perceived facilitators of systematic review uptake: knowledge

FACILITATOR	STUDIES IDENTIFYING THE FACILITATOR
KNOWLEDGE	
Familiarity with computers	Jordens et al. 1998
Authorship of a research paper	Jordens et al. 1998
Being full-time (mode of practice)	Jordens et al. 1998
Being a recent graduate (clinical experience)	Jordens et al. 1998

The individual perceived facilitators falling under the *attitude* heading are given in table 6.11.

Table 6.11. Perceived facilitators of systematic review uptake: attitude

FACILITATOR	STUDIES IDENTIFYING THE FACILITATOR
Perceived ease of use of systematic reviews	Dobbins et al. 2001a Dobbins et al. 2004
Expectation of use	Dobbins et al. 2001a
Saves much time	Dobbins et al. 2001b. Paterson-Brown et al. 1995 Dobbins et al. 2007
Perceived ability to overcome limited critical appraisal skills	Dobbins et al. 2001a
Does your work for you	Paterson-Brown et al.1995
Useful for revision of protocols	Paterson-Brown et al.1995
Useful medico-legally	Paterson-Brown et al. 1995
Useful to support EBM	Young and Ward, 2001
Useful to influence programme justification	Dobbins et al. 2001b
Useful to influence programme planning	Dobbins et al. 2001b
Useful for guidelines decisions	Dobbins et al. 2004
Useful for policy makers	Yousefi-Nooraie et al. 2009
Useful for end-users	Yousefi-Nooraie et al. 2009
Relative importance in comparison with other forms of evidence	Dobbins et al. 2004
Systematic reviews improve self-confidence and self-efficacy	Dobbins et al. 2007
Willingness and competency to use	Yousefi-Nooraie et al. 2008
Priority of and support for systematic reviews	Yousefi-Nooraie et al. 2009
An increased number of deliveries per year	Jordens et al. 1998
Percentage of articles read	Dobbins et al. 2001b
Years since graduation	Dobbins et al. 2001b
Expecting to use systematic reviews	Dobbins et al. 2001a

Facilitators falling under the *behaviour* heading can be associated with the individual systematic review or they may be associated with external environmental variables (Table 6.12).

The respondents and investigators used different words to describe facilitators of the use of research evidence. However, several common factors or themes were described across studies.

Table 6.12. Perceived facilitators of systematic review uptake: behaviour

FACILITATOR	STUDIES IDENTIFYING THE FACILITATOR
Systematic reviews factors	
Information about benefits, harms, and cost: Content	Lavis et al. 2007
Information on 'uncertainty': Content	Lavis et al. 2007
Information on variation in estimates by subgroups: Content	Lavis et al. 2007
Quality of local primary research: Content	Yousefi-Nooraie et al, 2009
Quality and reliability: Content	Dobbins et al. 2004
Relative risk reduction: Content	Fahey et al. 1995
Using a 1:3:25 format: Format	Lavis et al. 2007
Executive summary: Format	Dobbins et al. 2007
Executive summary: Format	Dobbins et al. 2004
Customizability: Format	Dobbins et al. 2004
Customizibility: Format	Ciliska at al. (1999)
The Conclusion and Discussion and Results receive most attention: Format	Ciliska et al. (1999)
Mode of delivery: Electronic	Dobbins et al. 2004
Mode of delivery: Electronic	Hyde, 1995
Environmental facilitators	
Training in searching: Training	McColl et al. 1999
Attending a workshop: Training	Martis et al. 2008
Attending a RHL workshop: Training	Martis et al. 2008
Appraisal of systematic review: Training	Dobbins et al. 2004
On-going training in critical appraisal	Dobbins et al. 2001b
Decision maker's position	Dobbins et al. 2001a
Value the organization places on research	Dobbins et al. 2001b
Divisional membership of a Royal College	Young and Ward, 1999
Group practice	Young and Ward, 1999
Attendance at professional conferences	Jordens et al. 1998.
Specialist colleagues	Young and Ward, 2001
Working in a teaching hospital	Paterson-Brown et al. 1995
Access	Yousefi-Nooraie et al. 2009
Ability to overcome barrier of cost and timeliness	Dobbins et al. 2007
Organisational support	Dobbins et al. 2001a

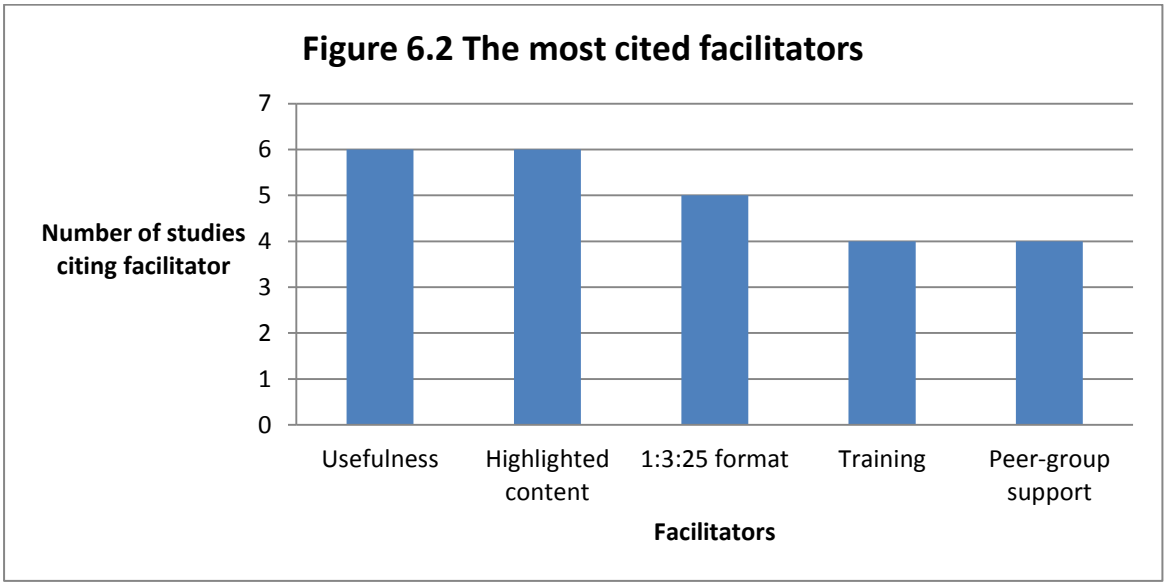
It was found that the 15 studies investigating facilitators to uptake of evidence from systematic reviews identified 51 facilitators. Twenty-six facilitators can be viewed as impacting on knowledge, 21 on attitude and 4 on behaviour. The facilitators could be grouped into a number of themes (Table 6.13).

Table 6.13. Ordered list of detected facilitators to uptake of evidence from systematic reviews

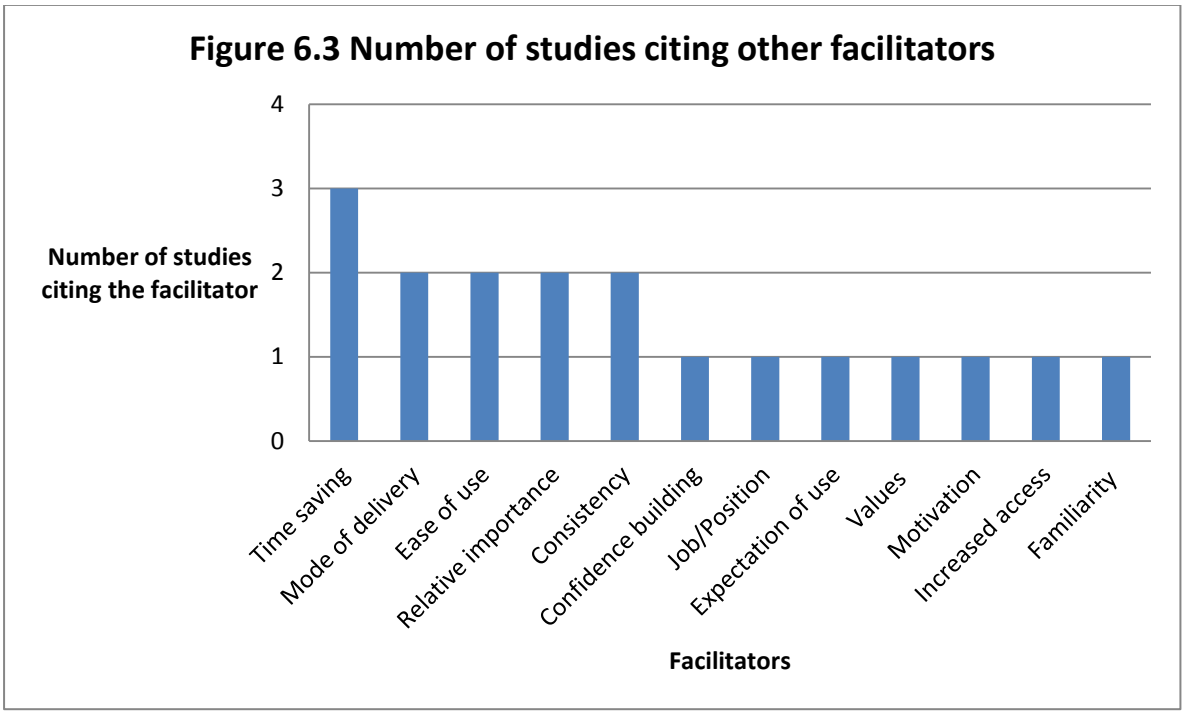
Usefulness (6/15)
Highlighted content (6/15)
A 1:3:25 format (5/15)
Training (4/15)
Peer-group support (4/15)
Time-saving (3/15)
Mode of delivery: CD ROM or Web-based (2/15)
Perceived ease of use (2/15)
Importance relative to other sources of information (2/15)
Consistent presentation: recognisable logos (1/15)
Ability to improve confidence (1/15)
Position in an organisation (1/15)
Expectation of use (1/15)
Value that organisation places on systematic reviews (1/15)
Motivation (1/15)
Increased access (1/15)
Familiarity with computers (1/15)

In order of frequency, the five most often identified facilitators of systematic review uptake in the 15 studies were (1) their usefulness (2) a highlighted content (3) a 1:3:25 format (4) training in use and (5) peer group support. The perception of usefulness of systematic reviews can facilitate uptake. Systematic reviews can be used for education, for revision of childcare protocols, to improve personal knowledge, and to guide research (n=6). Aspects of content viewed as facilitating the uptake of systematic reviews included highlighting benefits and costs in a transparent, timely and transparent way (n=6). Another facilitator of uptake was a format that incorporated an executive summary and a

1:3:25 page staged access (n=5). Training was regarded as an important facilitator to improve usage of systematic reviews (n=4). Support and encouragement from colleagues in accessing and using systematic reviews can also encourage use of this evidence resource (n=4). Figure 6.2 illustrates the number of studies highlighting the five most cited facilitators.



Other facilitators of uptake include the perception that systematic reviews are easy to use, are important relative to other sources of information, and can have a facilitating mode of delivery, either CD ROM or online. Figure 6.3 illustrates the number of studies highlighting the remaining themes.



The methods used by the different studies to detect the identified facilitators are outlined in Table 6.14 at the end of this chapter.

6.5 Discussion

This review identified factors that if built on would improve the uptake of evidence from systematic reviews (Lawrence et al. 2012). Advice about how to enhance uptake of evidence from systematic reviews is usually based on personal experience supported by anecdote. The results of this review provide a context in which to assess such advice and provide a menu of factors to consider. The investigation offers a rational approach towards improving systematic review uptake and also a framework for future research (Wallace et al. 2012b).

The synthesized results expand our understanding of the facilitators to knowledge translation and evidence implementation. The synthesis provides a greater appreciation of how multiple factors facilitate the knowledge-to-action process and the findings help to understand how knowledge gaps can be narrowed and closed (Cochrane et al. 2007). While the primary studies had limitations, the review aggregated the findings of individual studies to identify trends in the facilitators addressed. This writer recorded the frequency of studies reporting the information extracted in order to map facilitator themes found in the literature.

This writer was interested in the methodologies employed to specify the facilitators. Identified facilitators were highlighted by responses to surveys or questionnaires, themes emerging from focus groups, key informant interviews, or data supported by combinations of methodologies. Quantitative survey type assessments continue to dominate facilitator research, as in barrier research. However, this writer also found a number of qualitative and mixed-method study designs.

No factor was mentioned in more than 6 of the 15 studies as a facilitator, even when similar factors were grouped together. Given the diversity of participants, included studies and contexts, it is perhaps striking that factors were identified as often as they were.

Limitations

Because much of the research in this area is poorly indexed in the electronic databases, relevant studies may have been missed, despite the searching of 19 databases.

The limitations of the review largely reflect the limitations of the literature reviewed. Few facilitator studies employ strong designs. Randomized trials, comparative control groups, or mixed-method designs are infrequent. This bears on the trustworthiness of findings (Cochrane et al. 2007). The value of this systematic review was limited by the small number of studies available and by how the studies frequently used only one method of data collection.

Some surveys were small and used non-random samples confined to specific groups, inhibiting the extent to which the results can be generalised. Inadequate descriptions of the participants and contexts of many of the included studies also pose a difficulty. However, by including all types of decision makers, this systematic review allows better understanding of how cross-cultural variation impacts on systematic review uptake.

Another limitation of the investigation is the use of participant self-ratings rather than objective, criterion-based assessments. The surveys depend on decision maker's perceptions and views rather than an audit of actual practice.

Most primary studies do not look at a theoretical framework or conceptual model to guide the design and analysis of their investigation. Furthermore, many studies examine just a few facilitators and the questions are usually closed. So results can be biased by the researchers' selection of identified factors (Cochrane et al 2007). By not considering the full variety of facilitators, interventions to improve uptake are less likely to address all the important factors impacting on evidence uptake and, as a result, are less likely to be successful.

Implications for research

Closed-ended questions used in surveys tend to measure pre-defined facilitators. In the future, the use of more open-ended questions, and exploratory studies, is likely to reveal unanticipated facilitators to targeted audiences. There is also a need for future research to use a conceptual framework of processes and factors that facilitate or challenge professional performance (Cochrane et al. 2007).

Lastly, mixed-methods systematic reviews constitute an emerging field of research. Ways need to be developed to synthesise results from qualitative, quantitative, and mixed-methods studies.

Since the utilisation of evidence, and in particular evidence from systematic reviews, is a pressing issue, this research is timely. The global stock of systematic reviews will better inform decision makers if local adoption processes are evaluated (Lavis et al. 2005). Interventions designed to change practice should be based on an accurate assessment of the variables that support and impede targeted health outcomes. The results outlined here provide direction for research into the development of broad dissemination strategies and can advance evidence-based interventions to enhance knowledge translation.

Implications for practice

Facilitators of clinical practice guideline use include a positive attitude, easy access, and workplace encouragement (Bernhardsson and Larsson, 2012). From the results of this review of 15 studies that met the inclusion criteria, based on the views of 2,495 participants from eight counties, researchers who wish to increase the use of systematic

reviews should emphasise a number of attributes. They should highlight the multiple uses of this form of evidence synthesis, including the ability of systematic reviews to improve knowledge, guide research, and overcome cost barriers. The advantages of systematic reviews for research and protocol development should also be stressed relative to other forms of evidence. The results illustrate the importance of emphasising the time-saving function of systematic reviews over searching for, and critically appraising, individual studies. The medico-legal uses of reviews are also an advantage.

The format of systematic reviews is important for uptake enhancement. A great deal of effort should go into writing the summary of the review which should be brief, easy to read and easy to understand. It should contain the key messages with implications for policy and practice (Davies et al. 2005). Staged access with a one-page take-home message, a three-page summary, and an opportunity to access a 25-page version, should increase uptake. Multiple formats, together with a take-home message, address the concern that different audiences have different needs. Finally, systematic reviewers should ensure that the content specifically highlights benefits, harms, and costs, in a current and transparent manner.

The provision of training in searching for, and using, systematic reviews and the databases that contain them is important (Sur et al. 2005). Peer groups and professional organisations can impact positively on enhancing the uptake of reviews. The identification of the perceived importance an organisation attaches to research evidence is an important predictor of the influence reviews will have on decisions. There is a need to promote reviews at the organisational level (Dobbins et al, 2001b).

Health researchers disseminating systematic reviews to the appropriate target audience need to link the key messages of the evidence with the level of decision making. Reviews need to be presented in ways that are perceived as being easy to use. A marketing approach demonstrating that systematic reviews will overcome the barrier of limited time and limited critical appraisal skills may need to be employed.

6.6 Conclusion

To this writer's knowledge, this systematic review represents the first review of such a large group of decision makers' perceptions of the facilitators to the uptake of evidence from systematic reviews, meta-analyses and related databases. Following searches of 19 databases, this review attempted to pull together the views of 2,495 decision makers, from 8 countries, contained in 15 included studies. In order to mitigate loss of trustworthiness in the analysis procedures, all steps were established in a data extraction and analysis plan. From the primary studies included in this review, it is apparent that the facilitators exist across continents and various professional backgrounds, such as medicine and nursing.

This review helps identify facilitators to the translation of knowing to doing. It provides support for the need to examine multiple factors within the knowledge-to-action process. The results have immediate and practical relevance for organisations such as universities, government agencies, and speciality colleges that are trying to improve access to the best available evidence and promote its use.

The strengths of this investigation include the extensive and systematic literature search, explicit inclusion criteria and a systematic and transparent approach to collecting and

presenting data. Results of this systematic review can inform researchers, educators and practitioners about the factors that will need to be built on to enhance the uptake of evidence from systematic reviews in policy making and clinical practice.

The abstract of this systematic review follows.

6.7 ABSTRACT

Title

Facilitators of the uptake of systematic reviews and meta-analyses: a systematic review of decision makers' perceptions.

Objective

To identify the facilitators of the uptake of research evidence from systematic reviews and meta-analyses by all decision makers.

Methods

Inclusion criteria: Studies were included if they addressed perceived enhancers of uptake of evidence specifically from systematic reviews, meta-analyses and the databases that contained them. Facilitators could be reported via surveys or qualitative research such as interviews and focus groups. The views of all decision makers were eligible and reports in any language were included.

Information sources: This writer searched 19 databases including PubMed, Embase and The Cochrane Library, covering the full range of publication years from inception to December 2010, utilised three search engines, and also personally contacted investigators. Reference lists of primary studies and related reviews were also consulted.

Risk of bias assessment: Two reviewers independently assessed the quality and the relevance of retrieved reports. In order to assess the quality of the studies, the sampling strategy of the primary studies, response rate, and methodological approach, including data collection strategies, were assessed.

Data extraction: The methods of included studies were described and extracted data were summarised in tables and then analysed. Using a pre-established taxonomy, the facilitators were organized into a framework according to their effect on knowledge, attitudes, or behaviour.

Results

Included studies: Of articles initially identified, published studies describing at least one facilitator to the uptake of evidence from systematic reviews were selected. The 15 unique studies reported 10 surveys, three qualitative investigations and two mixed studies that addressed potential facilitators. Six studies were from Canada, five from the UK, three from Australia, one from Iran and one from South-east Asia (Indonesia, Malaysia, Thailand and the Philippines), with one study covering both Canada and UK. In total, the 15 studies covered eight countries from four continents. Of 2,495 participants in the 15 studies, at least 1343 (53.8%) were physicians.

Synthesis of results: The 15 studies yielded 54 potential facilitators to systematic review uptake. Perceived facilitators to the use of evidence from systematic reviews varied. The five most commonly reported perceived facilitators to uptake of evidence from systematic reviews were the following: the perception that systematic reviews have multiple uses for improving knowledge, research, clinical protocols and EBM skills (6/15); a content that included benefits, harms and costs and is current, transparent and timely (6/15); a format with a 1:3:25 staged access and executive summary (5/15); training in use (4/15); and peer-group support (4/15).

Discussion

Strengths and limitations of the evidence: Most of the studies were surveys using closed-ended questions, dependent on investigator preference. Much of the research in the field is poorly indexed so relevant studies may have been overlooked. The extensive and systematic literature search using 19 databases, with a special emphasis on grey and qualitative literature, is one of the strengths of this systematic review.

Interpretation

The results expand our understanding of how multiple factors act as facilitators to optimal practice. This review reveals that interventions aimed at fostering systematic review uptake can build on a wide variety of facilitators.

Funding: No internal or external funding was received

Key words: knowledge translation, systematic review, meta-analysis, facilitator

Next Chapter

The next chapter focuses on outcome studies or interventions that can enhance the uptake of evidence from systematic reviews and meta-analyses.

Table 6.4. Duplicates removed during the selection process: the facilitator systematic review

Paterson-Brown S, Fisk M, Wyatt J. Are clinicians interested in up to date reviews of effective care? BMJ 1993; 307:1464.

Ciliska D, Hayward S, Underwood J, Dobbins M. Transferring public health nursing research to health system planning. Can J Nurs Res 1999;31:23-36.

Dobbins M, Cockerill R, Barnsley J. Factors affecting the utilisation of systematic reviews. Int J of Technol Assess in Healthcare 2001;17(2):203-214.

Davies H, Denis JL, Ferelie E, Golden-Biddle K, Lavis J, Oxman A. Towards systematic reviews that inform health care management and policy making. J Health Serv Res Policy 2005; 10, 1 Supplement: 35.

Yousefi-Nooraie R, Rashidadehian A, Nedjat S, Majdzdeh R, Mortaz-Hedjri S, Etemadi, A, Salmasian H. Promoting development and use of systematic reviews in a developing country. Int J of Public Health Policy and Health Services Research 2009;15:1029-1034.

Table 6.14. Methods of included facilitator studies

Study	Sample frame Sample strategy	Response rate	Measurement of use of evidence	Description of methods
Fahey et al. 1995	Well-described sampling frame, purposive sample	140/182 (75%)	Reported use in health policy decisions, mean	Analysis of variance MANOVA. scores calculated
Hyde et al. 1995.	Well-defined sampling frame, purposive sample	274/387 (71%)	Reported use of Cochrane databases	Numbers reporting use
Patterson-Brown et al. 1995	Well-defined sampling frame, random sample	98/98 (100%)	Reported use of the Oxford Database	Percentages and volunteered comments
McColl et al. 1998	Well-defined sampling frame, random sample	302/452 (67%)	Reported use reporting use	Percentages
Jordans et al. 1998	Well-described sampling frame, a random sample	224/248 (90%)	Reported use of systematic reviews and practice change	Percentages reporting facilitator
Young and Ward 1999	Well-described sampling frame, random sample	311/ 428 (73%)	Reported use of Cochrane Library	Logistic regression
Ciliska, et al. 1999	Well-described sampling frame, purposive sample	225/270 (83%)	Reported use, awareness, attitudes	Percentages reporting facilitators
Dobbins et al. 2001	Well-described sampling frame, purposive sample	141/147 (96%)	Reported use in developing new policies, new practice	Multiple linear regression model, descriptive summaries
Young and Ward 2001,	Well-described sampling frame, purposive sample	60/60 (100%)	Reported use to support EBP	Percentages reporting facilitator
Dobbins et al. 2004	Well-described sampling frame, purposive sample	46/60 (77%)	Reported use	A modified grounded-theory approach

Dobbins et al. 2004	Well-described sampling frame, purposive sample	51/60 (85%)	Reported use of 5 systematic reviews for	Multiple linear regression analyses public health decision making
Lavis et al. 2005	Well-described sampling frame, purposive sample	29 participants RR not known	Reported use to inform management and policy making	Thematic analysis
Dobbins et al 2007	Well-described sampling frame, purposive sample	RR not known 16 participants	Reported use of research information	Qualitative descriptive study, content analysis
Martis et al. 2008	Well-described sampling frame, purposive sample	RR not known 660 participants	Reported use of different outcome Measures	Percentages reporting facilitators
Yousefi-Nooraie et al. 2009	Well-described sampling frame, purposive sample	131/150 **(**87%)	Reported use of systematic reviews in a developing country	Scaling methods and content. analysis

CHAPTER 7

INTERVENTIONS TO ENHANCE UPTAKE OF SYSTEMATIC REVIEWS

CONTENTS

7.1 Background **289**

7.2 Problem **289**

7.3 Knowledge gap **292**

7.4 Contribution **293**

7.5 Introduction **293**

7.6 Search methods **294**

7.7 Risk of bias assessment **298**

7.8 Results **300**

7.9 Discussion **312**

7.10 Conclusion **316**

7.11 Abstract **317**

The previous chapter addressed natural facilitators to uptake of evidence from systematic reviews, meta-analyses and the databases containing them. This chapter focuses on interventions or strategies that increase uptake of systematic review evidence.

7.1 Background

There is growing international interest in encouraging public policy and clinical management to be better informed by the results of reliable and relevant research. Accountability is central (Gough et al. 2012). The aim is to shift the centre of gravity of clinical decision-making to a more explicit consideration of high-quality evidence (Sheldon, 2005).

7. 2 The problem

The object of synthesis is to better map our knowledge base (Sheldon, 2005). Good quality reviews are a good method of taming continuously proliferating evidence (Knottnerus and Tugwell, 2012). Systematic reviews help present the literature in a more digestible form (Gough et al. 2012). But there is a lack of effective uptake of results of systematic reviews by clinicians, policy makers and managers. Policy and practice decisions often proceed on the basis of a single famous study rather than any comprehensive assessment of available evidence.

Not only is it necessary to synthesize evidence but also it is also important to develop mechanisms to promote implementation of the synthesized knowledge. Translational research should be a priority. However, the lack of evidence to support the use of translation interventions is an issue (Grol and Wensing, 2004). A recent study by Kuo and

colleagues in Taiwan identified several helpful strategies used by Taiwan's hospitals to enhance dissemination of The Cochrane Library (Kuo et al. 2012). These included awareness raising, active delivery of information, mentoring relationships, and also educational training. Kulier and colleagues also found that a clinically integrated e-learning EBM course, incorporating the Reproductive Health Library (RHL), resulted in higher knowledge and skill (Kulier et al. 2012).

Systematic reviews are themselves pieces of research (Gough et al. 2012). So there needs to be a payback in conducting systematic reviews (Volmink et al. 2004). In order that pre-appraised, quality reviews are applied in clinical problem solving, research needs to focus on increasing the uptake of knowledge synthesis (Straus et al. 2009b).

It is important to know what interventions work in enhancing evidence-based care and patient outcomes (Melnyk et al. 2004). When a problem is detected, it is important to look at interventions that address the problem (Mitchell et al. 2012b). Any approach aimed at improving evidence uptake should be carefully selected, as choosing the right strategy is an essential component of developing evidence-based practice. Research evidence is needed to support the use of one intervention over the other (Eastwood et al. 2008). It is essential to identify the effective strategies so as not to waste resources.

The aim of this systematic review was to identify interventions that enhance the uptake of systematic reviews, meta-analyses, and the databases containing them. The databases included the Reproductive Health Library and The Cochrane Library.

The Cochrane Collaboration

The Cochrane Collaboration is an international organisation established to conduct and publish systematic reviews of healthcare interventions. The Collaboration is committed to high quality reviews that are regularly updated, published electronically in The Cochrane Library, and meet the needs of a wide variety of decision-makers (Gartlehner and Flamm 2013). It supports physicians and others by providing reviews synthesising the best available knowledge. Over 30,000 people from 120 countries contribute to the work of the Cochrane Collaboration. Through The Cochrane Library, Cochrane initiatives, especially systematic reviews, address some of the information management difficulties faced by physicians and other decision makers.

Reproductive Health Library

The WHO Reproductive Health Library (RHL) is an annually updated electronic publication. It includes predominantly Cochrane systematic reviews in the field of reproductive health. It is published in English and Spanish with new topics added and updated annually. The Library addresses some of the difficulties faced by reproductive health care professionals in low-to-middle income countries.

On their own however, systematic reviews contained in the Reproductive Health Library and The Cochrane Library, are unlikely to change physician behaviour, so further dissemination and implementation strategies are required.

7. 3 The knowledge gap

Despite the potential value of systematic reviews, little evidence of their direct impact on decisions made by consumers and policy makers is available. There are capacity constraints for using reviews. This involves not only the capacity to read and understand reviews but also the capacity to interpret and apply them in a useful way (Gough et al. 2012). Changing clinical practice to incorporate the best available evidence needs to be informed by the integration of the research-into-practice literature. This literature is concerned with strategies that are clearly formulated interventions that use explicit methods to convey relevant research findings to decision makers.

The process of integrating research findings into practice is a foundational procedure that should be used by healthcare professionals to change their practice on the basis of the best available evidence. These strategies should be a priority as a means of optimizing safe patient care (Eastwood et al. 2008). While systematic reviews assist in identifying best available evidence, the next step is to select a strategy that will assist in the integration of the findings of systematic reviews into clinical practice in a sustained way.

Scientific journals remain the main conduit for disseminating research evidence (Pimm, 2013). Traditional approaches to improve uptake of research findings have focused on better availability and presentation. This is enough for simple changes (Grol and Grimshaw, 2003). The uptake of most innovations requires further efforts however. Even if a decision maker is aware of a systematic review and willing to alter their behaviour based on it, changing well-established patterns of care is difficult.

Knowledge translation initiatives should be saved for interventions of known efficacy that are documented by systematic reviews (Tugwell et al. 2006). Some knowledge translation strategies can fail. They can be ineffective, function poorly, and result in errors if moved too quickly into a healthcare system. Consequently, the science of developing effective knowledge translation interventions is challenging.

There is a gap in our knowledge regarding effective interventions to enhance the uptake of evidence from pre-appraised, integrative reviews. The aim of the study outlined here was to bridge a specific knowledge gap by identifying interventions that might overcome the problem of insufficient uptake of systematic reviews and meta-analyses.

7.4 Contribution

The objective of this study was to estimate which strategies were effective in enhancing systematic review uptake. By identifying such interventions, an incremental step was taken in bridging an important knowledge gap.

7.5 Introduction to interventions' systematic review

The connection between research activity and clinical practice is loose (Asch et al. 2006). Despite initiatives to improve the use of research, variation in the uptake of evidence exists (Murthy et al. 2011). Strategies accelerating the use of research evidence by practitioners should run alongside knowledge creation (Grimshaw et al. 2001). Researchers are now looking for more effective ways to improve uptake of research knowledge. Indeed, there is evidence that efforts to communicate, and improve

concordance with treatment guidelines for certain psychiatric conditions has met with some success (Paterniti and Bisserbe, 2013)

Lack of uptake of systematic reviews and the development of specific interventions to improve uptake of reviews pose particular challenges. Research into interventions for enhancing uptake of evidence by clinical practitioners (Perrier et al. 2011a) and by policy makers (Perrier et al. 2011b) indicates that further examination of the problem is required.

7.6 Search methods

A wide range of databases and search engines were used to find enhancers of evidence uptake from systematic reviews, with a particular emphasis on knowledge translation and also grey literature (Wallace, 2012a). This researcher searched 19 databases and used 3 search engines for articles, not limited to the English language, and covering the full range of publication years available in each database up to December 2010. A combination of index terms and text words derived from relevant articles previously identified was used (Table 7.1). References from included studies and related review articles were scanned, experts in the field contacted, and bibliographies of textbooks were reviewed.

Table 7.1. PubMed was searched for intervention studies from December 2010 to May 2013 using the following search terms and combinations

1	systematic review AND facilitators AND knowledge uptake
2	meta-analysis AND facilitators AND knowledge uptake
3	systematic review AND enhance* AND knowledge uptake
4	meta-analysis AND enhance* AND knowledge uptake
5	systematic review AND facilitator* AND knowledge utilisation
6	meta-analysis AND facilitator* and knowledge utilisation
7	systematic review AND improve* AND knowledge utilisation
8	meta-analysis AND improve* AND knowledge utilisation
9	overview* OR review* AND intervention AND knowledge translation
10	systematic review* OR meta-analys* AND intervention* AND evidence uptake

In addition to the main search, a briefer 'updated' search was conducted for any new or on-going studies (Baker et al. 2010). This writer repeated parts of the search for the period December 2010 to May 2013 with PubMed and EMBASE. This writer also searched all active registers in the *meta*Register of controlled trials (http://www.controlledtrials.com/mrct/) in May 2013, for reports of relevant on-going or completed trials that could then be mentioned without being incorporated fully in the completed review.

Study Selection

Two reviewers, including this writer, independently assessed studies for inclusion in the systematic review and discrepancies were resolved by consensus or by discussion with a third party. Multiple reports of the same study were screened for, and duplicates identified.

All decision makers were included. Studies recruiting lay participants and members of the public were encompassed. Any outcome measure of the utilisation of systematic review evidence informing health care decision making was considered. Self-reported use of evidence was included as well as outcome measures of actual use.

Inclusion criteria

To be included in the review, primary studies had to meet the following criteria:

- Addressed interventions aimed at increasing the uptake of evidence specifically from systematic reviews, meta-analyses and the databases that contained them

- Databases could include The Cochrane Library, The Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Pregnancy and Childbirth Database, Oxford Database of Perinatal Trials, and the Reproductive Health Library
- All decision makers, including doctors, nurses, policy makers, the public and patients, were eligible
- Reports in any language were included
- Studies could be randomised trials, cluster randomised trials, controlled clinical trials and before-and-after studies
- Interventions could arise from within the research community or from within an organisation using systematic review evidence
- Strategies could be single-stranded or multi-faceted, or combine two or more interventions
- The mode of delivery of the intervention could be print, electronic, audio/visual or face-to face
- When a comparison was employed, the comparator could be no intervention or an alternative intervention
- It was not required that the interventions had to be specifically tailored to overcome specified, pre-identified barriers in a systematic review
- Measures of impact on decision makers' knowledge, attitude or behaviour, and impact on patient care were included

Exclusion criteria

Studies were excluded if

- They were exclusively about interventions to increase evidence uptake in general but did not include systematic review uptake
- They were interventions to enhance uptake of policy briefs and position statements
- They were studies dealing exclusively with interventions aimed at increasing the use of clinical practice guidelines
- They were studies not investigating an intervention with a measured outcome but instead focusing on general perceptions and views captured by surveys, focus groups and interview studies

Data extraction

After the first screening, two reviewers independently abstracted specific information from full-text studies according to standardized data extraction checklist items derived from the Cochrane Effective Practice and Organisation of Care Group checklist (EPOC, 2002). EPOC reviews encompass professional interventions such as educational meetings and use of local opinion leaders, as well as financial, organisational or regulatory interventions. Details extracted from primary studies included the unit of allocation such as the clinician, practice or hospital, the characteristics of the intervention, including the content, format, recipient, setting and timing, and a description of the main outcome measure. Discordances between the two reviewers were resolved by consensus or discussion with a third party.

For randomized trials, primary outcomes were compared between the control group and the intervention group. A determination was made regarding the degree to which the intervention in each study was effective, had mixed effects or was ineffective. An efficacy qualitative scale was applied to each study (Eastwood et al. 2008). The heterogeneity of studies can prevent formal statistical analysis of aggregate results (Joly et al. 2013). Reviews of research-to-action strategies add up the number of positive and negative comparisons and conclude whether interventions were effective on that basis (Grol and Grimshaw, 2003). This avoids an overly statistical approach to outcomes (Eccleston et al. 2013). Reviews can aggregate or simply organise or configure the findings of primary studies (Gough et al. 2012).

Strategies with a negative effect, compared with the primary objective of the authors, were classified as "ineffective"; "mixed effects" was ascribed to studies that partially reached their objectives; and strategies with a significant positive effect were classified as "effective" (Chaillet et al. 2006). This classification allowed for a narrative synthesis with tabulation. The aim here was to answer a question rather than simply cover a topic area (Gough et al. 2012). No meta-analysis was performed because of the high heterogeneity between the outcome measures used in each study.

7.7 Assessment of risk of bias

There should be a cohesive interpretation of intervention effects incorporating risk of bias for outcomes (Hrobjartsson et al. 2013). This reviewer assessed the risk of bias of included studies using criteria described by EPOC. Given the potential heterogeneity of the targeted behaviours, skills, and organisational factors relevant to the review, this

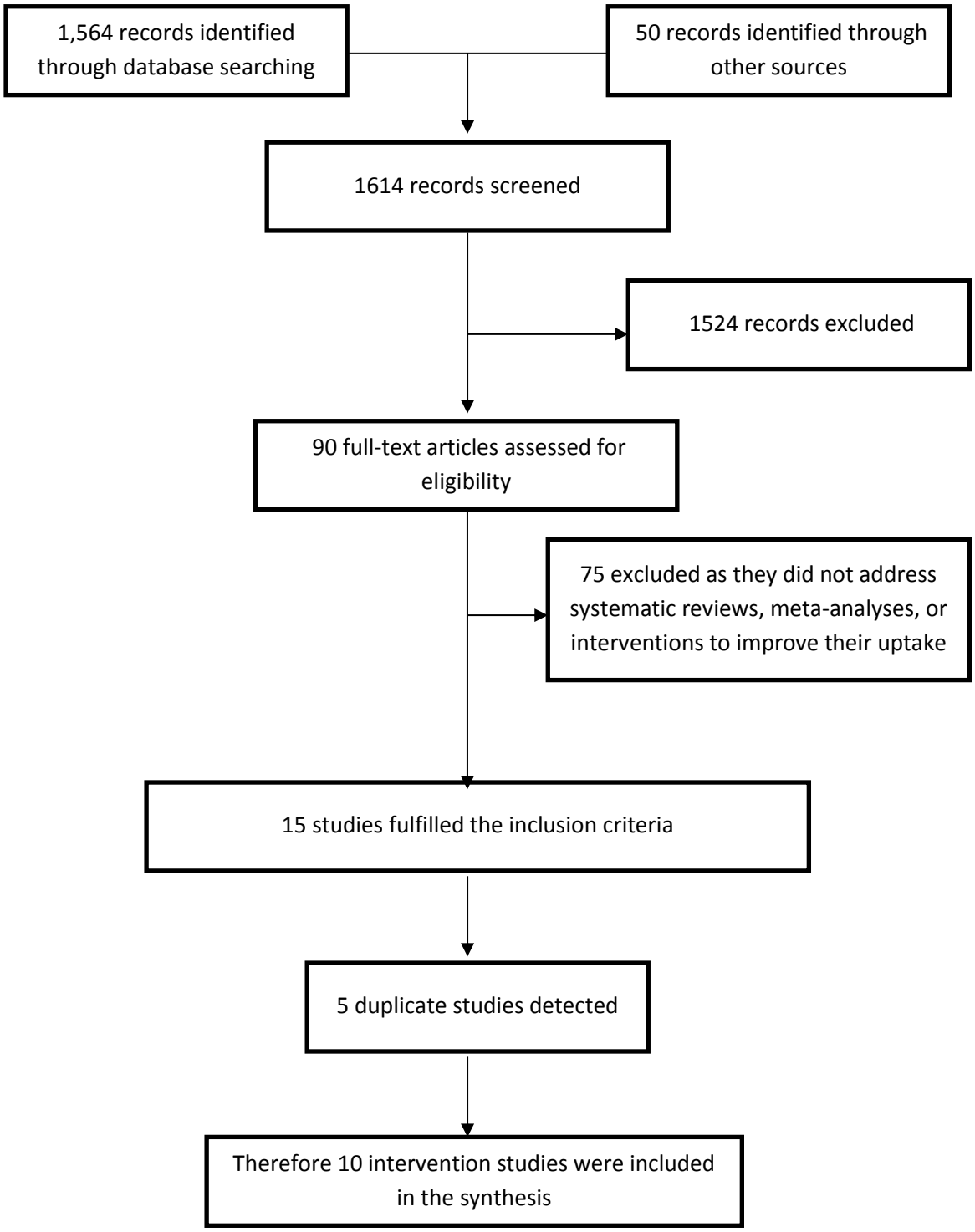
reviewer did not base study inclusion on a minimum cut-off for methodological quality. The risk of bias for each of the included studies was addressed. This writer assigned an overall risk of bias rating such as high, moderate and low to all studies included in the review, based on the standard criteria used in EPOC reviews.

Like Baker and colleagues, this writer assigned a rating of low risk of bias if the first three criteria were scored as done and there were no concerns related to the last three criteria; moderate if one or two criteria were scored as not clear or not done; and high if more than two criteria were scored as not clear or not done (Baker et al. 2010). Each criterion was noted as “Done,” “Not clear,” or “Not done”. Only studies with a low to moderate risk of bias were used to draw conclusions about the effectiveness of interventions to enhance uptake of reviews.

7.8 Results

The results of the extensive, systematic search are given in Figure 7.1.

Figure 7.1. PRISMA Flow diagram: flow of intervention studies through selection process



Results of the search

Some 1,564 records were identified through database searching covering the full range of publication years available in each of the 19 databases up to December 2010 and 50 records identified through other sources, such as bibliographies of related reviews and primary studies, textbooks and contact with authors in the field. Of the total number of 1,614 titles and abstracts screened from all sources, including qualitative and grey literature searching, 1,524 records were excluded as not meeting inclusion criteria. Then 90 full-text articles were retrieved and assessed for eligibility, with 75 studies excluded as they did not address systematic reviews or meta-analysis, or because they addressed natural, non-intervention facilitators derived from surveys, focus groups and interviews (Wallace et al. 2012b). The 5 duplicate studies detected are outlined in appendix 6. Ten intervention studies were then included and form the evidence base for this systematic review (Table 7.2).

Table 7.2. Types of interventions and number of studies addressing them

Interventions	**Number of studies**
Educational visits	1
Brief summaries of systematic reviews	1
Multi-faceted educational intervention	1
Manual of Cochrane reviews	1
Clinically integrated e-learning course	3
Access to online registry, tailored messaging, and knowledge brokers	1
Computer-based (CD-ROM) session	2
Total number of studies	**10**

On completion of the synthesis, an 'updated' search of EMBASE and PubMed from January 2011 to May 2013 was conducted but failed to identify further studies. The *meta*Register of controlled trials was also searched in May 2013 and no eligible studies were identified.

Included studies

Of the ten included studies, there were 5 randomised controlled trials, 3 cluster randomised controlled trials, 1 controlled clinical trial, and 1 before-after study. There were 8 two-arm trials, 1 single-arm trial and 1 three-armed trial. The unit of allocation was the health professional, such as a doctor, in 3 studies, the patient in 1 report, and a larger grouping such as the hospital or geographical location in 6 studies.

Settings and characteristics of professionals

The nature of the desired change, professionals targeted, and the intervention settings, differed from one study to the next. Four studies were undertaken in the UK, 1 each in Australia, USA and Canada while 1 study was conducted across five countries: Germany, Hungary, Spain, Switzerland and the UK. The remaining 2 studies were carried out in the Netherlands and the UK, and in Mexico and Thailand, respectively. The studies were conducted in 11 countries in total.

Eight studies took place in a hospital setting while the remaining two investigations were conducted in a government department and a medical school. In 6 studies, the professionals included doctors of different disciplines and at varying stages of training.

Two studies dealt with obstetricians, 1 study included psychiatrists, another GPs, and 2 studies involved Interns (Foundation year). Three reports also included nurses or mid-wives, one targeted patients as participants exclusively, while another looked at programme managers.

Prospective identification of barriers to change

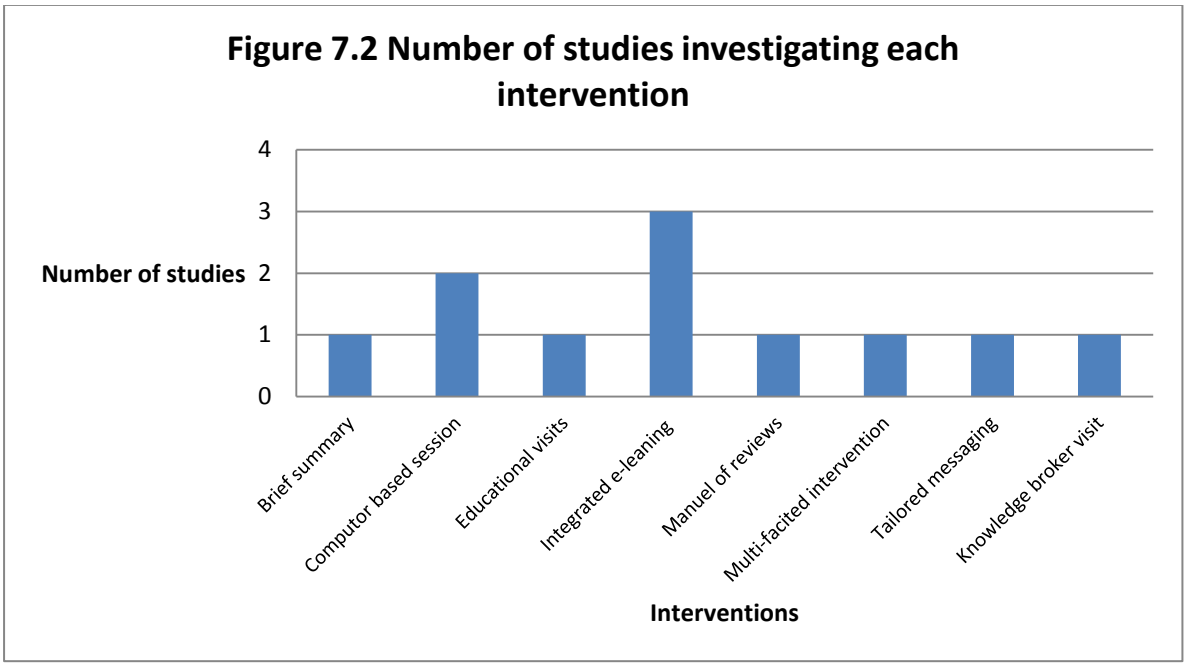
None of the 10 studies tailored the intervention to specific, prospectively identified barriers to uptake of evidence from systematic reviews or meta-analyses.

Theoretical underpinning

Eight studies identified a theoretical underpinning underlying their choice of intervention. One study included a costing for their intervention to improve uptake of evidence from systematic reviews (Wyatt et al. 1998).

Characteristics of interventions

Among these reports, interventions included clinically integrated e-learning courses (3/10), educational visits (2/10), a computer-based (CD-ROM) session focusing on critical appraisal and application of systematic reviews (2/10), brief summaries of systematic reviews (1/10), a manual of Cochrane reviews (1/10), and access to online registry, tailored messaging and knowledge brokers (1/10) (Figure 7.2).



Descriptions of the strategies are outlined in Table 7.3. One study investigated three interventions (Dobbins et al. 2009b).

Table 7.3. Description of intervention strategy and effectiveness

Effectiveness	Strategy	Description
Consistently Effective		
Variable		
	Short summaries of systematic review	Four short, one-page systematic review summaries delivered by e-mail or post.
	Clinically integrated e-learning course	5 e-learning modules focusing on systematic reviews: self-directed learning delivered over 4-6 weeks.
	E-learning course	5 e-learning modules focusing on systematic reviews.
	E-learning course	3 e-learning modules focusing on systematic reviews, with unlimited access over 6 weeks.
	Computer-based Session	1 computer (CD-ROM) session focusing on systematic reviews.
	Computer-based session[13]	1 computer (CD-ROM) session focusing on systematic reviews .
	Multi-faceted intervention: interactive workshops	3 interactive workshops using RHL over 6 months. The focus was to provide access and facilitate use.
	Educational visit	Educational visit by a respected obstetrician advancing ways to apply evidence from Cochrane reviews with The Cochrane database donated.
	Tailored, targeted, messaging	Summarised from 7 rigorous systematic reviews with a series of e-mails with link to full reference, abstract and summary.
	On-line Registry	Access to a registry of systematic reviews.
	Knowledge broker	Visits from a respected knowledge broker.
Little or unknown effect	Patient manual	Patient manual of summaries of Cochrane reviews: 80 page, A5 size manual with 22 summaries of evidence organized into tagged sections.

Outcome measures

Use of correct outcome measures in this area is of considerable importance (Burton et al. 2013). Six of the interventions were geared to improving knowledge of, or attitude to, systematic reviews (Table 7.4). Some 4 trials targeted a change in practice such as clinical management of pre-term delivery, optimum use of analgesia, clinical management of chronic obstructive pulmonary disease, or a change in healthy body weight promotion policies.

Risk of bias in included studies

Some 8 studies had adequately addressed allocation concealment. Follow-up of professionals was carried out adequately in 6 studies. Blinded assessment of the primary outcome was carried out in 9 studies. Baseline measurement was conducted adequately in 5 studies. A reliable primary outcome measure was reported in all 10 studies. Protection against contamination was assessed as adequate in 7 studies. Regarding overall risk of bias, 6 studies were regarded as of moderate risk of bias, 2 at low risk of bias while 2 studies were assessed as being at high risk. Risk of bias assessment and results are given in Table 7.4.

Table 7.4. Risk of bias assessment and results of intervention studies

Study	Risk of Bias	Primary Measures	Outcome	Authors' Conclusions
Wyatt et al. 1997	Low	Ventouse usage. Steroid usage. Suture usage. Antibiotics usage and concordance of guidelines with systematic review.	Overall baseline rate increased from 43% to 54%. Only one clinical practice improved significantly.	Educational visits added little to uptake of systematic review evidence. Significant change in ventouse delivery only.
Gulmezoglu et al. 2006	Mod.	Social support in labour MgSO4 for eclampsia. Corticosteroids-preterm Selective episiotomy. Uterotonic use after birth. Breastfeeding on demand. External cephalic version. Iron/folate supplementation. Antibiotic use at CS. Vacuum extraction for assisted birth. Knowledge of RHL. Use of RHL.	No consistent/substantive changes in 10 clinical practices. RHL awareness (24.8%-65.5% in Mexico, 33.9-83.3% in Thailand) and use (4.8-34.9% in Mexico and 15.5-76.4% in Thailand) increased substantially after the intervention.	Results were negative regarding practices targeted, but there was increased awareness, use of RHL.
Harris et al. 2006	Mod.	Rates of flu vaccination, bone density testing, increased satisfaction, improved communication, reduced anxiety, improved quality of life.	No pattern of statistically benefit in primary or secondary outcome measures but virtually all trends favoured the intervention group. High levels of use, little impact on clinical practice.	Advantages for the intervention were seen as trends.
Davis et al.2007	Mod.	Knowledge gain, attitude gain.	Similar results for attitude and knowledge.	Computer-based teaching as effective as lecture-based.
Oermann et al. 2007	Mod.	Awareness, understanding, usefulness, and preferred mode of delivery of reviews.	Awareness improved significantly (p=0.001). Understanding improved non-significantly.	Short summaries of systematic reviews improve awareness of review evidence.

Kulier et al. 2008	High	Change in knowledge and attitude scores.	On average, knowledge scores improved significantly (p<0.001). Attitudinal gains on two questions only (p=0.00, p=0.007).	E-learning about systematic reviews can be harmonised across different languages and specialities.
Davis et al. 2008.	Mod.	Knowledge gain Attitude gain. .	Difference between groups: -0.5 (95% CI -1.3, 0.3: p=0.24).	Computer-based teaching and typical lectures have similar gains in knowledge and attitude.
Kulier et al. 2009	Mod.	Change in knowledge and attitude scores	The intervention group outperformed by control group by 3.5 points (95% CI: -2.7, 9.8) for knowledge gain: not statistically significant.	Both groups had an improvement in attitude and knowledge but the intervention group had a tendency to better performance.
Dobbins et al. 2009	Mod.	Use in a program decisions and change in healthy body weight promotion policies.	No significant effect for primary outcome (p=0.45). For policies, a significant effect for targeted, tailored messages (p<0.01). All groups improved.	Targeted, tailored, messages are more effective that knowledge brokering and online registry.
Hadley et al. 2010	High	Knowledge gain.	Adjusted post-course difference: only 0.1 scoring points (95% CI 1.2, 1.4) between groups: no difference in improvement in knowledge between groups.	E-learning and standard classroom-based teaching both improve knowledge.

Outcome measures

The specific outcomes were chosen by the primary study investigators because of clinical relevance and suitability. Six studies were concerned about changing knowledge and

attitudes. One report analysed both knowledge and decision-maker behaviour (Gulmezoglu et al. 2007) while another addressed practice and quality of life (Harris et al. 2006). Two studies analysed specific practice or behaviour change (Wyatt et al. 1998, Dobbins et al. 2009b). Details of behaviours targeted are given in Table 7.5.

Table 7. 5. Types of behaviour targeted by interventions (Adopted from Oxman et al. 1995)

Behaviour	Number of trials
Ventouse usage	1
Steroid usage for pre-tern delivery	1
Rates of polyglycolic acid sutures	1
Antibiotics usage in caesarean section	1
Awareness, understanding and likely use of analgesia evidence	1
MgSO4 for eclampsia	1
Corticosteroids-preterm	1
Selective episiotomy	1
Breastfeeding on demand	1
External cephalic version	1
Iron/folate supplement	1
Antibiotic use at CS	1
Vacuum extraction for assisted birth	1
Knowledge of RHL	1
Use of RHL	1
Rates of influenza vaccination	1
Bone density testing	1
Increased satisfaction	1
Improved communication	1
No increase in anxiety	1
Knowledge	5
Attitude	4
Use in a research programme	1
Change in healthy body weight promotion policies	1

Of the 12 interventions investigated in the 10 studies, none of the interventions were consistently effective across all outcome measures. Eleven of the 12 interventions were of variable effectiveness while 1 had little effect on the primary outcome measure.

Specific interventions were single, two-method, or multifaceted interventions. Only one study described itself as 'multi-faceted' and the intervention had no consistent or substantive impact on the 10 clinical practices that they targeted (Gulmezoglu et al. 2007).

Importantly, three studies of low-to-moderate risk of bias, showed a statistically significant improvement in some relevant outcomes. These interventions included educational visits (Wyatt et al. 1998), short summaries of systematic reviews (Oermann et al. 2007), and targeted messaging (Dobbins et al. 2009b).

Wyatt and colleagues employed a single informal, 1.5-3 hour visit by a respected obstetrician (Wyatt et al. 1998). The educational visit included a discussion of evidence-based obstetrics, guidance on implementation, and a donation of The Cochrane database and other materials. The intervention was targeted at a particular setting. They felt that their intervention overcame specific barriers, was brief, but could benefit from the addition of other strategies.

Oermann and her colleagues disseminated the results of systematic reviews directly to nurses in the form of short summaries, written in an easy-to-understand style, and sent by e-mail (Oermann et al. 2007). They felt that the brief reports overcame the barriers of limited time and also a lack of expertise and resources. The language and presentational style employed were easy to use and the short, one-page reports were sent directly to

nursing staff outlining different outcomes from a systematic review over a 4 week period. The brief report format allowed easy consideration of the use of systematic review evidence in clinical practice. The intervention was targeted at a particular discipline.

Dobbins and her colleagues used tailored, targeted messaging in the form of a series of e-mails offering a link to short summaries of systematic reviews, giving the abstract as well as a link to the full text (Dobbins et al. 2009b). This modification of an intervention to take account of a person's preferences and abilities is important (Lawrence et al. 2012). The tailored messaging was felt to have overcome a number of barriers and was also directed at a particular setting.

What these three interventions have in common is that they were believed to overcome certain barriers, were intended to be brief, and were targeted at a specific group or setting. The interventions used e-mail or an electronic version of a database containing systematic reviews.

Other interventions such as interactive workshops produced 'substantial' benefits (Gulmezoglu et al. 2007). Clinically integrated e-learning courses brought about some knowledge and attitude gain from baseline. A further computer-based series of teaching sessions also showed an improvement in knowledge and attitudes from baseline. However, one study using a Cochrane review-based patient manual found no pattern of benefit in their chosen outcome measures (Harris et al. 2006).

7.9 Discussion

This study is important, as to this writer's knowledge, it is the first systematic review of interventions to enhance uptake of evidence specifically from systematic reviews and meta-analyses, by all decision makers, using an extensive range of databases. The evidence provided by this synthesis supports some tentative conclusions. First, there is a dearth of research assessing the effects of interventions to enhance uptake of evidence from systematic reviews. However, there is also a discernible move away from the traditional, didactic educational model aimed at enhancing evidence uptake.

This systematic review confirms that knowledge and attitudes may be altered by a number of interventions across a range of disciplines and levels of training. Healthcare practices were changed to a lesser extent. Importantly, no study showed an impact on patient outcomes. Statistically significant alterations were made on a limited number of outcome measures, in studies of low to moderate risk of bias, by targeted messaging, short summaries of systematic reviews and also educational visits.

Limitations

A frequent disappointment in the conduct of systematic reviews is the relative paucity of primary studies on which to base the review (Matson, 2013). Identification of published studies on evidence uptake is difficult because they are poorly indexed and scattered across generalist and specialist journals. Some publications may have been missed, though an extensive search was conducted using over 19 databases. Reporting was sometimes incomplete so that data extraction was problematic (Stewart, 2013). Reporting

inadequacies in trial publications constitute a continuing concern (Hrobjartsson et al. 2013).

Important methodological limitations and inconsistencies among the available studies make it extremely difficult, currently, to underpin policy initiatives on the basis of current evidence (Joly et al. 2013). Undertaking reviews in this area is difficult because of the complexity inherent in the interventions, the variability of the methods used, and the difficulty of generalising findings across healthcare settings.

The impact of the interventions was not consistent across users, settings, or behaviours. Positive studies had just one or two of many outcome measures that yielded a significant result. Some studies presented a positive trend, others, statistically significant outcomes. Certain interventions appeared to improve knowledge and attitudes, and to a lesser extent, performance. None were shown to impact on patient outcomes. The issue of patient-centred outcomes is likely to become more prominent as a topic in the coming years (Gartleher and Flamm, 2013). It is also important to increase not just perceived usefulness but also the actual utilisation of a resource (Skapetis et al. 2013).

Some investigations compared the relative effectiveness of different strategies. However, the control condition, such as traditional lectures, may themselves be effective thus obscuring the contribution of the experimental intervention.

The research in this area is often conducted by small numbers of researchers in specific settings, limiting generalizability. However, while a lack of European studies is sometimes a problem in the interpretation of the applicability of reviews, most studies included here were conducted in Europe rather than North America.

None of the studies used interventions tailored prospectively to identify barriers. However, interventions may improve performance regardless of tailoring. Prospective identification of barriers and tailoring requires extra steps and tailoring may cost more.

Despite the limited number of studies found, it should be remembered that conclusions may still be elusive even when hundreds of data sets are included in a review based on years of cumulative research activity. A review with little data may still yield valuable findings (Cook et al. 2013).

Implications for research

We need to standardize reporting of trials of interventions to improve professional performance. A broad framework should be developed for designing and selecting appropriate interventions across a wide range of professional activities in which gaps between evidence and practice are found (Oxman et al. 1995). Clarification of the contextual factors that modify the effectiveness of an intervention is required (Wallace, 2013). More information is needed about relative effectiveness and also cost effectiveness.

There is an imperfect evidence base to support decisions about what dissemination and implementation strategies are likely to be effective under different circumstances (Grimshaw et al. 2004). This systematic review provides specific information about strategies used to improve uptake of systematic reviews, meta-analysis and the databases associated with them. More studies are necessary to address the efficacy and active components of these strategies. Future research should focus on interventions that

improve patient satisfaction, health-related quality of life, and population-level indicators of health (Nabulsi et al. 2007).

An emphasis on real-life settings is required (Tricco et al. 2013). Both clinical practice but also more patient outcome data are required. Efforts might be better focused on more clinically integrated interventions (Coomarasamy and Khan, 2004). Information is also needed on the sustainability of effective knowledge translation interventions beyond one year's duration. This research is ongoing (Tricco et al. 2013).

There also needs to be agreement on how to structure future reviews. In this systematic review, the EPOC taxonomy of interventions was used. This taxonomy is based on descriptions of components of interventions. Interventions could, however, be classified differently in future research.

Implications for practice

In the design of interventions to improve uptake of research evidence, the implementation process appears to possess at least 2 stages. The primary dissemination strategy involves information being made available to as many professionals as possible. The secondary implementation strategy enables or reinforces changes in the practice setting. Several approaches to improving uptake of evidence from systematic reviews have a significant effect, such as educational visits, systematic review summaries and targeted messaging. Promising interventions include e-learning, computer (CD-ROM) based learning, inactive workshops, the use of knowledge brokers, and an e-registry of systematic reviews.

7.10 Conclusion

The creation of systematic reviews and meta-analyses without attention to their uptake can waste precious resources. There are no magic solutions for improving the uptake of evidence from systematic reviews. There are however a number of interventions available to enhance uptake of review evidence that if used appropriately, could lead to improvements in knowledge and clinical practice. The choice of intervention should be guided by the evidence on the effectiveness of the strategy. A number of useful uptake strategies were identified here.

The results expand our understanding of how multiple factors act as facilitators to optimal practice. This review reveals that interventions aimed at fostering systematic review uptake can build on a wide variety of facilitators.

7.11 Abstract

Title

Found in translation: a systematic review of interventions to enhance the uptake of systematic reviews and meta-analyses

Context

The increased uptake of evidence from systematic reviews is advocated because of their potential to improve the quality of patient care by quickly expediting the application of current, effective advances to everyday practice. However, evidence from systematic reviews has not been widely adopted by health professionals. Little is known about the strategies that enhance uptake of evidence specifically in response to systematic reviews.

Objective

To identify interventions enhancing the uptake of research evidence from systematic reviews and meta-analyses by all decision makers.

Methods

Inclusion criteria: Studies were included if they addressed interventions enhancing the uptake of evidence specifically from systematic reviews, meta-analyses and the databases containing them. Reports in any language were included. All decision makers were

eligible. Studies could be randomised trials, cluster-randomised trials, controlled-clinical trials and before-and-after studies.

Information sources: This writer searched 19 databases including PubMed, Embase and The Cochrane Library, covering the full range of publication years from inception to December 2010, utilised three search engines, and also personally contacted investigators. Reference lists of primary studies and related reviews were also consulted.

Risk of bias assessment: Studies of systematic review uptake strategies were selected and evaluated according to the Effective Practice and Organisation of Care criteria. Two reviewers independently assessed the quality of the retrieved reports. For all of the studies included in the review an overall risk of bias rating, such as high, moderate and low, was assigned based on the standard criteria used in EPOC reviews.

Results

Included studies: The search found 10 studies from 11 countries, containing 12 interventions that met our criteria. Eight of the studies took place in a hospital setting, two investigations were conducted in a government department and a medical school. In 6 of the studies, the professionals included doctors of different disciplines and at varying stages of training. Three reports also included nurses or mid-wives while one targeted patients as participants exclusively. Six of the interventions were geared to improving knowledge of, or attitude to, systematic reviews. Some 4 trials targeted a change in practice such as clinical management of pre-term delivery, optimum use of analgesia, clinical management of chronic obstructive pulmonary disease, or a change in healthy body weight promotion policies.

Synthesis of results: Three studies of low-to-moderate risk of bias, showed a statistically significant improvement in some relevant outcomes. These interventions included educational visits, short summaries of systematic reviews, and targeted messaging.

Interpretation

Strategies such as targeted, tailored messaging, educational visits, and summaries had a statistically significant impact on at least one outcome measure. Promising interventions include e-learning, computer (CD-ROM) based learning, inactive workshops, the use of knowledge brokers, together with an e-registry of systematic reviews and meta-analyses.

Discussion

Strengths and limitations of the evidence: Much of the research in the field is poorly indexed and a limited number of studies were found for inclusion in the review. However, the extensive and systematic literature search using 19 databases, with a special emphasis on grey literature, is one of the strengths of this systematic review.

Funding: No internal or external funding was received

Next chapter

Together with information on the effects of interventions, decision makers' preferences and abilities are also important in selecting an intervention aimed at enhancing uptake of systematic reviews (Lawrence et al. 2012). Taking account of these views or perspectives,

certain detected strategies can then be recommended, promising interventions highlighted and novel interventions explored. These issues are addressed in the next chapter.

CHAPTER 8

SYSTEMATIC REVIEW OF BARRIERS, FACILITATORS, AND INTERVENTIONS

CONTENTS

8.1	**Introduction**	**323**
8.2	**Mixed-Knowledge Synthesis**	**326**
8.3	**Steps**	**331**
8.4	**Methodology**	**331**
8.5	**Results**	**333**
8.6	**Discussion**	**337**
8.7	**Conclusion**	**342**

8.1 Introduction

In this chapter, the different reviews are brought together in order to expand our understanding of the factors influencing systematic review uptake. The individual reviews are not treated as isolated products but are contextualized. The findings are brought together as a coherent statement (Gough et al. 2012). An attempt was made to understand the different perspectives and then summarise them in an overarching narrative (Wong et al. 2013). This review differs from the others conducted by this writer in that it involves a synthesis of both qualitative and quantitative research.

The impetus to develop and disseminate systematic reviews is well established. It is rooted in the need to curtail practice variation and is linked to the evidence-based medicine movement. While systematic reviews are not appropriate to every problem, given the expense, time and expertise involved, it is important to ensure improved uptake (Cook et al. 2013). After a systematic review has been completed, it is disseminated, usually by traditional means such as publishing in recognised professional clinical journals. Next, various groups may attempt to enhance the uptake of the research more actively. This is done by using different methods to assist, convince, and otherwise influence physicians, patients and other decision makers to become aware of, familiar with, adopt and eventually use systematic review evidence.

While science- and investigator-driven research is important, engagement with other decision makers can help address issues that are considered relevant by stakeholders (Knottnerus and Tugwell, 2013). The final overview of this thesis was aimed at combining, systematically and appropriately, the results of the three previous reviews (Gough and Thomas, 2013). By integrating the reviews of barriers, natural facilitators and

interventions, the aim of this final over-arching synthesis was to illuminate a complex area from different angles (Wong et al. 2013). This is in keeping with the emphasis that some authors place on the value of a plurality of perspectives, questions, and methods (Gough et al. 2012).

From the results of the reviews outlined in the previous chapters, this writer identified the barriers, facilitators and interventions impacting on the uptake of evidence from systematic reviews, meta-analyses, and the databases associated with them. Some approaches seek not only to address the question of 'what works' but also to clarify a complex topic area that has been differently conceptualized by different groups of researchers (Wong et al. 2013).

Readily accessible endpoints and outcomes are important to trial designers. However, attention to other vantage points that decision makers adopt when confronted with an innovation is important (Gartleher and Flamm, 2013). The perspective of the different shareholders is central in research (Knotterus and Tugwell, 2013). A plurality of reviews expands rather than limits our understanding of a topic and can add to a theory of change (Gough et al. 2012). We can see what has had an impact but also understand why.

Background

Synthesis has the potential to provide relevant knowledge. The choice of synthesis will depend on the aim of the systematic review and the nature of the evidence available. However, frequently more than one approach to synthesis will be required (Mays et al. 2001).

Synthesis, of course, is a rapidly developing area of research methodology. There is a tendency for more recent systematic reviews to include a wider range of different study designs (Anglin et al. 2013). The incorporation, in reviews, of a broader range of evidence types is proposed (Cook et al. 2013). A broader focus including not just non-randomized studies is advocated (Gartleher and Flamm, 2013). The aim can be to supplement and extend the findings of individual, focused reviews (Wong et al. 2013).

Qualitative methods can be used to elucidate the context in which different interventions can be optimized (Lawrence et al. 2012). Qualitative research can steer researchers towards interventions that are more likely to be effective (O'Cathain et al. 2013). There are challenges however, to synthesizing such diverse evidence sources (Pope et al. 2007). A hybrid approach is used here where two parallel systematic reviews address different, but related, elements of an overall review question (Oliver et al. 2005).

Two separate syntheses of intervention and non-intervention studies, with an overall narrative commentary, are described here. The studies to be included in this review were diverse and included surveys, focus groups, interviews, but also intervention studies. Data were extracted from these disparate studies, a synthesis carried out and the results reported (Noyes et al. 2008). Every effort was made to make sure that the syntheses were transparent and rigorous (Anglin et al. 2013).

There is an imperfect evidence base to support decisions regarding evidence transfer strategies that are likely to be appropriate and effective under varying circumstances **(**Grimshaw et al. 2002). It is important to estimate the efficacy of dissemination and implementation strategies in the presence of different effect modifiers **(**Grimshaw et al. 2002).

The aim here was to undertake a systematic mapping of research on the barriers to, and facilitators of, uptake of evidence from systematic reviews, to synthesize what is known from these studies about barriers and facilitators, and importantly, to evaluate how these specified factors are addressed by the identified interventions. The aim was to place the different interventions in perspective (Leucht et al. 2012). It is acknowledged that more than one type of overview may be required with complex problems (Eccleston et al. 2013). Using heterogeneous sets of studies in a review can be a strength rather than a problem (Gough and Thomas, 2012).

Combining qualitative and quantitative methods to identify not just what works but why, can help develop and deliver effective interventions in real life settings (Lawrence et al. 2012). The resulting narrative synthesis can then provide a summary of the current state of knowledge. Recommendations can then be made to clinicians and other decision makers interested in enhancing uptake of evidence from systematic reviews.

8.2 Synthesis of different types of reviews

The EPPI approach involves posing a very broad review question and then developing separate review sub-questions (Pope et al. 2007). This approach is developed by the Evidence for Policy and Practice Information Co-ordinating (EPPI) Centre at the Institute of Education in London. The EPPI process involves first asking a broad review question. Initially, the reviewer describes the different types of study to be included in the remit of the overall review question. The next step entails outlining the searching and screening process to answer a number of separate sub-questions. Finally, the different findings are synthesized. It is important that all stages of this process are conducted with methodological rigor (Pieper et al. 2012).

In this synthesis, three parallel systematic reviews were conducted and are described here. The focus was on sub-questions about barriers, facilitators and interventions to enhance the uptake of evidence specifically from systematic reviews and meta-analyses. The aim was for a coherent configuration (Gough and Thomas, 2012).

This writer was concerned not just with views and perspectives on barriers and enablers, but also with the effectiveness of interventions to make systematic reviews more wanted. Sequential systematic reviews were conducted. First, a review of the perspectives of decision makers on the barriers to uptake of evidence from systematic reviews was carried out. Then the views and perspectives on facilitators were researched. Finally, an effectiveness outcome review was conducted. Lastly, in this final synthesis, the results of these three parallel syntheses are brought together to address an overall review question: How can systematic review uptake be improved?

With the EPPI approach, there is no statistical pooling of results but a gradual building up of a mosaic of findings to produce an overall picture from the different pieces of evidence. The results of the separate syntheses are combined in a so-called 'meta-synthesis' aiming to address the review question in its entirety. The quantitative and qualitative findings are arranged or configured (Gough and Thomas, 2012). The views and perceptions of barriers and facilitators are compared with the outcomes of intervention studies. Qualitative research can complement, enhance, extend, and supplement quantitative analysis in systematic reviews (Higgins and Green, 2011). The aim is that the overall synthesis will be more helpful to decision makers than the presentation of the reviews singly.

The objective of the research presented here was to find out the extent to which the interventions, found by comprehensive searching, addressed and incorporated the barriers and facilitators to uptake of knowledge from systematic reviews and meta-analyses. Different recommendations about the intervention can then be made (Pope et al. 2007). Available options can be to (1) recommend the intervention, (2) develop the intervention further, or (3) generate a new intervention.

The advantage of the panoramic, mixed-methods approach employed here is that it uses a larger proportion of research evidence relevant to the review question. It enhances explanatory power (Cook et al. 2013). The approach provides a transparent path to evidence synthesis with recommendations for action and also future research (Pope et al. 2007).

A framework

Oliver has described a model of research synthesis (Oliver et al. 2005). The model provides a framework for combining the findings of different types of studies, including those that collect qualitative data, within a systematic review. The framework facilitates addressing questions that move beyond effectiveness. The framework was developed while conducting a series of reviews on the barriers to, and facilitators of, young people's mental health, healthy eating, and physical activity (Oliver et al. 2005).

The framework employs theoretical and methodological dimensions for synthesizing empirical data extracted from a diversity of studies. Key features include identifying a clear research question, selecting appropriate study designs for each synthesis, choosing a

quality assessment and a synthesis method according to the types of studies and findings to be synthesized. Lastly, a theoretical framework is employed to juxtapose the findings from each synthesis in order to facilitate comparison.

In line with empirical evidence that demonstrates that controlled trials provide the most reliable evidence for generating findings about effectiveness, this writer grouped studies according to whether or not they employed these designs. Like Oliver and colleagues, methodological priorities were for rigorous evaluations of the effects of interventions such as employment of a control or comparison group. Also prioritized were non-intervention studies that directly reported decision maker's views, such as doctors, nurses and policy makers, where available. The substantive reviews presented a diversity of study designs and methods of data collection and synthesis.

Each set of studies independently entered a quality assessment together with a narrative and tabular synthesis. Then the findings from each synthesis were juxtaposed in a cross-study synthesis. Details of the quality assessments were presented in the original reports. This writer extracted from the studies of decision maker's views, their identification of influences on their decision making behaviour in a qualitative analysis. This writer then compared the findings with the populations, interventions and outcomes addressed in the outcome-evaluation studies.

The overarching research question concerned how to improve the uptake of evidence from systematic reviews. This question determined the study types eligible. Two further sub-questions, 'What factors are associated with uptake?' and 'What interventions are effective?' also framed the within-study type synthesis. The final 'cross-study type' synthesis was directed by the sub-questions: 'To what extent have interventions addressed

the barriers to uptake?' and, 'To what extent have the interventions built on the facilitators?'

Theory also influenced this review process. Theoretical models to conceptualise categories of interventions, or barriers and facilitators were drawn on. Barriers and facilitators were seen as operating on 3 interrelated spheres: the individual, the community and wider society (Tones and Tillford, 1994).

Both quantitative and qualitative research methods were incorporated and used in this overarching, mixed-knowledge review. The aim was to fully integrate the views being expressed, with both types of research, qualitative and quantitative research, utilized.

Detailed procedures were drawn on for gathering and making sense of the findings from diverse studies. Thematic analysis was employed. A narrative synthesis was used to identify patterns of factors relating to the success or otherwise of interventions (Oliver et al. 2005).

Cross-study type synthesis

This writer juxtaposed findings from the synthesis of intervention studies with the findings from the synthesis of decision maker's views using a barriers and facilitators conceptual framework. By constant comparison of the findings from each synthesis, this writer looked for interventions that diminished identified barriers and interventions that built on identified facilitators (Oliver et al. 2005). The aim of this final synthesis was to increase information gain (Evangelos et al. 2012).

8.3 Steps

Initially, the review question was stated: How can uptake of evidence from systematic reviews and meta-analyses be enhanced? Then a mapping and screening exercise was carried out. The total number of citations in the three systematic reviews was calculated. Then, retrieval, screening and classification of full reports resulted in a specific number of included intervention and non-intervention studies. Next, an in-depth review was conducted within each study type. Lastly, a synthesis of findings was carried out aimed at finding the extent to which the interventions overcome the identified barriers and build on the detected facilitators. A number of previously reported studies, in related fields, informed the conduct of this review (Davis and Taylor-Vasey, 1997, Shepherd et al. 2006, Oliver et al. 2005).

8.4 Methodology

A conceptual framework of barriers and facilitators to uptake of evidence was adopted here (Shepherd et al. 2005, Tones and Tillford, 1994). This framework has been successfully applied in other related systematic reviews (Rees et al. 2001, Harden et al. 2001, Brunton et al. 2003, Thomas et al. 2004).

This review utilized a 'mixed-methods' approach. Data from effectiveness outcome studies were combined with data from studies that described decision maker's views of factors influencing uptake of evidence from systematic reviews, in a negative or positive fashion. The main source of decision makers' perspectives included surveys, focus groups, and interview studies that were conducted independently of intervention evaluations. The purpose of this review was to ascertain whether evaluated interventions

addressed issues important to decision makers and utilized their views on barriers and facilitators as a marker of the appropriateness of different interventions.

It is increasingly difficult to overview the literature not only with regard to content but also with regard to quality (Knottnerus and Tugwell, 2012). A significant challenge is to identify a sufficiently broad range of sources so as to be able to build a comprehensive map of research undertaken on a topic (Wong et al. 2013).

This writer conducted a systematic review of the literature to identify barriers and facilitators, both natural and interventional, to evidence uptake from systematic reviews, meta-analyses, and the data-bases containing them. This writer searched 19 databases and used 3 search engines, for articles, not limited to the English language, and covering the full range of publication years available in each database initially up to December 2010 using a combination of index terms and text words derived from relevant articles. The individual search strategies, associated selection criteria, methods of data collection, data analysis, and quality assessment have been described in the preceding chapters for each of the individual systematic reviews and will not be repeated here (Sturmey et al. 2012).

Data synthesis

Three types of analyses were performed in this final review: a synthesis of non-intervention studies, a synthesis of intervention, outcome evaluations, and lastly a synthesis of intervention and non-interventions studies. For this last synthesis, a matrix was constructed which laid out the barriers and facilitators alongside descriptions of the interventions included in the in-depth systematic review of outcome evaluations. The mode of synthesis was configuration rather than aggregation (Gough and Thomas, 2012).

By configuring or arranging results, it was possible to see where barriers have been modified, or facilitators built upon, by relatively sound interventions. It was also possible to identify promising interventions that need further evaluation (Oliver et al. 2005). It was also reasonable to ascertain where factors had not been addressed or not built upon by any intervention, necessitating the development and rigorous evaluation of new interventions. The overall aim was to aid understanding of a complex phenomenon (Wong et al. 2013).

8.5 Results

Figure 8.1 outlines the number of studies included at various stages of the review. Systematic and exhaustive searches identified 3,329 citations. Retrieval, screening, and classification of full reports resulted in the identification of 27 studies addressing barriers, 15 studies that included natural facilitators and 10 studies evaluating interventions to enhance systematic review uptake (Wallace et al. 2014b). Intervention study characteristics, barrier study characteristics and facilitator studies were tabulated in previous chapters. The synthesis of the three components is outlined in Figure 8.1.

Figure 8.1 An overview of all stages of the mixed knowledge review and the approach taken

Review question

'What is known about the barriers to, and facilitators of, uptake of evidence from systematic reviews?'

Stage 1: Mapping and quality screening exercise

Systematic and exhaustive searches identified 3,329 citations
Retrieval, screening, and classification of full reports resulted in the identification of 27 studies addressing barriers, 15 studies identifying natural facilitators and 10 studies evaluating interventions.

Non-intervention studies	Intervention studies
Studies of decision makers' views Focus on addressing influences on knowledge, attitude, and behaviour	Rigorous evaluation of intervention studies

Stage 2: in-depth review

Synthesis across study types to answer sub-question:
'To what extent do interventions address the barriers identified by decision makers and build upon the facilitators to uptake of evidence from systematic reviews?'

Non-intervention (Views studies)	Intervention studies (outcome evaluations)
Application of inclusion criteria resulted in 27 studies addressing barriers and 15 addressing facilitators Data extracted for description of characteristics and quality Findings extracted Findings synthesised to answer sub-question: 'What are the views on uptake of evidence from systematic reviews?'	Application of inclusion criteria resulted in 10 studies Data extracted for description of characteristics and quality Findings extracted Eight out of 10 studies: of low-to- moderate risk of bias Findings synthesised to answer: 'What are the effect of interventions on uptake of systematic reviews?'

Outcome evaluations

Ten studies, evaluating strategies to improve systematic review uptake were conducted in 11 countries in total. Six studies were regarded as of moderate risk of bias, two at low risk and two studies were assessed as being at high risk.

Details of the interventions can be found in the previous chapter. Statistically significant alterations were made on a limited number of outcome measures using targeted messaging

(Dobbins et al. 2009), short summaries of systematic reviews (Oermann et al. 2007), and educational visits (Wyatt et al. 1998). Other interventions such as interactive workshops produced some benefit (Gulmezoglu et al. 2007), while clinically integrated e-learning courses brought about knowledge (Hadley et al. 2010) and attitude gain from baseline (Kulier et al. 2009). A further computer-based series of teaching sessions also showed an improvement in knowledge and attitudes from baseline (Davis et al. 2007, Davis et al. 2008).

Decision makers' views

The 27 barrier studies encompassed 2 qualitative investigations, and 25 surveys asking a total of 57 questions regarding possible barriers to uptake of evidence from systematic reviews. Included studies reported data from 10,218 decision makers in 91 countries, 64% of whom were physicians. The most commonly investigated barriers were lack of use, lack of awareness, lack of access, lack of familiarity, lack of perceived usefulness, and external barriers such as negative organisational culture.

Regarding facilitators, the 15 identified studies reported 10 surveys, 3 qualitative investigations and 2 mixed studies that addressed potential facilitators. Of 2,495 participants drawn from eight countries in the fifteen studies, at least 1,343 (53.8%) were physicians. The five most commonly reported facilitators to uptake of evidence from systematic reviews were: the perception of systematic reviews as having multiple uses; a content that included benefits, harms and costs; a format with a staged access; training in use; and peer support for use.

Synthesis

Table 8.1, at the end of this chapter, shows the synthesis matrix which juxtaposes barriers and facilitators alongside results of outcome evaluations, with the 3 effective interventions listed first. There were some matches but also significant gaps between what decision makers see as helpful to evidence uptake and, on the other hand, soundly evaluated interventions that address facilitators and barriers to systematic review uptake.

Three interventions from studies of low-to-moderate risk of bias had statistically significant results on at least one outcome measure: targeted messaging, educational visits, and summaries of systematic reviews. Tailored, targeted messaging addressed the specific barriers of limited access to, impaired awareness of, and restricted familiarity with systematic reviews. Targeted messaging also built on the enhancers of systematic review uptake such as a choice of format, with web-based delivery, and an overall increased access. A graded format takes into account the disparate information needs of various disciplines at different positions in an organisation. It addresses the concern that one size does not fit all.

Educational visits overcame and built on a wide range of factors identified and confirmed by qualitative and survey research. Knowledge barriers such as lack of access, lack of awareness and familiarity; attitudinal barriers such as limited motivation, perceived lack of usefulness and relevance; and external barriers such as an adverse organisational climate, were impacted on by this complex intervention. Increased access and training were among the facilitators of uptake of systematic reviews built on by this strategy that also took into account the information needs of the target audience and their level of training.

Brief summaries of systematic reviews, another effective intervention, overcame the knowledge barriers of lack of access, impaired awareness and familiarity; attitudinal barriers of perceived lack of usefulness and relevance; and the external barrier of systematic reviews having a large standard format for all readers, regardless of level of training. This intervention facilitated the uptake of evidence from systematic reviews by providing a one-page, web-based, useful summary that took into account the information needs and time demands of the target audience.

The patient manual, devised by Harris and colleagues (Harris et al. 2006), addressed similar barriers and facilitators as did the brief summaries of systematic reviews (Oermann et al. 2007). While showing a trend in favour of the intervention, the patient manual did not achieve statistically significant results. The multifaceted educational intervention by Gulmezoglu and colleagues addressed a wide range of knowledge, attitude, and external barriers, and also built on facilitators to produce some, non-significant, knowledge and attitudinal gains (Gulmezoglu et al. 2007).

A further three studies, using e-learning to improve uptake of evidence from systematic reviews, each addressed a comparable number of barriers and facilitators. The two computer-based interventions addressed very similar barriers and facilitators in terms of number and content and brought about some non-significant improvement between pre- and post-assessment.

8.6 Discussion

This integrative, mixed-knowledge review has systematically highlighted the barriers and facilitators impacting on uptake of evidence from systematic reviews. Importantly, the

mixed-methods approach illustrated the extent to which these modifiers have been addressed by a number of evaluated interventions.

Unlike other systematic reviews, this mixed-knowledge review adopted a wider perspective through inclusion of studies of decision makers' views as well as effectiveness studies. Qualitative research has the potential to improve attempts to generate evidence of effectiveness (O'Cathain et al. 2013).

Juxtaposing barriers and facilitators alongside effectiveness studies allowed this reviewer to examine the extent to which the needs of decision makers had been adequately addressed by evaluated interventions. To some extent they had. Lack of access, awareness, and familiarity were frequently addressed as barriers. Fewer of the identified facilitators, appear to have been targeted by the identified interventions however.

This synthesis tells us the extent the interventions overcome barriers and build on the facilitators to uptake of knowledge from systematic reviews. Different recommendations can then be made (Pope et al. 2007). This writer recommends 3 interventions: tailored, targeted messaging, systematic review summaries, and educational visits. These address a wide range of factors impacting on review uptake. Other interventions such as e-learning, computer-based learning, multifaceted educational interventions, access to an on-line registry and use of a knowledge broker, are strategies that need to be developed further.

Many of the gaps in the evidence tended to be in relation to building on the facilitators identified by decision makers. Despite a wide search, we found few evaluations of strategies that emphasized the time-saving aspect of systematic reviews, their perceived ease of use, their importance relative to other sources of information and their ability to improve confidence. Furthermore, there was little emphasis on consistent presentation

and use of logos. New interventions need to be developed that take account of these enhancers of uptake.

A surprising finding by Dobbins and colleagues was that, despite the wider range of barriers and facilitators addressed by use of a knowledge broker, this intervention was not as effective as targeted, tailored messaging (Dobbins et al. 2009). The more complex intervention was not more effective. That targeted, tailored messaging overcame and built on a smaller number of barriers and facilitators suggests that it is not the number of factors addressed that is central but their relevance and intensity.

Limitations

This review is constrained by the fact that its conclusions can only be supported by a relatively small evidence base. We found just 10 intervention studies in all, with 8 of these studies having moderate-to-low risk of bias. The interventions may have been successful in ways other than the outcomes that the investigations employed.

Furthermore, we do not know how to pick out from amongst all the barriers identified those that are most important (Baker et al. 2010). There is insufficient evidence on how barriers should be identified and how interventions should be selected to overcome them. There is also little evidence about the cost effectiveness of interventions to change professional practice.

Lastly, we cannot be sure that research in this area has exhausted decision makers' views on uptake of evidence from systematic reviews. New primary research may reveal more

themes. However, though the current evidence base is incomplete, it provides valuable insights into the likely effectiveness of different interventions.

Implications for research

It is important to improve and standardize reporting of trials of interventions to improve professional performance. A broad framework should be developed for designing and selecting appropriate interventions across a wide range of professional activities in which gaps between evidence and practice are found (Oxman et al. 1995). Efforts should move beyond focusing on short-term acquisition of just knowledge and skills (Nabulsi et al. 2007).

Barriers and facilitators can be used as starting point for intervention relevance (Oliver et al. 2005). This review can be used as a resource. The conclusions suggest recommendations for a research agenda based on appropriate and feasible interventions that could be evaluated for their effectiveness. Barriers and facilitators which were not addressed adequately in any of the intervention evaluations led this writer to draw conclusions about opportunities for researching new interventions and their subsequent evaluation.

This mixed-knowledge review showed that several barriers to, and facilitators of, uptake of systematic reviews have received little attention in evaluation research. Systematic reviews are perceived as having a limited range, a narrow focus, are poorly promoted and not updated frequently enough. The medico-legal importance of systematic reviews has not been highlighted and built on sufficiently (Paterson-Brown et al. 1995). Further work

is needed to develop and evaluate interventions which modify or remove identified barriers and build on detected facilitators.

Implications for practice

In general, convenience of access, habit, reliability, quality, speed of use, and applicability makes information seeking likely to be successful and to occur (Dawes and Sampson, 2003). The synthesis presented here suggests that factors encouraging and discouraging usage of systematic reviews are more complex than simple connectivity.

This framework allows reviewers to address some of the criticisms of systematic reviews by taking account of social and structural influences on their uptake (Oliver et al. 2005). It is important to carefully select the interventions most likely to be effective in the light of the diagnosed problem (Oxman et al. 1995). Choosing the right strategy is an essential component of developing evidence-based practice and ultimately improving patient care (Eastwood et al. 2008). More than one intervention may be needed to improve uptake of systematic reviews.

The contextualisation and the format of the presentation of systematic reviews appear to be relevant issues. The reviews are often technical, contain complex statistics, and are written in an academic style. Presentation is as important as results. However, little attention has been paid to the presentation of the review (Tetzlaff et al. 2009).

It is important to consider the target audience, their values and preferences while linking the key message to the level of decision maker. The review should be presented as easily understood with information given in small doses. The identification of take-home messages is advantageous. It is important to refocus efforts on improving and promoting graded access to summaries of evidence. This may be more effective than teaching skills in searching and critical appraisal.

8.7 Conclusion

Evidence-based approaches have added value (Knottnerus and Tugwell, 2012). This review has added value compared with conventional reviews of effectiveness (Oliver et al. 2005). The advantage is in the ability to examine systematically a much wider literature so as to draw conclusions and suggest recommendations for practice. The review has added breadth and depth (Gough and Thomas, 2012). A conventional review of effectiveness in this area would have been able to access 10 outcome evaluation reports in order to draw conclusions about effectiveness and make recommendations. This writer was able to utilise an additional 27 studies encompassing decision makers' views about barriers and a further 15 studies addressing facilitators.

Mixing specific methods has strengthened the reviews and increased their relevance by combining evidence of the effectiveness of interventions with issues of appropriateness together with a qualitative understanding of people's lives. Using multiple data sources can enhance the credibility of findings (Lawrence et al. 2012). This approach uses a larger proportion of research knowledge relevant to the review question (Gough and Thomas,

2012). The evidence synthesized here is important to a broad sweep of institutions concerned with evidence uptake in general and systematic review use in particular.

This mixed-knowledge review raises awareness of the variety and complexity of factors impacting on systematic review uptake (Wallace et al. 2014b). It can be used as a platform to develop strategies to improve review uptake. It can be seen as a basis for rational and fair selection of interventions to enhance evidence uptake (Strech et al. 2013).

A key theme to emerge was the value decision makers place on choice and autonomy in relation to the mode of delivery, degree of access, type of format, and style of presentation, of systematic reviews. Increasing the choice of access, method of delivery, formatting, and degree of detail provided, will enable clinicians and policy makers to better avail of evidence from systematic reviews. Taking account of decision maker's views of barriers and facilitators is clearly important if we are to develop not just effective but also appropriate interventions to enhance the uptake of evidence from systematic reviews. Such an advance is likely to lead to benefits for the individual patient.

Next chapter

The next chapter will build on the series of six systematic reviews conducted as part of this doctoral project. The series is used to develop a proposal and outline a strategy to improve the uptake of evidence from systematic reviews, meta-analyses and the databases associated with them in the field of mental health.

Table 8.1. Synthesis matrix juxtaposing interventions, barriers and facilitators

Interventions	Barriers addressed	Facilitators addressed
Educational visits Wyatt et al. 1998	Lack of use Lack of awareness Lack of access Lack of familiarity Lack of usefulness Lack of motivation External barriers	Usefulness Training Peer-group support Delivery: CD ROM Perceived ease of use Position in an organisation Organisational value Motivation, Increased access
Brief summaries Oermann et al 2007	Lack of awareness Lack of access Lack of familiarity Lack of usefulness External barriers Lack of relevance Ignore target audience	Usefulness Highlighted content A graded format Delivery: Web-based Position in an organisation Increased access
Tailored, targeted messaging Dobbins et al. 2009	Lack of access Lack of awareness Lack of familiarity	A graded format Delivery: Web-based Consistent presentation Increased access
Multi-faceted educational intervention Gulmezoglu et al. 2006	Lack of use Lack of awareness Lack of access Lack of familiarity Lack of usefulness Lack of motivation External barriers Lack of relevance Lack of implementation strategies Ignore target audience	Training Peer-group support Delivery: Web-based Organisational value Motivation Increased access Familiarity with computers
Manual of Cochrane Reviews Harris et al. 2006 .	Lack of use Lack of awareness Lack of access Lack of familiarity Lack of usefulness External barriers Lack of relevance Ignore target audience Lack of implementation strategies	Usefulness Highlighted content Format: summaries Delivery: paper-based Ability to improve confidence Position in an organisation Motivation Increased access
E- learning course Kulier et al. 2009 Kulier et al. 2008 Hadley et al. 2010	Lack of use Lack of awareness Lack of access Lack of familiarity Lack of usefulness External barriers Lack of relevance Lack of implications Ignore target audience Lack of implementation strategies	Usefulness Training Peer-group support Delivery: Web-based Position in an organisation Motivation Increased access Increased confidence Organisational values

Computer-based (CD-ROM) session Davis et al. 2007 Davis et al. 2008	Lack of use Lack of awareness Lack of access Lack of familiarity Lack of usefulness External barriers Lack of implications for practice Lack of implementation strategies Ignore target audience	Usefulness Training Peer-group support Delivery: CD ROM Position in an organisation Organisational value Increased access Familiarity (computers)
Access to online registry Dobbins et al. 2009	Lack of awareness Lack of access	Delivery: Web-based Increased access
Knowledge brokers Dobbins et al. 2009	Lack of awareness Lack of access Lack of familiarity Lack of usefulness Lack of use Lack of relevance Lack of implications for practice Lack of implementation strategies Ignore target audience Lack of workshop attendance Lack of positive climate	Usefulness Graded format Training Peer-group support Delivery: Web-based Consistent presentation Position in an organisation Organisational value Increased access

CHAPTER 9

ENHANCING UPTAKE OF SYSTEMATIC REVIEWS: A PROPOSAL

CONTENT

9.1 Introduction **348**

9.2 Barriers **349**

9.3 Facilitators **350**

9.4 Interventions **351**

9.5 The Setting **351**

9.6 The Community Mental Health Team **352**

9.7 The Intervention **352**

9.8 Recommendations **354**

9.9 Barriers, Facilitators, Interventions **356**

9.10 Mixed-knowledge synthesis **357**

9.11 Proposal **359**

9.12 Summary **372**

9.1 Introduction

The utilisation of evidence in general and the uptake of systematic review evidence in particular, is a pressing issue. In this penultimate section, these six reviews, dealing with knowledge generation and translation, inform the development of a proposal for enhancing uptake of evidence from systematic reviews and meta-analyses, in the field of mental health.

The data so far gathered is useful for shaping future interventions aimed at improving uptake of evidence from systematic reviews. The barrier analysis conducted as part of this thesis can assist with the planning and implementation of clinical practice improvement (Martis et al. 2008). Efforts to improve practice can be focused on interventions tailored to address specific barriers and facilitators. This process is seen by some as the recommended approach (Simson and Doig, 2007).

To this writer's knowledge, there were no previous systematic reviews that had searched such a wide range of databases or dealt with such a variety of decision makers that identified and synthesized barriers, natural facilitators, and interventions impacting on uptake of evidence from pre-appraised, integrative reviews. This project made an incremental contribution by conducting a series of systematic reviews that identified a range of factors impinging on utilization of evidence from reviews, meta-analyses and the databases containing them, and then synthesizing the results.

Having addressed an important knowledge gap regarding a relevant problem, the information gained has been used to develop a proposal aimed at enhancing uptake of systematic review evidence in the field of mental health, which is presented in this

chapter. Improved uptake of evidence may increase the therapeutic potency of psychiatrists, psychologists and members of the mental health team (Kingdom, 2013).

9.2 Barriers

In the proposal developed here, the objectives were first chosen. Then the barriers to the change required were identified as there needs to be an understanding of the contextual factors that modify ability to bring about a change, such as increased uptake of evidence. Next, specific knowledge translation interventions were chosen and linked to the selected barriers. This process is similar to a clinical treatment that is tailored to a diagnosed health problem.

The reasons for the failure of adequate systematic review uptake are numerous. Many of these obstacles were identified in the earlier chapters of this thesis. The reasons for impaired uptake require an understanding of a large number of forces and variables. Results of the previous reviews suggest that primary dissemination strategies need to be buttressed by secondary, effective implementation methods and that these need to be both practice- and community-based.

In the review of barriers to uptake of evidence from systematic reviews, 27 unique published studies described at least 1 barrier to the uptake of evidence from pre-appraised, integrated reviews. Perceived barriers to the use of systematic reviews varied and included lack of actual use in a work setting, limited access to reviews depending on the decision maker's role in the organisation, impaired awareness and a lack of appreciation of the varied uses of reviews, together with an organisational culture that

undervalues systematic reviews. Effective interventions would need to take account of these disparate obstacles (Wallace et al. 2014b).

9.3 Facilitators

In order of frequency, the five most identified enhancers of uptake of systematic reviews in the 15 unique studies detected as part of this project included their perceived usefulness (Wallace et al. 2012b). In addition to their role in healthcare, systematic reviews can be used for education, for revision of childcare protocols, to improve personal knowledge, to guide research, and also for medico-legal protection.

Graded access was also seen as important. The perception that systematic reviews were time saving in terms of drawing on the best evidence was another much quoted advantage. Training in use was also seen as central. Aspects of the content of systematic reviews viewed as potentially increasing their use included highlighting benefits and costs of a treatment in a transparent manner. Other enhancers included the perception that systematic reviews are time-saving, easy-to-use, are important relative to other sources of information, and have a preferred mode of delivery, either CD ROM or online.

Interventions to improve the uptake of systematic reviews and meta-analyses can build on a wide range of enhancers of systematic review use, as identified in this project (Wallace et al. 2012b).

9.4 Interventions

Ten outcome studies from 11 countries were found containing 12 interventions aimed at promoting uptake of evidence from systematic reviews. Most interventions were effective under some circumstances; none were effective under all circumstances.

Strategies such as targeted, tailored messaging, educational visits, and summaries had a significant impact. Promising interventions include e-learning, computer (CD-ROM) based learning, inactive workshops, the use of knowledge brokers, together with an e-registry of systematic reviews.

9.5 The setting

Key elements to progress in advancing EBM include the integration of EBM with clinical specialties, tutor training and the availability of high-quality teaching resources (Meats et al. 2009). Organisational characteristics are an important influence on the success of strategies to promote the transfer and uptake of research evidence. Peer groups and professional organisations can impact positively on enhancing the uptake of reviews. The biggest facilitator of the impact of systematic reviews on public health decisions was the perceived value the organisation places on using research evidence (Dobbins et al. 2001a). Therefore, it is advantageous to promote the value of reviews at an organisational level. And evidence-based medicine, where possible, should be clinically integrated (Kulier et al. 2012).

Much work has already been done to make evidence-based mental healthcare more accessible and acceptable in an Irish healthcare context (McGorry, 2013). The

organisation targeted in the proposed intervention outlined here in order to enhance the uptake of evidence from systematic reviews, is the Irish Health Service Executive (HSE). The Health Service Executive was established in 2005 and is responsible for providing health and personal social services to everyone living in Ireland. The part of the HSE specifically targeted in this proposal is the mental health service.

9.6 Community Mental Health Teams

Community mental health teams (CMHTs) are composed of doctors, social workers, nursing staff, clinical psychologists, addiction counsellors and occupational therapists. Intuition, experience, political values, fashion and ideology, rather than evidence, can impact on the thinking of team members in the field of mental health (Geddes et al. 1997). This is compounded by a differential access to information resources between the different professions (Wilson et al. 2003). A way to improve performance in the mental healthcare field may be to provide all members of mental health teams with the best available evidence regardless of professional boundaries.

Tailoring research to stakeholders is central (Knotterus and Tugwell, 2013). In this proposal, the group targeted for the improvement of systematic review uptake is the community mental health team (CMHTs), the core unit for the delivery of care in the mental health service.

9.7 The Intervention

Selecting the right strategy to ensure the uptake of best available evidence is an important component of developing evidence-based practice and ultimately improving patient care.

Effective communication is an interaction between two or more people that produces a desired effect (Fawole et al. 2012). But effective communication of knowledge from systematic reviews in an accurate, efficient, and understandable manner remains a challenge. Some systematic reviews are complex, requiring an understanding of research methods, statistics and critical appraisal that many users do not have.

The choice of knowledge translation intervention should be guided by the evidence on the effectiveness of the strategy, the recognition of the external barriers, and an understanding of the identified facilitators to change (Baker et al. 2010). It is important to consider the target audience, their values and preferences. All these factors should underpin the choice of intervention.

Factors that influence the use of any web-based knowledge exchange intervention are very important (Curran et al. 2013). Knowledge of the identified barriers to systematic review uptake informed the generation of the strategy developed here. Ideally an intervention should overcome the knowledge barriers of impaired access to, awareness of, and familiarity with systematic reviews. Attitudinal obstacles, such as a negative perception of the utility of reviews, also need to be overcome. External barriers such as a negative organisational climate discouraging initial use of evidence synthesis together with a lack of training and resources for review uptake should also ideally be addressed.

The results of the mixed-knowledge review of outcome studies informed the general recommendations and the choice of intervention to be developed in the strategy proposed here.

9.8 Recommendations

Quality is fundamental in systematic reviews (Burton, 2013). To improve their usefulness, the first step is to improve the reporting of systematic reviews (Glasziou et al. 2010). Access, awareness and familiarity also need to be improved. Accessible databases are an essential resource for all disciplines in a clinical setting. Access impacts on awareness and familiarity. Casual awareness does not guarantee familiarity with systematic reviews or the ability to use them.

Trust and confidence in using this form of pre-appraised integrative evidence needs to be enhanced. Encouraging practical usage of systematic reviews should lead to improved knowledge of and attitudes to, this form of pre-appraised evidence. Once a review is used once then the behaviour can be generalized to other times and situations.

The results obtained by this writer from the barrier and facilitator reviews, also illustrate the importance of emphasising the time-saving function of systematic reviews over searching for, and critically appraising, individual studies (Wallace et al. 2012a). A further enhancer of uptake would involve increased access, incorporating a graded format with an executive summary, and a consistent, reliable presentation (Wallace et al. 2012b).

A key component of a knowledge translation process is to know decision makers' needs and preferences for receiving research evidence from systematic reviews (Dobbins et al. 2007). The context and setting is important. Evidence from barrier and facilitator research indicates that audience-specific messages are needed from systematic reviews for the many different types of decision maker. Tailoring is becoming more central (Knotterus and Tugwell, 2013).

Evidence users want choice and control over the content, format and delivery of research evidence. Staged access to more detailed information may be required, in addition to a summary (Dobbins et al. 2004**)**. Simple access is not in itself sufficient (Dobbins et al. 2009b). Relevant, high quality, synthesized evidence must be actively delivered directly to decision makers. Access to the evidence, even if available in one place, can be problematic. What is required most is facilitated access to summarized, relevant research personalized to a decision maker's requirements. The process of translation can be assisted by the tailoring and targeting of research findings to the decision maker's needs. It is important to disseminate the information to the appropriate target audience linking the key message to the level of decision maker (Dobbins et al. 2001).

The format of systematic reviews is important for uptake enhancement. A great deal of effort should go into writing the executive summary, which should be brief, easy-to-read and easy-to-understand. It should contain the key messages including the implications for practice (Dobbins et al. 2001). Staged access with a one-page, take-home message, a three-page summary, and the opportunity to view a 25-page version, should increase uptake (Dobbins et al. 2009b). Short and multiple formats, together with a take-home message, address the concern that different audiences have different needs. One size does not fit all. Furthermore, most readers tend to focus on the discussion and conclusion, and few focus on tables or methods.

The characteristics of the innovation account for most of the observed variation in innovation adoption. This occurs even when other characteristics, such as organizational and environmental variables, were included in a regression model (Meyer and Goes, 1988). Presentation is as important as results and reviews need to be presented in ways that are perceived as being easy to use. All materials sent out as part of a transfer strategy

should be distributed regularly and have a consistent look (Dobbins et al. 2004). They should be presented in an accessible and appealing fashion (Bero and Jadad, 1997). Decision makers' needs and concerns should be considered in the design phase of the strategy (Dobbins et al. 2004).

Simple interventions can be as effective as complex ones because they don't dilute the key message (Grimshaw and Eccles, 2004). Targeted messaging employs personalization and content matching, with individualized information matched to the decision maker's needs.

9.9 Barriers, facilitators and interventions

When summarizing knowledge, utilising evidence from a number of systematic reviews is becoming increasingly frequent (Knottnerus and Tugwell, 2012). In the final systematic review presented in this thesis, this writer found that some of the barriers and facilitators identified by systematic review methodology had been addressed by a number of evaluated interventions. But significant gaps were also identified.

Fewer of the identified facilitators however appear to have been built on by interventions. There were limited evaluations of strategies that utilized the time-saving aspect of systematic reviews, their perceived ease of use, their importance relative to other sources of information, their ability to improve confidence, together with the facilitating effect of logos and consistent presentation. Strategies need to be developed that address a number of identified but neglected barriers and facilitators.

Complex factors affect the acquisition, generation, and application of evidence by mental health clinicians. The information gleaned in the systematic reviews just outlined provided the basis for the development of a protocol aimed at improving the uptake of systematic reviews in a mental health setting.

9.10 Mixed-knowledge synthesis

The final systematic review of the series linked interventions with the identified barriers and facilitators. Tailored, targeted messaging addressed the specific barriers of limited access to, limited awareness of, and restricted familiarity with, systematic reviews and meta-analyses. It also surmounts a training deficit and increases the likelihood of actual use of systematic reviews in practice. This strategy also overcomes negative attitudinal barriers such as the perception of limited usefulness of systematic reviews.

Targeted messaging also builds on a number of identified facilitators or enhancers of systematic review uptake. These included an availability in a graded format, with content highlighted, web-based delivery, overall increased access, improved familiarity, and increased confidence in using research. Targeted messaging can also utilise the positive effect of logos and consistent presentation. Messaging can be time saving, increase the perception of ease of use of systematic reviews, and potentially increase the value an organisation places on this valuable form of evidence. Tailored messaging also takes into account the information needs of the target audience and their level of training and position in an organisation.

A single informal educational visit can overcome and build on a wide range of the factors identified by qualitative and survey research. Knowledge barriers such as lack of access and awareness; attitudinal barriers such as limited motivation, perceived lack of usefulness and relevance; and external barriers such as a lack of training or lack of workshop attendance, an adverse organisational climate, can all be impacted upon by these visits. The usefulness of systematic reviews can be highlighted and peer-group support enhanced. Increased access and training were among the facilitators of uptake of systematic reviews built on by educational visits which also take into account the information needs of the target audience and their position in the organisation.

Brief summaries of systematic reviews overcame the knowledge barriers of lack of access, awareness, and familiarity; attitudinal barriers of perceived lack of usefulness and relevance; and the external barrier of systematic reviews having a long, standard format for all readers. One-page summaries can highlight content, are time saving and easy to use, can be e-mailed, improve access and take account of a decision maker's position in an organisation. The summaries addressed the information needs and time demands of the target audience.

These three interventions are recommended for use in increasing the uptake of systematic reviews. They overcame a range of barriers and built on a variety of facilitators. The studies identifying the interventions were of low or moderate risk of bias and the interventions showed a clinically significant impact on at least one outcome measure.

New technologies are facilitating innovation (McGorry, 2013). Building on the evidence just outlined and derived from the systematic reviews conducted as part of this thesis, a

proposal was developed aimed at enhancing the uptake of evidence from systematic reviews and meta-analyses using e-mail-based, tailored messaging.

9.11 Proposal

Title

A randomized trial to evaluate the impact of targeted, tailored messaging of systematic review evidence in a mental-health setting

Objectives

The objectives are to conduct a randomized trial to assess the effectiveness of a knowledge translation strategy consisting of targeted, tailored messaging as a method of promoting the uptake of evidence from systematic reviews and meta-analyses, by the multi-disciplinary team (CMHTs) in a mental health setting.

Background

Like other specialists, mental health professionals have found it difficult to change their practice in accordance with mounting evidence. However, psychiatrists are willing to change in line with evidence and wish to improve their data search and analysis skills (Carey and Hall, 1999). Integrating research and clinical practice in mental health is vital (Geddes, 2010). Psychiatry is not substantially more or less evidence-based than other medical specialities (Sackett et al. 1997). Some 95% of psychiatrists felt that adoption of more effective care based on evidence was a desirable goal (Carey and Hall, 1999). The main perceived barrier to evidence-based psychiatry is a lack of resources and deficient

technical support (Lawrie et al. 2000). Other barriers include a lack of knowledge, lack of access with support, and negative attitudes towards evidence (Yang et al. 2013).

Much time and effort are being invested in preparing and maintaining systematic reviews. However, we do not know if these reviews can be used directly by community mental health teams (CMHTs) to inform and improve local practice and patient outcome (Wyatt et al. 1998). Here, a method is proposed to enhance uptake of evidence from systematic reviews and meta-analyses in order to better inform the clinical practice of CMHTs.

E-learning is becoming increasingly popular as a tool to aid learning in medical education (Kulier et al. 2008). It allows flexibility, enabling busy clinicians, including mental health professionals, to choose the time and place for learning within their clinical duties. Learning can be timed at an individual's own pace and revisited when necessary. It also allows standardization of the message over large geographical areas (Kulier et al. 2008). Tailored, targeted messaging is one form of communication, via the Internet, where information is tailored to a need and can be targeted at a stage of behaviour change (Yap et al. 2009).

A short message service has been shown to be effective in escalating adherence to diabetes control recommendations (Zolfaghari et al. 2012). Summaries can be an effective tool for increasing clinical guideline use in depression (Yang et al. 2013). On-line messaging has the potential to impact on proximal outcomes such as awareness and recall, as well as directly affecting behaviour (Latimer et al. 2010). In creating a greater appreciation of evidence-based medicine, it is best to target individuals who are well placed to determine local barriers to change and adjust team policy (Oxman et al. 1995).

Messaging is about moving the message through people to whom the final audience is likely to relate (Latimer et al. 2010). To ensure that evidence from systematic reviews informs the clinical practice of CMHTs, those who lead the teams should appreciate evidence-based medicine and incorporate research evidence into team deliberations. It is best to target two team members at the same time (Hodnett et al. 1996). In taking up pre-appraised, integrative evidence, team leaders can then reflect on local barriers to implementation and be sensitive to local circumstances.

It is widely accepted in health education that instructional material will be more effective when audience characteristics are taken into account at the outset of program development (Stellefson et al. 2008). Systematic reviews aimed at the identification of barriers, facilitators, and interventions impacting on uptake of evidence from reviews and meta-analyses by a wide variety of decision makers, have already been carried out by this author (Wallace et al. 2012a, Wallace et al.2012b, Wallace et al. 2014b). Having identified the factors impacting on systematic review uptake by a broad range of decision makers, an intervention was developed in order to enhance uptake of systematic review evidence in the field of mental health.

Barriers and facilitators

Tailoring increases message salience and the impact of the message on behaviour (Latimer et al. 2010). Tailored, targeted messaging addresses the specific, identified barriers of limited access to, limited awareness of, and impaired familiarity with, systematic reviews and meta-analyses. Targeted messaging can also build on a number of previously identified enhancers of uptake, such as use of a graded format, with web-based delivery and an overall increased access. The tailored element takes into account the

disparate information needs of various disciplines at different positions in an organisation. The message itself is targeted, addressing the concern that one size does not fit all.

Summarised evidence from systematic reviews has proved effective in enhancing uptake of evidence (Oermann et al. 2007). Summaries do not require a background in research and statistics to be understood (Harris et al. 2006). Good writing also helps to convey a message to an audience (Knottnerus and Tugwell, 2013). The Global Health Council's *Evidence for Action* series provides one-page synopses of reviews for its world-wide membership (Volmink et al. 2004). *Evidence update* also provides short summaries. Tailored, targeted messaging can incorporate the advantages of summaries (Latimer et al. 2010).

The intervention proposed is based on a stages-of-change model that involves pre-contemplation, contemplation, preparation, action and maintenance stages (Prochaska, Redding and Evers, 2002). The trans-theoretical model offers a framework that assumes that an individual progresses over time through a series of stages.

We need to know if CMHTs will benefit from tailored, targeted messaging, with the advantages of e-mail delivery of summarized evidence, incorporating an educational component. The strategy draws on elements of the three interventions already shown to have had a significant beneficial effect in the studies already conducted by this writer.

Targeted messaging

Tailored, targeted messaging takes account of individual information processing needs (Stellefson et al. 2008). Messaging is the process of physically getting the message to a

group, through a medium such as the Internet that the target audience is most likely to use (Latimer et al. 2010). Tailored and targeted messages have gained visibility as a popular knowledge translation strategy. They are a customized approach to health communication (Stellefson et al. 2008).

'Tailored' means that the message is focused on the specific scope of decision-making authority of the intended user. Tailored messages are individualized for their receivers, with the expectation that this individualization will lead to larger intended effects of these communications (Hawkins et al. 2008). Tailored messages suit the individual characteristics of the message recipients (Latimer et al. 2010). The individual should be able to say of the message, 'This applies to me' (Yap and Davis, 2009).

The 'targeted' element indicates that the content of the message is relevant and directly applicable to the decision currently faced by the intended audience (Dobbins et al. 2009). The targeted message often aims to change self-efficacy and systematic review evidence shows that these messages can affect an individual's beliefs (Latimer et al. 2010).

Tailored messaging is designed to catch the person's attention and have a positive impact on their response to it (Stellefson et al. 2008). Electronic targeted messages to sub-groups with common interests are effective in promoting evidence-informed decision-making (Kumpers et al. 2006).

Audience-specific messages from systematic reviews are needed for different decision makers (Dobbins et al. 2007). Tailored, targeted messages connect relevant research evidence to specific decision makers (Dobbins et al. 2009). The messaging can give just the right amount of information, and can have direct relevance to behaviour, making it

easier to incorporate evidence into clinical practice. Tailored messaging employs the advantages of personalisation and content matching that facilitates research use (Hawkins et al. 2008).

The aim is to test the hypothesis that tailored, targeted messaging to the consultant psychiatrist and team co-ordinator in CMHTs, outlining the principles of evidence-based medicine, systematic review methodology, and evidence from two systematic reviews, would enhance uptake of this evidence over a 5 week period.

Methods

Participants

Catchment areas will be allocated to receive tailored, targeted messaging, or allocated to a control group. All catchment areas within the Irish Health Service Executive will be included. A number of catchment areas associated with teaching hospitals will be excluded as the professional roles and relationships in these may differ from the non-teaching teams (Wyatt et al. 1998).

The messaging will be targeted at the team leader and the team co-ordinator, equated with opinion leaders identified by Lomas and colleagues (Lomas et al. 1991). These participants are in a stronger position to identify and remove barriers to evidence-based practice in their own unit than outsiders (Wyatt et al. 1998). Eligible participants will be all members of community mental health teams (CMHTs). These participants are responsible for input into the decision making process of referring patients for CBT or

prescribing antidepressants. CMHTs will be identified through the Health Service Executive and other databases.

Participants will be recruited in a two-stage process. First, consent will be sought from the executive clinical director of each mental health catchment area, each one currently composed of approximately four CMHTs. Once written consent is obtained, the name of the consultant psychiatrist most directly responsible for making decisions relating to offering CBT and antidepressants will be identified and contacted. A letter will be sent directly to the potential precipitant with a prepaid envelope for return of the completed form. A remainder will be sent if no response is received after three weeks. Consultants who indicate an interest in the study will be contacted by telephone to confirm consent to participate in the study and answer any questions (Harris et al. 2006). Initially, participants will fill in a pre-course assessment of knowledge, attitudes and behaviour. Participation will be voluntary and participants can leave the study at any point.

Intervention

The tailored, targeted messaging will include sending participants a series of 4 e-mails that will include an introduction to evidence-based health-care (Wallace, 2011), an introduction to systematic reviews (Wallace, 2012b), a summary of the advantages of systematic reviews derived from evidence obtained in this project (Wallace et al, 2012b), then the systematic review focusing on treatment of depression by antidepressants and CBT already conducted here (Wallace et al. 2014a). This will be followed by a link to the full reference, the abstract, a three-page summary, and the full article. Information on access to The Cochrane Library will also be included. The e-mailed messages will be sent

consecutively. Over 4 successive weeks, on the same day each week and at the same time, the intervention group will be sent an e-mail.

The short summaries will include information on the interventions (CBT and antidepressants) examined in the systematic review, the outcomes measured, patients and types of settings included in the studies, references for the individual studies, and results.

At the URL linked within the e-mail message, participants will receive access to the PDF version of the systematic review and the abstract of the review, as well as a short written summary. Participants will receive electronic communication reminding them that access to The Cochrane Library is available free.

The text of the intervention message will be worded to say, 'this message is number X in a series of 4 e-mails you will receive on EBM, systematic reviews, and a systematic review of CBT and antidepressants in depression. This is part of a knowledge translation strategy you are being exposed to in this randomized controlled trial'.

The articles on EBM and systematic reviews were already published in a journal of continuing education in psychiatry: Advances in Psychiatric Treatment (Wallace, 2011, Wallace, 2012b). The aim of these articles was clarity and simplicity. The outlined advantages of systematic reviews were based on results of the systematic review of facilitators conducted here (Wallace et al, 2012b).

The intervention incorporates elements of tailored, targeted messaging successfully used by Dobbins and her team (Dobbins et al. 2007). The intervention will also incorporate a

'summary' element (Oermann et al. 2007). Access to a systematic review and The Cochrane Library is adopted from Wyatt's successful study (Wyatt et al. 1998).

The mode of delivery used here retains some of the advantages of e-learning employed by Kulier and colleagues and also computer-based learning (Kulier et al. 2008, Hadley et al. 2010). The strategy draws on the elements of the successful interventions identified in the systematic review of interventions to improve uptake conducted by this author (Wallace et al. 2014b). The e-mails will be in presented in an interesting way but not so as to detract from the educational component. Information and a presentation style that recipients want and expect will be adopted (Yap et al. 2010). One week after the last tailored message is sent, the participants in the intervention and comparison group will be e-mailed the post-test questionnaire.

Control

The control intervention will be that participants are advised of free access, at the point of use, to The Cochrane Library in Ireland. All participants will receive electronic communication about the availability of this site. Both the control and intervention group will receive the same number of e-mails.

Trial design

The intention is to enhance the application of systematic review evidence by the whole team. So as to minimise contamination, the unit of randomisation will be the catchment area. The catchment areas will be allocated to the intervention or control group by computer-generated random numbers. Contamination between intervention teams and

control teams will be unlikely as randomisation will be by catchment area, rather than by patient or professional (Harris et al. 2007). Baseline differences are not expected between groups. The control and intervention catchment areas will have both high and low socio-economic disadvantage.

Participants will be blinded to their allocation to intervention or control status because all study documentation and explanation will state that different forms of information are being tested, and that each participant would receive one of them. But, of course, they will be aware of the material that is given to them.

Outcome measures

Participants will be asked whether they read the e-mails, how much, whether they raised questions about the e-mails with the team, and if management had changed as a result.

A variety of possible outcomes can be observed following an intervention. These occur in the area of knowledge and attitudes, decision making, and implementation (Rogers, 1995). Outcome measures include knowledge, attitudes, clinical performance and healthcare measures. The hypothesis is that catchment areas exposed to tailored, targeted, messages would report greater systematic review-informed decision making than those simply informed about access to a database of systematic reviews.

Data collection and analysis

Data collection

It is intended to collect the same baseline and follow-up data in all CMHTs. The data will be collected using a telephone-administered survey at baseline and immediately post-intervention. Items in the questionnaire were chosen from questionnaires previously tested and used in diffusion of innovation and research utilization studies (Ciliska et al. 1999). The questionnaire was previously tested for reliability and validity (Dobbins et al. 2009).

The questionnaire will be administered twice to participants, 6 weeks apart. Data will be collected on organisational, environmental, and individual characteristics related to evidence-informed decision making (Dobbins et al. 2001). Individual characteristics will include age, education, position, perceived influence over decision-making process, and the perception of the barriers to using research evidence. Key characteristics will be described, including the study participants, location, setting, intervention, comparisons and outcome measures.

Dependent variables

One researcher will collect the baseline data from the catchment areas and another will collect the follow-up data 6 weeks later. The researchers will be blind to allocation. Researchers will reassure participants that no data would be attributable to individual staff members or catchment areas.

A number of dependent variables will be used including knowledge, attitude, adoption and practice. Participants will be asked to report the extent to which evidence from systematic reviews was considered in a recent decision to manage depression. This is the most common way to measure evidence use in the field (Dobbins et al. 2009). Participants will be asked to quantify their response ranging from one (not at all) to seven (completely). The aim of targeted messaging is to change clinical practice as well as attitudes.

This writer will examine the effect of targeted, tailored messaging on participant's knowledge and attitudes measured with validated assessment tools by comparing outcomes between the randomly allocated groups. The completeness of data will be summarised briefly for each of the main outcomes and any excessive or differential drop-out will be reported. All outcomes, time points, and analyses will be collected.

The aim will be to determine if tailored, targeted messaging of systematic reviews will be effective in increasing CMHTs awareness and understanding of systematic reviews and to examine the usefulness of the disseminated information to CMHTs.

Data will be collected using the Research Dissemination Questionnaire (RDQ). The RDQ was developed by Oermann and colleagues (Oermann et al. 2007). This has 17 items examining awareness, understanding, and perception of usefulness of the disseminated information. Five items on the questionnaire will ask participants to rate their awareness of research evidence before and after receiving the messages, to indicate if prior to the study they had thought about the treatments, and to report how likely it was that they would think about the research evidence in the future.

Understanding will be evaluated by subjects' self-report with seven cognitive items measuring comprehension of the research evidence. Perception of usefulness of the disseminated information will be evaluated by three items on the RDQ rating likelihood of use in clinical practice, if the information was useful, and if the participants discussed the information with other clinicians.

The RDQ will be adopted for the comparison groups by omitting the items and wording that referred specifically to the e-mails and the questions that inquired about thoughts and knowledge prior to receiving the intervention. A third party will review the questionnaire for clarity and to ensure that it reflects the content disseminated in the targeted, tailored messaging. Demographic data will also be collected by the RDQ.

Data analysis

Data will be analysed using descriptive statistics, chi-squared tests of association, and independent and paired t-tests (Fisher's exact test for comparisons of groups with small sample sizes) (Oermann et al. 2007).

Because catchment areas are to be randomised in order to avoid 'unit of analysis' errors, change by catchment area will be analysed. No catchment area will be excluded after randomisation. An intention-to-treat analysis will be conducted.

Ethics

Permission from senior staff will be sought and from an ethics committee as necessary. Ethical advice indicates that since the project only provides information to clinicians there is no need to seek patient consent.

Potential conflict of interest

None

9.12 Summary

Recommendations are made here for increasing the uptake of systematic reviews and meta-analyses. A proposal is outlined for a trial assessing an intervention to enhance the uptake of pre-appraised, integrative evidence synthesized by this writer, aimed at multidisciplinary teams, by a process of targeted, tailored messaging of summarized evidence in an e-learning format, drawing on knowledge of barriers, facilitators, and interventions already identified in this DPhil project.

The next, concluding chapter will highlight the problems addressed, knowledge gaps identified, and the contributions made by the research outlined in this project. Issues of originality will also be discussed.

CHAPTER 10

CONCLUSION

CONTENTS

10.1 Introduction **375**

10.2 Knowledge generation: problem, knowledge gap, originality, contribution **375**

10.3 Knowledge translation: problem, knowledge gap, originality, contribution **377**

10.4 Summary **384**

10.1 Introduction

This final chapter describes how the academic debate is advanced by the six reviews outlined as part of this thesis. The original contribution of each systematic review to bridging a specified knowledge gap concerning a relevant problem is described.

10.2 Knowledge generation

Trials should begin and end with a systematic review (Gartleher and Flamm, 2013). The importance of the systematic reviews addressing antidepressants and CBT, presented here, lies in the attempts made to reduce heterogeneity. A major problem has been that until the 1970s, studies dealt with heterogeneous populations of patients by relatively unspecified methods (Murphy et al. 1984). Furthermore, common or reliable outcome measures were often not used. The first two systematic reviews, conducted as part of this doctoral project, decreased patient heterogeneity, used specified treatment methods together with well-accepted, reliable outcome measures.

In an effort to obtain a more clinically homogeneous sample, several selection criteria were applied. Excessive variation was decreased by only including CBT specifically as a treatment for depression, rather than psychotherapy in general. Heterogeneity was also addressed by concentrating on ‘antidepressants’ in particular rather than medication in general. Lastly, excessive variation was decreased by including only patients suffering from primary, unipolar depression uncomplicated, as much as possible, by other medical or psychiatric conditions.

The actions taken to reduce heterogeneity separate the two reviews from others in the field. To this writer's knowledge, this makes these two meta-analyses innovative and of value.

The first systematic review compared CBT versus antidepressants and encompassed 8 studies. Effect sizes favoured CBT over antidepressants with a significant advantage for CBT on some outcome measures, but not all.

Five studies met the inclusion criteria for the systematic review comparing combination treatment versus monotherapy. Combined treatment appeared more effective than antidepressants but not more effective than CBT.

Clinical depression constitutes a major health condition (WHO, 2012). These systematic reviews contributed incrementally to our knowledge of the relative effectiveness of CBT and antidepressant medication within a comparatively homogenous group of patients. The results are consistent with the view that antidepressants should not be considered to be superior to CBT for the acute treatment of depressed patients. The second systematic review tentatively suggests that combination therapy cannot be unreservedly regarded as more effective than CBT alone, on the basis of the limited evidence available here. The two systematic reviews, with their acknowledged limitations, can be seen as a positive statement for CBT.

This thesis contains empirical work that had not been conducted previously in this specific way. An extensive search strategy was used in these two systematic reviews together with rigorously applied inclusion and exclusion criteria. Studies were

synthesised that had not been assembled in this way before. The systematic reviews addressed an important topic and made a modest and incremental contribution to filling a relevant knowledge gap.

From knowledge gap to contribution

Following the completion of these two initial systematic reviews, the central issue of knowledge translation was then addressed in the form of a series of four innovative reviews. Problems associated with knowledge transfer from reviews could be dealt with more competently following the completion of the first two systematic reviews with meta-analyses which highlighted the process and difficulties that the undertaking entailed.

10.3 Knowledge translation

The Problem

With the huge worldwide investment in biomedical research there are many important advances in healthcare knowledge annually. Unfortunately, it can take considerable time for even the most important of these advances to be integrated into clinical practice. Patients receive about half the recommended evidence-based primary care for which they are eligible (Majumdar, 2010). Currently, because of the gap between evidence and practice, safety is compromised and public trust is also undermined (Cochrane et al. 2007).

Providing evidence-based information to clinicians and the public is an important topic (Knottnerus and Tugwell, 2013). The need to understand how to translate research into practice is central (Grimshaw et al. 2004). It is imperative to know how diffusion and dissemination of innovation occurs (Greenhalgh et al. 2004). Many potentially remediable factors are responsible for the gap that exists between research evidence and clinical practice (Wallace, 2013).

Despite the availability of vast quantities of evidence from basic biomedical and clinical studies, a gap often exists between the optimal approach suggested by the evidence and day-to-day clinical practice. It is important to link knowledge generation and synthesis to knowledge translation and practice (Tugwell et al. 2011). Of necessity, clinicians have become accustomed to relying on non-evidence-based tools to make decisions. Out of habit, they depend on these even when evidence becomes available in the form of systematic reviews. For instance, evidence from systematic reviews was not frequently used by the World Health Organisation policy makers despite knowledge synthesis being central to knowledge translation (Tugwell et al. 2011).

Lost in translation

The purpose of systematic reviews is to facilitate healthcare decision-making by patients, the general public, practitioners, administrators, and policy makers. Summary data can have a large impact on clinical practice and policy making (Shea, 2012). Systematic reviews seek to empower clinicians by providing review evidence most relevant to a specific clinical question (Wallace, 2012b). Automating even the smallest steps in the process will shorten further the time before reviews are published (Tsafnat et al. 2013).

Editors and publishers are concerned to ensure that what they publish is valid (Bauchner, 2013). Tricco reports that skilful summarization and contextualization of individual studies can help bridge the gap between research and decision making (Tricco, 2011). But knowledge distillation on its own is not sufficient to promote evidence-influenced decision making (Straus et al. 2011). Over the past 20 years systematic reviews have influenced medicine in unprecedented ways (Gartleher and Flamm, 2013). However, in a study of systematic review interpretation, only 30.1% of participants were able to correctly identify both the direction of effect and the strength of the evidence in a systematic review (Lai et al. 2011).

Much clinical evidence has been identified, synthesized and packaged in databases. Yet systematic reviews do not rank highly among information resources used in clinical practice (Dawes and Samson, 2003). Efforts in improving the uptake of systematic reviews have not achieved widespread success (CQRMG, 2007).

The Knowledge gap

There is an increasing awareness of the rupture between evidence and practice, especially in the area of research synthesis. We need to know the optimal approaches for enabling decision makers to use the best available evidence (Shea, 2011). An in-depth understanding of the barriers and incentives impacting on the chasm between evidence and clinical practice can lead to interventions that effect change towards optimal practice and thus better healthcare. The series of systematic reviews in this thesis add to our knowledge of the factors that affect the translation of knowing to doing.

Lack of empirical evidence to support effective interventions in the field of knowledge translation constitutes an important knowledge gap. When attempting to enhance use of reviews, like implementing clinical practice guidelines, it is important to first identify specific barriers to change, using theoretical frameworks of behaviour change, and then developing strategies that deal with these barriers (CQRMG, 2007).

In an effort to improve uptake of systematic reviews and meta-analyses, the systematic review methodology itself was taken and applied to three topics: barriers, facilitators, and interventions impacting on the uptake of evidence derived specifically from reviews and meta-analyses. Attitude, knowledge and behaviour research tends to focus on clinical guidelines, not systematic reviews (Bernhardson and Larsson, 2012). Here, by focusing on systematic reviews, knowledge has been added to in a way that was not done previously (Murray, 2011).

A mixed-knowledge overview of relevant international qualitative and quantitative research was also undertaken and completed. A wide range of systematic review methodology was employed as part of this thesis. Various primary study designs were utilised and they included surveys, focus groups, interview studies, intervention/outcome studies and mixed designs. Narrative synthesis with tabulation was executed with the later systematic reviews while meta-analysis, with aggregation rather than configuration, was used as the synthesis tool in the initial two reviews (Gough and Thomas, 2012).

Primary studies addressing the barriers and facilitators to uptake of evidence specifically from systematic reviews and meta-analyses had not previously been looked

for across such a wide range of databases. Nor had these particular studies been synthesised previously using the specific, transparent methods employed here. The primary intervention studies aimed at enhancing uptake from systematic reviews had not previously been sought using the extensive search strategies, the inclusion conditions, and synthesis method applied here.

Barriers

A significant knowledge gap existed regarding the identity of the barriers, facilitators, and interventions impacting on evidence uptake from an important source of evidence: systematic reviews and meta-analyses. A relevant problem, therefore, was addressed concerning the lack of uptake of knowledge from systematic reviews and meta-analyses. An important knowledge gap was also bridged by identifying the barriers that inhibit knowledge uptake from pre-appraised, integrative evidence.

This systematic review revealed that strategies to improve uptake of evidence from reviews and meta-analyses need to overcome a wide variety of obstacles. The review described the reasons why knowledge users, especially physicians, do not call on systematic reviews. This study can inform future strategies to enhancing systematic review uptake and also suggests potential avenues for future investigation.

Facilitators

To this writer's knowledge, the fourth systematic review presented in this thesis represents a novel overview of a large group of decision makers' perceptions of the facilitators to the uptake of evidence from systematic reviews and meta-analyses. Its

results provide a context and a range of enhancers to consider while attempting an increase in review uptake. The investigation offers a rational approach towards improving systematic review use in clinical practice and policy making by a wide variety of decision makers. The results also suggest avenues for future research.

Interventions

The review showed that there are a number of interventions in existence to enhance uptake of systematic reviews evidence by a wide variety of decision makers. Interventions require extra work (Lawrence et al. 2012). However, if used appropriately, the interventions could lead to improvements in knowledge and clinical practice.

Barriers, facilitators and interventions

Finally, a systematic review using a mixed-methods approach was conducted that integrated the barrier, facilitator and intervention research previously conducted as part of this project. The aim was to make sense of a complex topic area (Wong et al. 2013). Strategies such as targeted messaging, educational visits, and summaries of reviews, that addressed a range of identified barriers and facilitators, were recommended to enhance uptake of systematic reviews and meta-analyses. Promising approaches included interactive workshops and e-learning and they overcame a number of barriers and built on some facilitators. This review indicated that new strategies also need to be developed that address a number of identified but neglected barriers and build on an even greater number of overlooked facilitators.

In terms of an identifiable knowledge gap, there were no previous mixed-knowledge systematic reviews juxtaposing the various factors impacting on uptake of systematic reviews, meta-analyses and the databases associated with them. This final review enhances our appreciation not just of the effectiveness but also the appropriateness of the detected interventions. In this way, relevance as well as effectiveness was addressed.

Contribution

There can be insufficient evidence or insufficient translation (Straus, 2009). Collecting both quantitative and qualitative data allows us to better understand how the different elements of a sustainable intervention might work (Shea, 2012). The triangulation of quantitative data and qualitative data should be encouraged (Majumdar, 2010). It can allow a more holistic view of a debate (Joly et al. 2013). This DPhil research project was the first systematic effort to ascertain which barriers were addressed by the strategies detected and what facilitators had been built on by the identified interventions aimed at increasing systematic review uptake.

In these systematic reviews, comprehensive search strategies were employed in order to identify studies impacting on evidence uptake, assess their eligibility, extract data and assess risk of bias. A particular strength was the attempt to present the data in a consistent and uniform manner, so as to allow for comparison and combination (Anglin et al. 2013).

A serious problem was addressed here: lack of uptake of evidence from systematic reviews. A significant knowledge gap was bridged: identification of the factors

impacting on review uptake, with a final synthesis providing an overall view of what is known (Gough and Thomas, 2012). Accordingly, an important and original, incremental contribution was made to our knowledge.

Much work needs to be done in the relatively young field of evidence translation (Majumdar, 2010). Further exploration of strategies to enhance use of evidence in clinical practice is required (Paterniti and Bisserbe, 2013). The knowledge gained from this research project, in conjunction with the wider knowledge translation literature, will assist in the development of more effective dissemination strategies to enhance evidence uptake.

10.4 Summary

Systematic reviews are an essential part of the process of applying research findings so as to benefit society (Gough et al. 2013). While the current evidence base is incomplete, the systematic reviews presented here provide valuable insights into the likely effectiveness and the appropriateness, of different interventions aimed at increasing the uptake of evidence from systematic reviews, meta-analyses and the databases associated with them. Future strategies and research projects can be informed by the findings outlined here.

The backbone of systematic review methodology is the motivation to improve healthcare (Gartleher and Flamm, 2013). Improving the uptake of systematic reviews means that clinicians will have greater access to the best evidence available (Tsafnat et al. 2013). The incremental contribution made by this project can help improve the movement of evidence from systematic reviews to a variety of decision makers,

including clinicians, so as to enhance the care of the individual patient, in their best interests.

REFERENCES

AKL, E., A. and GUYATT, G., H., 2012. Making the best judgment of risk of bias. *Journal of Clinical Epidemiology,* 65**,** 1238-1239.

AKOBENG, K., 2005. Principles of evidence-based medicine. *Archives of Disease in Childhood,* 90, 837-840.

AL-ANSARY, LA., TRICCO, AC., ADI, Y., BAWAZEER, G., PERRIER L., Al-GHO, M., STRAUS, S., 2013. A Systematic Review of Recent Clinical Practice Guidelines on the Diagnosis, Assessment and Management of Hypertension. *PLoS ONE*, 8(1): e53744. doi/10.1371/journal.pone.0053744

ALBERANI, V., DE CASTRO PIETRANGELI, P. and MAZZA, A.M., 1990. The use of grey literature in health sciences: a preliminary survey. *Bulletin of Medical Library Association,* 78**,** 358-63.

ALLEN, R., 2000. *Penguin Complete English Dictionary*, UK: Penguin.

ALLAN, C, KALU, UG, SEXTON, C, EBMEIER, K., 2012. Transcranial stimulation in depression**.** *The British Journal of Psychiatry,* Jan;200(1):10-1. doi: 10.1192/bjp.bp.111.101188.

ANDREWS, G., 1996. Talk that works: the rise of cognitive behaviour therapy. *British Medical Journal,* 313**,** 1501-2.

ANDREWS, G., POULTON, R. and SKOOG, I., 2005. Lifetime risk of depression: restricted to a minority or waiting for most? *British Journal of Psychiatry,* 187**,** 495-6.

ANDREWS, J., GUYATT, G., OXMAN, AD., ALDERSON, P., DAHM, P., FALCK-YTTER, Y., NASSER, M. et al. 2013. GRADE guidelines: 15. Going from evidence to recommendations: the significance and presentation of recommendations. Journal of

Clinical Epidemiology, 66(7):719-25. doi: 10.1016/j.jclinepi.2012.03.013. Epub 2013 Jan 9.

ANGLIN, R. E., SAMAAN, Z., WALTER, S. D., and MCDONALD, S.D., 2013. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. British Journal of Psychiatry, 202, 100-7.

ARDITI, C., RÈGE-WALTHER, M., WYATT, J. C., DURIEUX, P. and BURNAND, B., 2012. Computer-generated reminders delivered on paper to healthcare professionals; effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews, 12, CD001175.

ASCH, S. M., KERR, E. A., KEESEY, J., ADAMS, J. L., SETODJI, C. M., MALIK, S. and MCGLYNN, E. A. 2006. Who is at greatest risk for receiving poor-quality health care? New England Journal of Medicine, 354, 1147-56.

AYERBE, L., AYIS, S., WOLFE, C. A., RUDD, A, 2013. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis British Journal of Psychiatry January 202:14-21; doi:10.1192/bjp.bp.111.107664

BAKER, R., CAMOSSO-STEFINOVIC, J., GILLIES, C., SHAW, E. J., CHEATER, F., FLOTTORP, S. and ROBERTSON, N., 2010. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews, CD005470.

BALAS, E. A. and BORAN, S. A., 2000. Managing clinical knowledge for health care improvement. Yearbook of Medical Informatics, Patient-Centred Systems. Stuttgart: Schattauer.

BAUCHNER, H., 2013. Scientific integrity in scholarly research - the challenge for publishers. In: HENEGHAN, C., and GODLEE, F., eds. EvidenceLive2013. 25-26 March, 2013. Oxford, UK.

BAUCHNER, H, R AND GOLUB, R. 2013. The restructuring of structured abstracts. Journal of the American Medical Association. 309, 491-492.

BECK, A. T., HOLLON, S. D., YOUNG, J. E., BEDROSIAN, R. C. & BUDENZ, D. 1985. Treatment of depression with cognitive therapy and amitriptyline. Archives of General Psychiatry, 42, 142-8.

BECK, A. T., STEER, R. A. and BROWN, G. K., 1996. Manual for the BDI-II. San Antonio, TX: The Psychological Corporation.

BEDI, N., CHILVERS, C., CHURCHILL, R., DEWEY, M., DUGGAN, C., FIELDING, K., GRETTON, V., et al., 2000. Assessing effectiveness of treatment of depression in primary care. Partially randomised preference trial. British Journal of Psychiatry, 177, 312-8.

BELLER, E.M., GLASZIOU, P.P., ALTMAN, D.G., HOPEWELL, S., BASTIAN, H., et al. (2013) PRISMA for Abstracts: Reporting Systematic Reviews in Journal and Conference Abstracts. PLoS Med 10(4): e1001419. doi:10.1371/journal.pmed.1001419.

BENNETT, S. and HOFFMANN, T., 2010. Evidence about effects of interventions. Evidence-based practice across the health professions (1st ed). Ed. T. Hoffmann, S. Bennett, & C. Del Mar. Sydney: Elsevier, 59-95.

BERO, L. A., GRILLI, R., GRIMSHAW, J. M., HARVEY, E., OXMAN, A. D. & THOMSON, M. A., 1998. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings.

The Cochrane Effective Practice and Organization of Care Review Group. British Medical Journal, 317, 465-8.

BERO, L. A. and JADAD, A. R., 1997. How consumers and policymakers can use systematic reviews for decision making. Annals of Internal Medicine, 127, 37-42.

BERNHARDSSON, S., LARSSON, ME., 2012. Measuring evidence-based practice in physical therapy: translation, adaptation, further development, validation, and reliability test of a questionnaire. Physio-Therapy, 2013 Jun; 93(6):819-32. doi: 0.2522/ptj.20120270. Epub 2013 Feb 21.

BHATTACHARYYA, O. K., ESTEY, E. A. and ZWARENSTEIN, M., 2011. Methodologies to evaluate the effectiveness of knowledge translation interventions: a primer for researchers and health care managers. Journal of Clinical Epidemiology, 64, 32-40.

BLACKBURN, I. M., BISHOP, S., GLEN, A. I., WHALLEY, L. J. and CHRISTIE, J. E., 1981. The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. British Journal of Psychiatry, 139, 181-9.

BLOOM, B. S., 2005. Effects of continuing medical education on improving physician clinical care and patient health: a review of systematic reviews. International Journal of Technology Assessment in Health Care, 21, 380-5.

BOWER, P., BYFORD, S. BYFORDS., SIBBALD, B., et al. 2000. Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. II: Cost effectiveness. BMJ, 321 doi: http://dx.doi.org/10.1136/bmj.321.7273.1389

BOWERS, D., 2008. Medical statistics from scratch: an introduction for health professionals, Chichester: Wiley.

BRIDLE, C., SPANJERS, K., PATEL, S., ATHERTON, N. M. & LAMB, S. E. 2012. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. British Journal of Psychiatry, 201, 180-5.

BROWN, T. 2013. It's time for All Trials registered and reported [editorial]. Cochrane Database of Systematic Reviews 2013 Apr 30; 4:ED000057. dx.doi.org/10.1002/14651858.

BROWNER, W. S., BARON, R. B., SOLKOWITZ, S., ADLER, L. J. & GULLION, D. S. 1994. Physician management of hypercholesterolemia. A randomized trial of continuing medical education. Western Journal of Medicine, 161, 572-8.

BRUGHA, T. S., MATTHEWS, R., MORGAN, Z., HILL, T., ALONSO, J. and JONES, D. R., 2012. Methodology and reporting of systematic reviews and meta-analyses of observational studies in psychiatric epidemiology: systematic review. British Journal of Psychiatry, 200, 446-53.

BRUNTON, G. 2003. Children and physical activity: a systematic review of barriers and facilitators. London, EPPI-Centre.

BURTON, M. Key tools for decision makers - how to find and interpret systematic reviews. In: HENEGHAN, C. & GODLEE G. eds. EvidenceLive2013. 25-26 March, 2013. Oxford, UK.

BURTON, L. J., TYSON, S. and MCGOVERN, A. 2013. Staff perceptions of using outcome measures in stroke rehabilitation. Disability and Rehabilitation, 35, 828-34.

CABANA, M. D., RAND, C. S., POWE, N. R., WU, A. W., WILSON, M. H., ABBOUD, P. A. & RUBIN, H. R., 1999. Why don't physicians follow clinical practice guidelines? A framework for improvement. Journal of the American Medical Association, 282, 1458-65.

CARY, S. and HALL, D., 1999. Psychiatrists views on evidence-based practice. Psychiatric Bulletin. 23, 159-161.

CHAILLET, N., DUBÉ, E., DUGAS, M., AUDIBERT, F., TOURIGNY, C., FRASER, W. D. & DUMONT, A., 2006. Evidence-based strategies for implementing guidelines in obstetrics: a systematic review. Obstetrics and Gynaecology, 108, 1234-45.

CHICKTE, U., and KHONDOWE, O., 2012. Evidence on facilitators and barriers of inter-professional education. First International Conference on evidence-based Healthcare. New Delhi: International Society of Evidence-based Healthcare and BMJ. 6-8 Oct, 2-12.

CHOI, K-H., WYKES, T., KURTZ, M.M. 2013. Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytic investigation of efficacy. The British Journal of Psychiatry, 203, 3, 172-178. doi:10.1192/bjp.bp.111.107359.

CILISKA, D., HAYWARD, S., DOBBINS, M., BRUNTON, G. & UNDERWOOD, J., 1999. Transferring public-health nursing research to health-system planning: assessing the relevance and accessibility of systematic reviews. Canadian Journal of Nursing Research, 31, 23-36.

COCHRANE EFFECTIVE PRACTICE AND ORGANISATION OF CARE REVIEW GROUP. Data collection checklist. Ottawa, Canada: Cochrane Effective Practice and Organisation of Care Review Group; 2002.

COCHRANE QUALITATIVE RESEARCH METHODS GROUP, 2007. Minutes of the 2007 Annual General Meeting of the Cochrane Qualitative Methods Research Group, Wednesday 24th October, Rotterdam Room, World Trade Centre, Sao Paulo, Brazil.

COCHRANE, L. J., OLSON, C. A., MURRAY, S., DUPUIS, M., TOOMAN, T. and HAYES, S., 2007. Gaps between knowing and doing: understanding and assessing the barriers to optimal health care. Journal of Continuing Education in Health Professions, 27, 94-102.

COLLINS, GARY S., OMAR, O., MILENSU, S. and LY-MEE, Y., 2013. A systematic review finds that prediction models for chronic kidney were poorly reported and often developed using inappropriate methods. Journal of Clinical Epidemiology, In PRESS.

COLLINS, P. Y., PATEL, V., JOESTL, S. S., MARCH, D., INSEL, T. R., DAAR, A. S., ANDERSON, W., ET AL., 2011. Grand challenges in global mental health. Nature, 475, 27-30.

COOK, C. N., POSSINGHAM, HP. AND FULLER, RA. 2013. Contribution of systematic reviews to management decisions. Conservation Biology, 00, 0, 1-14.

COOMARASAMY, A. AND KHAN, K. S., 2004. What is the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. British Medical Journal, 329, 1017.

COPPUS, S. F., EMPARANZA, J. I., HADLEY, J., KULIER, R., WEINBRENNER, S., ARVANITIS, T. N., BURLS, A. et al., 2007. A clinically integrated curriculum in evidence-based medicine for just-in-time learning through on-the-job training: the EU-EBM project. BMC Medical Education, 7, 46.

COX, G. R., CALLAHAN, P., CHURCHILL, R., HUNOT, V., MERRY, S. N., PARKER, A. G. & HETRICK, S. E. 2012. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database Systematic Review, 11, CD008324.

CRAIG, P., DIEPPE, P.A., MACINTYRE, S. et al. 2008. Developing and evaluating complex interventions: the new Medical Research Council guidance. British Medical Journal. 337:a1655

CRANNEY, M. and WALLEY, T., 1996. Same information, different decisions: the influence of evidence on the management of hypertension in the elderly. British Journal General Practice, 46, 661-3.

CUIJPERS, P., BEEKMAN, A. T. & REYNOLDS, C. F., 2012. Preventing depression: a global priority. Journal of the American Medical Association, 307, 1033-4.

CUIJPERS, P., VAN STRATEN, A., VAN OPPEN, P. & ANDERSSON, G., 2008. Are psychological and pharmacologic interventions equally effective in the treatment of adult depressive disorders? A meta-analysis of comparative studies. Journal of Clinical Psychiatry, 69, 1675-85; quiz 1839-41.

CUIJPERS, P., VOGELZANGS, N., TWISK, J., KLEIBOER, A., LI, J. and PENNINX, B. W., 2013. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. British Journal of Psychiatry, 202, 22-7.

CUIJPERS, P., SIJBRANDIJ, M., KOOLE., S.L., ANDERSSON, G., et al. 2014. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry. 13(1):56-67. doi: 10.1002/wps.20089.

CURRAN, J., MURPHY, AL., SINCLAIR, D., MC GRATH, P., 2013. Factors influencing rural and urban emergency clinicians' participation in an online knowledge exchange intervention The International Electronic Journal of Rural and Remote Health Research, Education, Practice, and Policy [Online], 12.

DAHM, P., POOLMAN, R. W., BHANDARI, M., FESPERMAN, S. F., BAUM, J., KOSIAK, B., CARRICK, T., PREMINGER, G. M. and MEMBERSHIP, A. U. A., 2009. Perceptions and competence in evidence-based medicine: a survey of the American Urological Association Membership. Journal of Urology, 181, 767-77.

DAVIES, H., DENIS, JL., FERELIE, E., GOLDEN-BIDDLE, K., LAVIS, J., OXMAN, A., 2005. Towards systematic reviews that inform health care management and policy making. Journal of Health Service Research Policy, 10, 35-48.

DAVIS, DA., THOMSON, MA., OXMAN, AD., HAYNES, RB., 1995. Changing physician performance. A systematic review of the effect of continuing medical education strategies. Journal of the American Medical Association. Sep 6; 274(9):700-5.

DAVIS, DA., THOMAS, MA., OXMAN, AD. et al., 1992. Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. Journal of the American Medical Association, 268:1111–17.

DAVIS, D. A. and TAYLOR-VAISEY, A. 1997. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Canadian Medical Association Journal, 157, 408-16.

DAVIS, J., CHRYSSAFIDOU, E., ZAMORA, J., DAVIES, D., KHAN, K. & COOMARASAMY, A., 2007. Computer-based teaching is as good as face to face

lecture-based teaching of evidence based medicine: a randomised controlled trial. BMC Medical Education, 7, 23.

DAVIS, J., CRABB, S., ROGERS, E., ZAMORA, J. & KHAN, K., 2008. Computer-based teaching is as good as face to face lecture-based teaching of evidence based medicine: a randomized controlled trial. Medical Teacher, 30, 302-7.

DAWES, M., DAVIES, P., GRAY, A., MANT, J., SEERS, K. & SNOWBALL, R. 2005. Evidence-based practice, London, Elsevier, Churchill Livingstone.

DAWES, M. & SAMPSON, U., 2003. Knowledge management in clinical practice: a systematic review of information seeking behaviour in physicians. International Journal of Medical Information, 71, 9-15.

DEEKS, JJ, HIGGINS, JPT. & ALTMAN DG 2008. Analysing data and undertaking meta-analysis. In: HIGGINS, JPT. and GREEN, S. (eds.) Cochrane Handbook of Systematic Reviews of Interventions. Chichester (UK): John Wiley and Sons.

DE MAAT, S. M., DEKKER, J., SCHOEVERS, R. A. & DE JONGHE, F., 2007. Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. European Psychiatry, 22, 1-8.

DE SILVA, M. J., COOPER, S., LI, H. L., LUND, C. & PATEL, V., 2013. Effect of psychosocial interventions on social functioning in depression and schizophrenia: meta-analysis. British Journal of Psychiatry, 202, 253-60.

DE BRUN, C. and PEARCE-SMITH, N., 2009. Searching Skills Toolkit: Finding the Evidence. Oxford, United Kingdom: Wiley-Blackwell. ISBN: 978-1-4051-7888-4.

DE RUBEIS, R. J., EVANS, M. D., HOLLON, S. D., GARVEY, M. J., GROVE, W. M. & TUASON, V. B., 1990. How does cognitive therapy work? Cognitive change and

symptom change in cognitive therapy and pharmacotherapy for depression. Journal of Consulting Clinical Psychology, 58, 862-9.

DE RUBEIS, R. J., GELFAND, L. A., TANG, T. Z. & SIMONS, A. D., 1999. Medications versus cognitive behaviour therapy for severely depressed outpatients: mega-analysis of four randomized comparisons. American Journal of Psychiatry, 156, 1007-13.

DE RUBEIS, R. J., HOLLON, S. D., AMSTERDAM, J. D., SHELTON, R. C., YOUNG, P. R., SALOMON, R. M., O'REARDON, J. P., 2005. Cognitive therapy vs. medications in the treatment of moderate to severe depression. Archives of General Psychiatry, 62, 409-16.

DE RUBEIS, R. J., SIEGLE, G. J. & HOLLON, S. D., 2008. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. Nature Reviews Neuroscience, 9, 788-96.

DICKERSON, K., MANHEIMER, E., WIELAND, S., ROBINSON, KA., LEFEBVRE, C., MCDONALD, S., 2002. CENTRAL development group. Development of the Cochrane Collaboration's CENTRAL register of controlled clinical trials. Evaluation and the Health Professions. 25: 38-64.

DIMIDJIAN, S., HOLLON, S. D., DOBSON, K. S., SCHMALING, K. B., KOHLENBERG, R. J., ADDIS, M. E., GALLOP, R., et al., 2006. Randomized trial of behavioural activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. Journal of Consulting and Clinical Psychology, 74, 658-70.

DOBBINS, M., CILISKA, D., COCKERILL, R., BARNSLEY, J. & DICENSO, A., 2002. A framework for the dissemination and utilization of research for health-care policy and practice. The Online Journal of Knowledge Synthesis for Nursing, 9, 7.

DOBBINS, M., COCKERILL, R. and BARNSLEY, J., 2001a. Factors affecting the utilization of systematic reviews. A study of public health decision makers. International Journal Technology Assessment Health Care, 17, 203-14.

DOBBINS, M., COCKERILL, R., BARNSLEY, J. and CILISKA, D., 2001b. Factors of the innovation, organization, environment, and individual that predict the influence five systematic reviews had on public health decisions. International Journal Technology Assessment Health Care, 17, 467-78.

DOBBINS, M., DECORBY, K. & TWIDDY, T., 2004. A knowledge transfer strategy for public health decision makers. Worldviews Evidence Based Nursing, 1, 120-8.

DOBBINS, M., HANNA, S. E., CILISKA, D., MANSKE, S., CAMERON, R., MERCER, S. L., O'MARA, L., DECORBY, K. & ROBESON, P., 2009a. A randomized controlled trial evaluating the impact of knowledge translation and exchange strategies. Implement Science, 4, 61.

DOBBINS, M., JACK, S., THOMAS, H. & KOTHARI, A. 2007. Public health decision-makers' informational needs and preferences for receiving research evidence. Worldviews Evidence-Based Nursing, 4, 156-63.

DOBBINS, M., ROBESON, P., CILISKA, D., HANNA, S., CAMERON, R., O'MARA, L., DECORBY, K. & MERCER, S. 2009b. A description of a knowledge broker role implemented as part of a randomized controlled trial evaluating three knowledge translation strategies. Implement Science, 4, 23.

DOLLE, K., SCHULTE-KOME, K. 2013. The treatment of depressive disorders in children and adolescents. Dtsch Arztebl Int. 110(50):854-60. doi: 10.3238/arztebl.2013.0854.

DOSHI, P., DICKERSIN, K., HEALY, D., VEDULA, SS., JEFFERSON, T., 2013. Restoring invisible and abandoned trials; a call for people to publish the findings. British Medical Journal. 346; f2865 doi: 10.1136/bmj.f2865.

DWAN, K., KIRKHAM, JJ., WILLIAMSON, PR., GAMBLE, C., 2013. Selective reporting of outcomes in randomised controlled trials in systematic reviews of cystic fibrosis. BMJ Open, 3(6): e002709. Published online 2013 May 31. doi: 10.1136/bmjopen-2013-002709. PMCID: PMC3669728.

EASTWOOD, G. M., O'CONNELL, B. & GARDNER, A., 2008. Selecting the right integration of research into practice strategy. Journal of Nursing Care Quality, 23, 258-65.

EATON, W. W., SHAO, H., NESTADT, G., LEE, H. B., LEE, B. H., BIENVENU, O. J. & ZANDI, P., 2008. Population-based study of first onset and chronicity in major depressive disorder. Archives of General Psychiatry, 65, 513-20.

ECCLESTON, C., WIFFEN, P., DERRY, S., MOORE, A., Growing pain [editorial]. Cochrane Database of Systematic Reviews 2013; 5:ED000059. dx.doi.org/10.1002/14651858.ED000059

EGGER, M., SMITH, G. D., 2001. Principles of and procedures for systematic reviews. In Eds. EGGER, M., SMITH, G. D. & ALTMAN, D. G., Systematic reviews in health care: meta-analysis in context, London: BMJ Books.

EGGER, M., SMITH, G. D. & STERNE, J. A. 2001. Uses and abuses of meta-analysis. Clinical Medicine, 1, 478-84.

ELKIN, I., SHEA, M. T., WATKINS, J. T., IMBER, S. D., SOTSKY, S. M., COLLINS, J. F., GLASS, D. R., et al.,1989. National Institute of Mental Health Treatment of

Depression Collaborative Research Program. General effectiveness of treatments. Archives of General Psychiatry, 46, 971-82; discussion 983.

EMSLIE, C., GRIMSHAW, J. & TEMPLETON, A., 1993. Do clinical guidelines improve general practice management and referral of infertile couples? British Medical Journal, 306, 1728-31.

ESPELAND, A. & BAERHEIM, A., 2003. Factors affecting general practitioners' decisions about plain radiography for back pain: implications for classification of guideline barriers-a qualitative study. BMC Health Services Research, 3, 8.

EVANGELOU, E., SIONTIS, K. C., PFEIFFER, T., and IOANNIDIS, J. P. A., 2012. Perceived information gain from randomized trials correlates with publication in high–impact factor journals. Journal of Clinical Epidemiology, 65, 1274-1281.

FAHEY, T., GRIFFITHS, S. & PETERS, T. J., 1995. Evidence based purchasing: understanding results of clinical trials and systematic reviews. British Medical Journal, 311, 1056-9; discussion 1059-60.

FAIRHURST, K. and HUBY, G., 1998. From trial data to practical knowledge: qualitative study of how general practitioners have accessed and used evidence about statin drugs in their management of hypercholesterolemia. British Medical Journal, 317, 1130-4.

FAWOLE, O. A., DY, S. M., WILSON, R. F., LAU, B. D., MARTINEZ, K. A., APOSTOL, C. C., VOLLENWEIDER, D., BASS, E. B. & ASLAKSON, R. A., 2012. A Systematic Review of Communication Quality Improvement Interventions for Patients with Advanced and Serious Illness. Journal of General Internal Medicine, Apr; 28(4):570-7. doi: 10.1007/s11606-012-2204-4. Epub 2012 Oct 26.

FEIGHNER, J.P., ROBINS, E., GUZE, S.B., WOODRUFF, R.A., WINOKUR, G., MUNOZ, R., 1972. Diagnostic criteria for use in psychiatric research. Archieves of General Psychiatry. 26:57-63.

FREEDLAND, KE. and CARNEY, M., 2013. Depression as a risk factor for adverse outcomes in coronary heart disease. BMC Medicine. 11:131 doi:10.1186/1741-7015-11-131

FRIEDMAN, M., DETWEILER-BEDELL, J., LEVENTHAL, H., HOME, R., KEITNER, G., MILLER, I., 2004. Combined psychotherapy and pharmacology for the treatment of major depressive disorder. Clinical Psychology Science and Practice, 11, 47-68.

GAGNON, M. L., 2011. Moving knowledge to action through dissemination and exchange. Journal of Clinical Epidemiology, 64, 25-31.

GALLO, JJ., MORALES, K., BOGNER, H., RAUE, P., ZEE, J., BRUCE, M., REYNOLDS, C., 2013 Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. British Medical Journal, 346:f2570. doi: 10.1136/bmj.f2570.

GARTLEHNER, G. & FLAMM, M., 2013. Is The Cochrane Collaboration prepared for the era of patient-centred outcomes research? Cochrane Database Systematic Reviews, 3, ED000054.

GEDDES, J., 2011. Candidate statement. Candidates' Election Statements, National Treasurer and Council Elections. London, Royal College of Psychiatrists. p6

GEDDES, J. and CARNEY, S., 2001. Recent advances in evidence-based psychiatry. Canadian Journal of Psychiatry, 46, 403-6.

GEDDES, J., REYNOLDS, S., STREINER, D. and SZATMARI, P., 1997. Evidence based practice in mental health. British Medical Journal, 315, 1483-4.

GEDDES, J. R. and HARRISON, P. J., 1997. Closing the gap between research and practice. British Journal of Psychiatry, 171, 220-5.

GERADA, C., 2013. Evidence, policy and politics. In: HENEGHAN, C. and GOODLEE, F., eds. EvidenceLive2013, 25-26 March, 2013. Oxford, UK.

GERSON, S., BELIN, TR., KAUFMAN, A., MIBTZ, J., JARVIK, L., 1999 Pharmacological and Psychological Treatments for Depressed Older Patients: A Meta-analysis and Overview of Recent Findings. Harvard Review of Psychiatry, 7, 1, 1-28.

GILBODY, S., BOWER, P. & RICK, J., 2012. Better care for depression in the workplace: integrating occupational and mental health services. British Journal of Psychiatry, 200, 442-3.

GLASZIOU, P. 2013. 'Knowledge is not enough: improving research's usability.' *Evidence, governance, performance.* 2nd Conference of International Society for EBHC, 6th International Conference for EBHC Teachers and Developers, Taormina, Italy, 30 October – 2nd November 2013. Available at: http://www.ebhc.org (Accessed 06/11/2013).

GLASZIOU, P., GUYATT, G. H., DANS, A. L., DANS, L. F., STRAUS, S. & SACKETT, D. L. 1998. Applying the results of trials and systematic reviews to individual patients. ACP Journal Club, 129, A15-6.

GLASZIOU, P. and HAYNES, B., 2005. The paths from research to improved health outcomes. ACP Journal Club, 142, A8-10.

GLAZIOU, P., CHALMERS, I., ALTMAN, DG., BASTIAN, H., BOUTRON, I., BRICE A., JAMTVEDT, G. et al., 2010. Taking healthcare interventions from trial to practice. British Medical Journal, 13; 341:c3852. doi: 10.1136/bmj.c3852.

GLASZIOU, P., HOFFMANN, T., ERUETI, C., 2012. Poor description of non-drug interventions: A remediable barrier to use of evidence in practice? First International Conference on Evidence-based Healthcare. AIIMS, New Delhi, India, 7-8 October, 2012.

GLASIOU, P., ALTMAN, D., BOSSUYT, P., BOUTRON, I., CLARKE, M., JULIOUS, S., MICHIE, S., et al. 2014. Reducing waste from incomplete or unusable reports of biomedical research. The Lancet, 283, 9913, 267-276. Doi:10.1016/SO140-6736(13)62228-X

GLOVER, G., WEBB, M., EVISON, F., 2010. Improving access to psychological therapies: a review of progress made by sites in the first roll-out year. UK: North East Public Health Observatory.

GOODWIN, G., 2003. Mood Disorder. In: JOHNSTONE, E., CUNNINGHAM OWENS, DG, LAWRIE, SM, SHARKE, M., FREEMAN, C.P. (ed.) Companion to Psychiatric Studies. UK: Churchill Livingstone.

GOODWIN G., 2012. Bipolar depression and treatment with antidepressants. The British Journal of Psychiatry 200: 5-6 doi: 10.1192/bjp.bp.111.095349

GOUGH, D., OLIVER, S., THOMAS, J. 2012. Introducing systematic reviews. In: GOUGH, D., OLIVER, S., THOMAS, J. (eds) An introduction to systematic reviews. London; Sage Publications.

GOUGH, D., THOMAS, J., 2012. Commonality and diversity in reviews. In: GOUGH, D., OLIVER, S., THOMAS, J. (eds) An introduction to systematic reviews. London; Sage Publications.

GRANT, J., COTTRELL, R., CLUZEAU, F. & FAWCETT, G. 2000. Evaluating "payback" on biomedical research from papers cited in clinical guidelines: applied bibliometric study. British Medical Journal, 320, 1107-11.

GRAVEL, K., LÉGARÉ, F. & GRAHAM, I. D. 2006. Barriers and facilitators to implementing shared decision-making in clinical practice: a systematic review of health professionals' perceptions. Implement Science, 1, 16.

GRAY, M. 2013. Transforming healthcare. In: HENEGHAN, C. and GOODLEE, F., eds. EvidenceLive2013. 25-26 March, 2013. Oxford, UK.

GRAY, B.H., 1998. Sources used in health policy research and implications for information retrieval systems. Journal of Urban Health, 75, 842-52.

GREENHALGH, T., ROBERT, G., MACFARLANE, F., BATE, P., KYRIAKIDOU, O., 2004. Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations. Milbank Quarterly, 82(4): 581–629. doi: 10.1111/j.0887-378X.2004.00325.x.

GREENHALGH, T. and PEACOCK, R., 2005. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. British Medical Journal, 331, 1064-5.

GRILLI, R., 2000. Toward the efficacy of clinical appropriateness: national program for guidelines. Epidemiologia & Prevenzione, 24, 54-6.

GRILLI, R., FREEMANTLE, N., MINOZZI, S., DOMENIGHETTI, G. & FINER, D. 2000a. Mass media interventions: effects on health services utilisation. Cochrane Database Systematic Review, CD000389.

GRILLI, R. and LOMAS, J., 1994. Evaluating the message: the relationship between compliance rate and the subject of a practice guideline. Medical Care, 32, 202-13.

GRILLI, R., MAGRINI, N., PENNA, A., MURA, G. and LIBERATI, A., 2000b. Practice guidelines developed by specialty societies: the need for a critical appraisal. Lancet, 355, 103-6.

GRIMSHAW, J. M. & ECCLES, M. P., 2004. Is evidence-based implementation of evidence-based care possible? Medical Journal of Australia, 180, S50-1.

GRIMSHAW, J. M., ECCLES, M. P., WALKER, A. E. & THOMAS, R. E., 2002. Changing physicians' behaviour: what works and thoughts on getting more things to work. Journal of Continuing Education in the Health Professions, 22, 237-43.

GRIMSHAW, J. M., SANTESSO, N., CUMPSTON, M., MAYHEW, A. and MCGOWAN, J. 2006. Knowledge for knowledge translation: the role of the Cochrane Collaboration., Journal of Continuing Education in the Health Professions, 26, 55-62.

GRIMSHAW, J. M., SHIRRAN, L., THOMAS, R., MOWATT, G., FRASER, C., BERO, L., GRILLI, R., HARVEY, E., OXMAN, A. & O'BRIEN, M. A., 2001. Changing provider behaviour: an overview of systematic reviews of interventions. Medical Care, 39, II2-45.

GRIMSHAW, J. M., THOMAS, R. E., MACLENNAN, G., FRASER, C., RAMSAY, C. R., VALE, L., WHITTY, P. et al., 2004. Effectiveness and efficiency of guideline

dissemination and implementation strategies. Health Technology Assessment, 8, iii-iv, 1-72.

GROL, R. and GRIMSHAW, J., 1999. Evidence-based implementation of evidence-based medicine. Joint Commission Journal on Quality Improvement, 25, 503-13.

GROL, R. and GRIMSHAW, J., 2003. From best evidence to best practice: effective implementation of change in patients' care. Lancet, 362, 1225-30.

GROL, R., AND WENSING, M., 2004.What drives change? Barriers to and incentives for achieving evidence-based practice. Medical Journal of Australia. 180 (6): 57

GRUEN, R. L., MORRIS, P. S., MCDONALD, E. L. and BAILIE, R. S., 2005. Making systematic reviews more useful for policy-makers. Bulletin of the World Health Organisation, 83, 480.

GUYATT, G. H., MEADE, M. O., JAESCHKE, R. Z., COOK, D. J. & HAYNES, R. B., 2000. Practitioners of evidence based care. Not all clinicians need to appraise evidence from scratch but all need some skills. British Medical Journal, 320, 954-5.

GÜLMEZOGLU, A. M., LANGER, A., PIAGGIO, G., LUMBIGANON, P., VILLAR, J. & GRIMSHAW, J., 2007. Cluster randomised trial of an active, multifaceted educational intervention based on the WHO Reproductive Health Library to improve obstetric practices. British Journal of Obstetrics and Gynaecology, 114, 16-23.

GÜLMEZOGLU, A. M., VILLAR, J., CARROLI, G., HOFMEYR, J., LANGER, A., SCHULZ, K. & GUIDOTTI, R., 1997. WHO is producing a reproductive health library for developing countries. British Medical Journal, 314, 1695.

HADLEY, J., KULIER, R., ZAMORA, J., COPPUS, S. F., WEINBRENNER, S., MEYERROSE, B et al., 2010. Effectiveness of an e-learning course in evidence-based

medicine for foundation (internship) training. Journal of the Royal Society of Medicine, 103, 288-94.

HAMILTON, M., 1960. A rating scale for depression. Journal of Neurosurgery and Psychiatry, 23, 56-62.

HANSON, B. P., BHANDARI, M., AUDIGE, L. & HELFET, D., 2004. The need for education in evidence-based orthopaedics: an international survey of AO course participants. Acta Orthopaedica Scandinavica, 75, 328-32.

HARDEN, A., BRUNTON, G., FLETCHER, A. & OAKLEY, A., 2009. Teenage pregnancy and social disadvantage: systematic review integrating controlled trials and qualitative studies. British Medical Journal, 339, b4254.

HARDEN, A., GARCIA, J., OLIVER, S., REES, R., SHEPHERD, J., BRUNTON, G. and OAKLEY, A., 2004. Applying systematic review methods to studies of people's views: an example from public health research. Journal of Epidemiology and Community Health, 58, 794-800.

HARDEN, A., REES, J., SHEPHERD, G., BRUNTON, S. & OLIVER, S., 2001. Young people and mental health: a systematic review of barriers and facilitators. London: EPPI-Centre: Social Science Research Centre.

HARRIS, M. and TAYLOR, G., 2008. Medical Statistics Made Easy. Oxfordshire; Scion Publishing.

HARRIS, M., SMITH, B. J., VEALE, A., ESTERMAN, A., FRITH, P. A. and SELIM, P., 2006. Providing patients with reviews of evidence about COPD treatments: a controlled trial of outcomes. Chronic Respiratory Disease, 3, 133-40.

HARRIS, M., SMITH, B. J., VEALE, A. J., ESTERMAN, A., FRITH, P. A. & SELIM, P., 2009. Providing reviews of evidence to COPD patients: controlled prospective 12-month trial. Chronic Respiratory Disease, 6, 165-73.

HARTLING, L., HAMA, MP., MILNEA, A., VANDERMEERA, B., SANTAGIDAB, L., ANARIC, M., TSERTSVADZEC, A., et al. 2013. Testing the risk of bias tool showed reliability between individual reviewers and across consensus assessments of reviewer pairs. Journal of Clinical Epidemiology, In press.

HAWKINS, R. P., KREUTER, M., RESNICOW, K., FISHBEIN, M. and DIJKSTRA, A., 2008. Understanding tailoring in communicating about health. Health Education Research, 23, 454-66.

HAWTON, K., SALKOVSKIS, P., KIRK, J., CLARKE, D., eds., 1989. Cognitive behaviour therapy for psychiatric problems: A practical guide. New York, NY, US: Oxford University Press.

HAYNES. B. 2013. 'Knowledge translation and implementation science; the missing links between research and practice.' *Evidence, governance, performance.* 2nd Conference of International Society for EBHC, 6th International Conference for EBHC Teachers and Developers, Taormina, Italy, 30 October – 2nd November 2013. Available at: http://www.ebhc.org (Accessed 06/11/2013).

HAYNES, R.B., ACKLOO E., SAHOTA, N., McDONALD HP., YAO X., 2008. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD000011. DOI: 10.1002/14651858.CD000011.pub3.

HEGEMAN, J. M., KOK, R. M., VAN DER MAST, R. C. and GILTAY, E. J., 2012. Phenomenology of depression in older compared with younger adults: meta-analysis. British Journal of Psychiatry, 200, 275-81.

HENEGHAN, C. & GODLEE, F., 2013. Where next for evidence based healthcare? British Medical Journal, 346, 766.

HIGGINS J. and GREEN, S. 2008. Guide to the contents of a Cochrane protocol and review. In: HIGGINS, J. & GREEN, S. P. eds., Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley and Sons.

HIGGINS, J. and ALTMAN DG. 2008. Assessing risk of bias in included studies. In HIGGINS, J. and GREEN, S. P., eds., Cochrane handbook for systematic reviews of interventions, Oxford, Wiley-Blackwell.

HIGGINS, JPT. and DEEKS, JJ. 2008. Selecting studies and collecting data. In: GREEN, H., A. eds., Cochrane Handbook for Systematic Review of Interventions. Chichester (UK): John Wiley and Sons.

HIGGINS, J. and GREEN, S. P., eds., 2008. Cochrane handbook for systematic reviews of interventions, Oxford, Wiley-Blackwell.

HIGGINS, J. and GREEN, S. P., eds., 2011. Cochrane handbook for systematic reviews of interventions, Oxford, Wiley-Blackwell.

HODNETT, E. D., KAUFMAN, K., O'BRIEN-PALLAS, L., CHIPMAN, M., WATSON-MACDONELL, J. & HUNSBURGER, W., 1996. A strategy to promote research-based nursing care: effects on childbirth outcomes. Research in Nursing and Health, 19, 13-20.

HOFFMAN, R., 2012. Improving the Communication of Benefits and Harms of Treatment Strategies: Decision aids for localized prostate cancer treatment decisions. Journal of the National Cancer Institute Monograph, (45): 197-201. doi: 10.1093/jncimonographs/lgs023

HOLLON, S., DE RUBIS, R., EVANS, M., WEIMER, M., GARVEY, M., GROVE, W. & TAUSON, V., 1992a. Cognitive Therapy and Pharmacotherapy for Depression. Archives of General Psychiatry, 49, 774-781.

HOLLON, S. D., DE RUBEIS, R. J., EVANS, M. D., WIEMER, M. J., GARVEY, M. J., GROVE, W. M. & TUASON, V. B., 1992b. Cognitive therapy and pharmacotherapy for depression. Singly and in combination. Archives of General Psychiatry, 49, 774-81.

HOLLON, S. D., DERUBEIS, R. J., SHELTON, R. C., AMSTERDAM, J. D., SALOMON, R. M., O'REARDON, J. P., LOVETT, M. L., et al. 2005. Prevention of relapse following cognitive therapy vs. medications in moderate to severe depression. Archives of General Psychiatry, 62, 417-22.

HOLLON, S. D., JARRETT, R. B., NIERENBERG, A. A., THASE, M. E., TRIVEDI, M. & RUSH, A. J., 2005c. Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? Journal of Clinical Psychiatry, 66, 455-68.

HOLLON, S. D., SHELTON, R. C. & DAVIS, D. D., 1993. Cognitive therapy for depression: conceptual issues and clinical efficacy. Journal of Consulting and Clinical Psychology, 61, 270-5.

HOLLON, S. D., SHELTON, R. C. & LOOSEN, P. T., 1991. Cognitive therapy and pharmacotherapy for depression. Journal of Consulting and Clinical Psychology, 59, 88-99.

HOPEWELL, S, MCDONALD, S., CLARKE, M., EGGER, M., 2007. Grey literature in meta-analyses of randomized trials of healthcare interventions. Cochrane Database of Systematic Reviews, 2, MR 000010.

HOLLON, SD., DeRUBEIS, RJ., FAWCETT, J., AMSTERDAM, JD., SHELTON, RC., ZAJECKA, J., et al. 2014. Effect of Cognitive Therapy With Antidepressant Medications vs Antidepressants Alone on the Rate of Recovery in Major Depressive Disorder A Randomized Clinical Trial. Jama Psychiatry, 71(10):1157-64.

HOPEWELL, S., LOUDON, K., CLARKE, M. J., OXMAN, A. D. and DICKERSIN, K., 2009. Publication bias in clinical trials due to statistical significance or direction of trial results. Cochrane Database Systematic Reviews, MR000006.

HROBJARTSSON, A, BOUTRON, I., TURNER, L., ALTMAN, DG, MOHER, D., 2013. Assessing risk of bias in randomised clinical trials included in Cochrane Reviews: the why is easy, the how is a challenge [editorial]. Cochrane Database of Systematic Reviews 4:ED000058. dx.doi.org/10.1002/14651858.ED000058

HUIBERS, MJH., van BREUKELEN, G., ROELOFS, J., HOLLON, SD., MARKOWITZ JC., van Os J, et al. 2014. Predicting response to cognitive therapy and interpersonal therapy, with or without antidepressant medication, for major depression: A pragmatic trial in routine practice. Journal of Affective Disorders, 152:146-54.

HUNTLEY, A. L., ARAYA, R. & SALISBURY, C., 2012. Group psychological therapies for depression in the community: systematic review and meta-analysis. British Journal of Psychiatry, 200, 184-90.

HYDE, C., 1995. Who uses the Cochrane Pregnancy and Childbirth Database? British Medical Journal, 310, 1140-1.

INNVAER, S., VIST, G., TROMMALD, M. and OXMAN, A., 2002. Health policy-makers' perceptions of their use of evidence: a systematic review. Journal of Health Services Research Policy, 7, 239-44.

JACOBSON, N. S. and HOLLON, S. D., 1996a. Cognitive-behaviour therapy versus pharmacotherapy: Now that the jury's returned its verdict, it's time to present the rest of the evidence. Journal of Consulting and Clinical Psychology, 64, 74-80.

JACOBSON, N. S. and HOLLON, S. D. 1996b. Prospects for future comparisons between drugs and psychotherapy: lessons from the CBT-versus-pharmacotherapy exchange. Journal of Consulting and Clinical Psychology, 64, 104-108.

JADAD, A. R., COOK, D. J., JONES, A., KLASSEN, T. P., TUGWELL, P., MOHER, M. and MOHER, D., 1998. Methodology and reports of systematic reviews and meta-analyses: a comparison of Cochrane reviews with articles published in paper-based journals. Journal of the American Medical Association, 280, 278-80.

JAMTVEDT, G., YOUNG, J. M., KRISTOFFERSEN, D. T., O'BRIEN, M. A. & OXMAN, A. D., 2006. Audit and feedback: effects on professional practice and health care outcomes. Cochrane Database Systematic Reviews, CD000259.

JOHNSTONE, E. C., OWENS, D.G., LAWRIE, S.M., SHARPE, M. AND Freeman, C.P.L., eds., 2004. Companion to psychiatric studies, Edinburgh, Churchill Livingstone.

JOLY, Y., NGUENG FEZE, I. and SIMARD, J., S., 2013. Genetic discrimination and life insurance: a systematic review. BMC Medicine [Online], 11:25.

JORDENS, C. F. and LONG, E., 1998. Use of systematic reviews of randomised trials by Australian neonatologists and obstetricians. Medical Journal of Australia, 169, 399-400.

JORM, A. F., KORTEN, A. E., JACOMB, P. A., RODGERS, B. & POLLITT, P., 1997. Beliefs about the helpfulness of interventions for mental disorders: a comparison of general practitioners, psychiatrists and clinical psychologists. Australia New Zealand Journal of Psychiatry, 31, 844-51.

KANTER, JW., PUSPITASARI, AJ., SANTOS, MM., NAGY GA., 2012. Behavioural activation: history, evidence and promise. British Journal of Psychiatry, 200, 361-363. DOI: 10.1192/bjp.bp.111.103390.

KAHN, N., BOWER, P. and ROGERS, A., 2007. Guided self-help in primary care mental health: meta-synthesis of qualitative studies of patient experiences. British Journal of Psychiatry, 191, 206-211.

KASTNER, M. and STRAUS, S. E., 2012. Application of the Knowledge-to-Action and Medical Research Council frameworks in the development of an osteoporosis clinical decision support tool. Journal of Clinical Epidemiology. 65(11):1163-70. doi: 10.1016/j.jclinepi.2012.04.011. Epub 2012 Aug 1.

KATON, W., VON KORFF, M., LIN, E., WALKER, E., SIMON, G. E., BUSH, T., ROBINSON, P. and RUSSO, J., 1995. Collaborative management to achieve treatment guidelines. Impact on depression in primary care. Journal of the American Medical Association, 273, 1026-31.

KELLER, M. B., MCCULLOUGH, J. P., KLEIN, D. N., ARNOW, B., DUNNER, D. L., GELENBERG, A. J., MARKOWITZ, J. C. et al. 2000. A comparison of nefazodone, the cognitive behavioural-analysis system of psychotherapy, and their combination for the treatment of chronic depression. New England Journal of Medicine, 342, 1462-70.

KERSE, N., ARROLL, B., LLOYD, T., YOUNG, J. & WARD, J., 2001. Evidence databases, the Internet, and general practitioners: the New Zealand story. New Zealand Medical Journal, 114, 89-91.

KINGDOM, D., 2013. The golden age of discovery. The British Journal of Psychiatry, 202: 394-5 doi: 10.1192/bjp.bp.112.125039

KIRSCH, I., DEACON, B.J., HUEDO-MEDINA, T.B., et al. 2008. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLos Medicine. 5:e45.

KISICKI, M. and C, VARLEY, C., 2013. Commentary on Relative effectiveness of antidepressants and psychological therapies for depression in children and adolescents unclear. Evidence-based Mental Health. Feb, DOI: 10.1136/eb-2012-101192.

KNOTTNERUS, J. A. and TUGWELL, P., 2012. The evidence base of taming continuously proliferating evidence. Journal of Clinical Epidemiology, 65, 1241-2.

KNOTTNERUS, A., and TUGWELL, P., 2013. Tailoring research to stakeholders, Journal of Clinical Epidemiology, 66, 583e 584.

KNOTTNERUS, A., and TUGWELL, P., 2013b. Heterogeneity and clinical reality. Journal of Clinical Epidemiology, 66, 809-11.

KNOTTNERUS, A., TUGWELL, P. and MCGOWEN, J., 2013. 'World series' to strengthen evidence-based medicine. Journal of Clinical Epidemiology, 66, 119-120.

KOESTERS, M., GUAIANA, G., CIPRIANI, A., BECKER, T., BARBUI, C. 2013. Agomelatine efficacy and acceptability revisited: systematic review and meta-analysis of published and unpublished trials. The British Journal of Psychiatry, 203, 179-187. doi: 10.1192/bjp.bp.112.120196.

KOTZ, D. AND CALS, JW. 2013. Effective writing and publishing scientific papers, part IV: methods. Journal of Clinical Epidemiology. 66(8):817. doi: 10.1016/j.jclinepi.2013.01.003. Epub 2013 Feb 19. PMID: 23434330.

KOVACS, M., RUSH, A. J., BECK, A. T. and HOLLON, S. D., 1981. Depressed outpatients treated with cognitive therapy or pharmacotherapy. A one-year follow-up. Archives of General Psychiatry, 38, 33-9.

KULIER, R., COPPUS, S. F., ZAMORA, J., HADLEY, J., MALICK, S., DAS, K., WEINBRENNER, S., 2009. The effectiveness of a clinically integrated e-learning course in evidence-based medicine: a cluster randomised controlled trial. BMC Medical Education, 9, 21.

KULIER, R., GÜLMEZOGLU, A. M., ZAMORA, J., PLANA, M. N., CARROLI, G., CECATTI, J. G., GERMAR, M. J. et al. 2012. Effectiveness of a clinically integrated e-learning course in evidence-based medicine for reproductive health training: a randomized trial. Journal of the American Medical Association, 308, 2218-25.

KULIER, R., HADLEY, J., WEINBRENNER, S., MEYERROSE, B., DECSI, T., HORVATH, A. R., NAGY, E., et al., 2008. Harmonising evidence-based medicine teaching: a study of the outcomes of e-learning in five European countries. BMC Medical Education, 8, 27.

KÜMPERS, S., MUR, I., HARDY, B., MAARSE, H. & VAN RAAK, A., 2006. The importance of knowledge transfer between specialist and generic services in improving health care: a cross-national study of dementia care in England and The Netherlands. International Journal of Health Planning and Management, 21, 151-67.

KUO, KN., CHIU, YW, WENG, YH, LO, HL, HSU CC, SHIH, YH. 2012. Dissemination of systematic reviews in a hospital setting: a comparative survey for diffusing The Cochrane Library. First International Conference on Evidence-based Healthcare. 6-8 October, 2012. New Delhi, India: ISEHCON2012,

LAI, N. M., TENG, C. L. & LEE, M. L., 2011. Interpreting systematic reviews: are we ready to make our own conclusions? A cross-sectional study. BMC Medicine, 9, 30.

LAMERS, F., BURSTEIN, M., HE, J. P., AVENEVOLI, S., ANGST, J. & MERIKANGAS, K. R., 2012. Structure of major depressive disorder in adolescents and adults in the US general population. British Journal of Psychiatry, 201, 143-50.

LANG, T. and SECIC, M., 2006. How to Report Statistics in Medicine, Philadelphia, American College of Physicians.

LANG, E., WEIR, P, and HAYNES, B. 2007. Knowledge translation; closing the evidence to practice gap. Annals of Emergency Medicine. 49(3). 355-363.

LATIMER, A. E., BRAWLEY, L. R. & BASSETT, R. L., 2010. A systematic review of three approaches for constructing physical activity messages: What messages work and what improvements are needed? The International Journal of Behavioural Nutrition and Physical Activity, 7, 36.

LAVIS, J., DAVIES, H., OXMAN, A., DENIS, J. L., GOLDEN-BIDDLE, K. and FERLIE, E., 2005. Towards systematic reviews that inform health care management and policy-making. Journal of Health Services Research and Policy, 10 Suppl 1, 35-48.

LAVIS, J. N., 2006. Research, public policymaking, and knowledge-translation processes: Canadian efforts to build bridges. Journal of Continuing Education in the Health Professions, 26, 37-45.

LAVIS, J. N., DAVIES, H. T., GRUEN, R. L., WALSHE, K. & FARQUHAR, C. M., 2006. Working within and beyond the Cochrane Collaboration to make systematic reviews more useful to healthcare managers and policy makers. Health Policy, 1, 21-33.

LAWRENCE, V., FOSSEY, J., BALLARD, C., MONIZ-COOK, E. & MURRAY, J., 2012. Improving quality of life for people with dementia in care homes: making psychosocial interventions work. British Journal of Psychiatry, 201, 344-51.

LAWRIE, S. M., SCOTT, A. I. & SHARPE, M. C., 2000. Evidence-based psychiatry--do psychiatrists want it and can they do it? Health Bulletin (Edinb), 58, 25-33.

LAWRIE, S. M., SCOTT, A. I. & SHARPE, M. C., 2001. Implementing evidence-based psychiatry: whose responsibility? British Journal of Psychiatry, 178, 195-6.

LEFEBVRE, C., MANHEIMER, E. and GLANVILLE, J., 2008. Searching for studies. In: Higgins JPT. & Green S. eds., Cochrane Handbook of Systematic Reviews of Interventions. Chichester (UK): John Wiley and Sons.

LERNER, F. and HAMBLEM J., 2013. Methodology and reporting of systematic reviews and meta-analyses. British Journal of Psychiatry, 202, 75-6.

LEUCHT, S., HIERL, S., KISSLING, W., DOLD, M. & DAVIS, J. M., 2012. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. British Journal of Psychiatry, 200, 97-106.

LEWIS, C., PEARCE, J. and BISSON, J. I., 2012. Efficacy, cost-effectiveness and acceptability of self-help interventions for anxiety disorders: systematic review. British Journal of Psychiatry, 200, 15-21.

LEWIS, G., 1997. Closing the gap between research and practice. New evidence is required. British Journal of Psychiatry, 171, 227.

LI, C. T., BAI, Y. M., HUANG, Y. L., CHEN, Y. S., CHEN, T. J., CHENG, J. Y. and SU, T. P., 2012. Association between antidepressant resistance in unipolar depression and subsequent bipolar disorder: cohort study. British Journal of Psychiatry, 200, 45-51.

LIBERATI, A., ALTMAN, D. G., TETZLAFF, J., MULROW, C., GØTZSCHE, P. C., IOANNIDIS, J. P., CLARKE, M. et al., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. British Medical Journal, 339, b2700.

LÉGARÉ, F., RATTÉ, S., GRAVEL, K. & GRAHAM, I. D., 2008. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Education and Counselling, 73, 526-35.

LÉGARÉ, F., RATTÉ, S., STACEY, D., KRYWORUCHKO, J., GRAVEL, K., GRAHAM, I. D. and TURCOTTE, S., 2010. Interventions for improving the adoption of shared decision making by healthcare professionals. Cochrane Database Systematic Reviews, CD006732.

LOMAS, J., ANDERSON, G. M., DOMNICK-PIERRE, K., VAYDA, E., ENKIN, M. W. & HANNAH, W. J., 1989. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. New England Journal of Medicine, 321, 1306-11.

LOMAS, J., 1991. Words without Action? The Production, Dissemination, and Impact of Consensus Recommendations. Annual Review of Public Health. 12: 41-65. DOI: 10.1146/annurev.pu.12.050191.000353.

MACLEHOSE, H., and HILTON, J., 2013. Changes to the Cochrane Library during The Cochrane Collaboration's first 20 years. Cochrane Database of Systematic Reviews. Jan 31. ED000050.

MAJUMDAR, S. R., 2011. Successful high-quality knowledge translation research: three case studies. Journal of Clinical Epidemiology, 64, 21-24.

MAJUMDAR, S. R., MCALISTER, F. A. and FURBERG, C. D., 2004. From knowledge to practice in chronic cardiovascular disease: a long and winding road. Journal of the American College of Cardiology, 43, 1738-42.

MANHEIMER, E. & ANDERSON, D., 2002. Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility. British Medical Journal, 325, 528-31.

MARKKULA, N., HÄRKÄNEN, T., PERÄLÄ, J., PARTTI, K., PEÑA, S., KOSKINEN, S., LÖNNQVIST, J., et al., 2012. Mortality in people with depressive, anxiety and alcohol use disorders in Finland. British Journal of Psychiatry, 200, 143-9.

MARKOWITZ, J. C., 2008. When should psychotherapy be the treatment of choice for major depressive disorder? Current Psychiatry Reports, 10, 452-7.

MARTIS, R., HO, J. J., CROWTHER, C. A. and GROUP, S., 2008. Survey of knowledge and perception on the access to evidence-based practice and clinical practice change among maternal and infant health practitioners in South East Asia. BMC Pregnancy Childbirth, 8, 34.

MATSON, J., 2013. Narrative overview of systematic reviews and meta-analyses: evidence on many treatments for psychopathology in people with developmental disabilities is limited. Evidence Based Mental Health, 16, 44.

MAYER, J. & PITERMAN, L., 1999. The attitudes of Australian GPs to evidence-based medicine: a focus group study. Family Practice, 16, 627-32.

MAYS, N., ROBERTS, E. and POPAY, J. 2001. Synthesising research evidence. In. FULOP, N., ALLEN, P., CLARKE, A., and BLACK, N., eds., Studying the Organisation and Delivery of Health Services: Research Methods. London: Routledge, 88-220.

MACALISTER, F. A., GRAHAM, I., KARR, G. W. & LAUPACIS, A., 1999. Evidence-based medicine and the practicing clinician. Journal of General Internal Medicine, 14, 236-42.

MCALLISTER-WILLIAMS, R. H. 2008a. Do antidepressants work? A commentary on "Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration" by Kirsch et al., Evidence Based Mental Health, 11, 66-8.

MCALLISTER-WILLIAMS, R. H., 2008b. Misinterpretation of randomized trial evidence: do antidepressants work? British Journal of Hospital Medicine (London), 69, 246-7.

MCCAW, B., MCGLADE, K. & MCELNAY, J., 2007. The impact of the internet on the practice of general practitioners and community pharmacists in Northern Ireland. Informing Primary Care, 15, 231-7.

MCCOLL, A., SMITH, H., WHITE, P. and FIELD, J. 1998. General practitioner's perceptions of the route to evidence based medicine: a questionnaire survey. British Medical Journal, 316, 361-5.

MCGLYNN, E. A., ASCH, S. M., ADAMS, J., KEESEY, J., HICKS, J., DECRISTOFARO, A. & KERR, E. A., 2003. The quality of health care delivered to adults in the United States. New England Journal of Medicine, 348, 2635-45.

MCGORRY, P., 2013. Prevention, innovation and implementation science in mental health: the next wave of reform. British Journal of Psychiatry Supplement, 54, s3-4.

MCGORRY, P., BATES, T. & BIRCHWOOD, M., 2013. Designing youth mental health services for the 21st century: examples from Australia, Ireland and the UK. British Journal of Psychiatry Supplement, 54, s30-5.

MCLEAN, P. D. and HAKSTIAN, A. R., 1979. Clinical depression: comparative efficacy of outpatient treatments. Journal of Consulting and Clinical Psychology, 47, 818-36.

MEATS, E., HENEGHAN, C., CRILLY, M. & GLASZIOU, P., 2009. Evidence-based medicine teaching in UK medical schools. Medical Teacher, 31, 332-7.

MELNYK, B. M., FINEOUT-OVERHOLT, E., FEINSTEIN, N. F., SADLER, L. S. and GREEN-HERNANDEZ, C., 2008. Nurse practitioner educators' perceived knowledge, beliefs, and teaching strategies regarding evidence-based practice: implications for accelerating the integration of evidence-based practice into graduate programs. Journal of Professional Nursing, 24, 7-13.

MELNYK, B. M., FINEOUT-OVERHOLT, E., FISCHBECK FEINSTEIN, N., LI, H., SMALL, L., WILCOX, L. and KRAUS, R., 2004. Nurses' perceived knowledge, beliefs, skills, and needs regarding evidence-based practice: implications for accelerating the paradigm shift. Worldviews Evidence-Based Nursing, 1, 185-93.

MEYER, A. and GOES, J. 1988. Organisational assimilation of innovations: A multi-level contextual analysis. The Academy of Management Journal, 31, 4, 897-923. doi: 10.2307/256344

MICHIE, S., 2013. Translating evidence to policy and practice: the role of behavioural science. CEBM lecture delivered at Kellogg College, Oxford. 6 June.

MILLS, E. J., THORLUND, K. and IOANNIDIS, J. P. A., 2012. Calculating additive treatment effects from multiple randomized trials provides useful estimates of combination therapies. Journal of Clinical Epidemiology, 65, 1282-8.

MITCHELL, A. J., LORD, O. & MALONE, D., 2012a. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. British Journal of Psychiatry, 201, 435-43.

MITCHELL, A. J., MEADER, N., BIRD, V. & RIZZO, M., 2012b. Clinical recognition and recording of alcohol disorders by clinicians in primary and secondary care: meta-analysis. British Journal of Psychiatry, 201, 93-100.

MOHER, D., COOK, D. J., EASTWOOD, S., OLKIN, I., RENNIE, D. and STROUP, D. F., 1999. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet, 354, 1896-900.

MOHER, D., LIBERATI, A., TETZLAFF, J., ALTMAN, D. G. and GROUP, P. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology, 62, 1006-12.

MORRISON, AP., FRENCH, P., STEWART, S. L., 2013. Cognitive therapy may reduce psychotic symptom severity but not risk of transition to psychosis in young people at risk. Evidence-based Mental Health, May 21. doi: 10.1136/eb 2012 100808.

MULROW, C. D., 1987. The medical review article: state of the science. Annals of Internal Medicine, 106, 485-8.

MURPHY, E, SIMONS, A., N. WETZEL, R., LUSTMAN, P., 1984, Cognitive therapy and pharmacology. Archives of General Psychiatry, 41, 33-41.

MURPHY, G. E., CARNEY, R. M., KNESEVICH, M. A., WETZEL, R. D. & WHITWORTH, P. 1995. Cognitive-behaviour therapy, relaxation training, and tricyclic

antidepressant medication in the treatment of depression. Psychological Reports, 77, 403-20.

MURRAY, R. 2011. How to write a thesis. UK, OUP. ISBN-13: 978-0-33-524428-7.

MURRAY, C. J., VOS, T., LOZANO, R., NAGHAVI, M., FLAXMAN, A. D., MICHAUD, C., EZZATI, M. et al., 2013. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 380, 2197-223.

MURTHY, L., SHEPPERD, S., CLARKE, M. J., GARNER, S. E., LAVIS, J. N., PERRIER, L., ROBERTS, N. W. and STRAUS, S. E., 2012. Interventions to improve the use of systematic reviews in decision-making by health system managers, policy makers and clinicians. Cochrane Database Systematic Reviews, 9, CD009401.

MÖLLER, H. J., 2008. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. World Journal of Biological Psychiatry, 9, 102-14.

NABULSI, M., HARRIS, J., LETELIER, L., RAMOS, K., HOPAYIAN, K., PARKIN, C., PORZSOLT, F. et al., 2007. Effectiveness of education in evidence-based healthcare: the current state of outcome assessments and a framework for future evaluations. International Journal of Evidence-Based Healthcare, 5, 468-76.

NARDELLA, A., PECHET, L. and SNYDER, L. M., 1995. Continuous improvement, quality control, and cost containment in clinical laboratory testing. Effects of establishing and implementing guidelines for preoperative tests. Archives of Pathology and Laboratory Medicine, 119, 518-22.

NASSER, M., WELCH, V., TUGWELL, P., UEFFING, E., DOYLE, J. & WATERS, E., 2012. Ensuring relevance for Cochrane reviews: evaluating processes and methods for prioritizing topics for Cochrane reviews. Journal of Clinical Epidemiology, 66(5):474-82. doi: 10.1016/j.jclinepi.2012.01.001. Epub 2012 Apr 20.

NICE Guideline for the treatment and management of depression in adults. 2010. UK: The British Psychological Society and the Royal College of Psychiatrists. ISBN: 978-1-904671-85-5

NOYES, J., POPAY, J., PEARSON, A, HANNES, K., BOOTH, A. 2008. Qualitative research and Cochrane Reviews. In: eds., HIGGINS, JP AND GREEN, S., Cochrane Handbook of Systematic Reviews of Interventions. Chichester UK: John Wiley and Sons.

O'CAITHAIN, A, THOMAS, KJ, DRABBLE, SJ, RUDOLPH, A, HEWISON, J., 2013. What can qualitative research do for randomized controlled trials? A systematic mapping review. BMJOpen, 3:e002889 doi: 10.1136/bmjopen-2013-002889.

O'CONNOR, D., GREEN, S., HIGGINS, J., 2008. Defining the review question and developing criteria for including studies. In: HIGGINS, J. & GREEN, S. P. (eds) Cochrane handbook for systematic reviews of interventions, Oxford: Wiley-Blackwell.

OERMANN, M. H., ROOP, J. C., NORDSTROM, C. K., GALVIN, E. A. & FLOYD, J. A., 2007. Effectiveness of an intervention for disseminating Cochrane reviews to nurses. Medsurg Nursing Journal, 16, 373-7.

OERMANN, M. H., ROOP, J. C., NORDSTROM, C. K., GALVIN, E. A. & FLOYD, J. A., 2009. Effectiveness of an intervention for disseminating Cochrane Reviews to nurses. Urology Nursing, 29, 35-9, 54.

OGILVIE, D., FAYTER, D., PETTICREW, M., SOWDEN, A., THOMAS, S., WHITEHEAD, M. and WORTHY, G., 2008. The harvest plot: a method for synthesising evidence about the differential effects of interventions. BMC Medical Research Methodology, 8, 8.

OLATUNBOSUN, O. A., EDOUARD, L. & PIERSON, R. A., 1998. Physicians' attitudes toward evidence based obstetric practice: a questionnaire survey. British Medical Journal, 316, 365-6.

OLFSON, M., MARCUS, S. C., DRUSS, B. and PINCUS, H. A. 2002. National trends in the use of outpatient psychotherapy. American Journal of Psychiatry, 159, 1914-20.

OLIVER, S., HARDEN, A., REES, R., SHEPHERD, J., BRUNTON, G. and OAKLEY, A., 2008. Young people and mental health: novel methods for systematic review of research on barriers and facilitators. Health Education Research, 23, 770-90.

OLIVER, S., HARDEN, A., REES, R., SHEPHERD, J., BRUNTON, G. and OAKLEY, A., 2005. An emerging framework for including different types of evidence in systematic reviews for public policy. Evaluation, 11 (4): 428-46.

OXMAN, A. D. and GUYATT, G. H., 1988. Guidelines for reading literature reviews. Canadian Medical Association Journal, 138, 697-703.

OXMAN, A. D., LAVIS, J. N. and FRETHEIM, A. 2007. Use of evidence in WHO recommendations. Lancet, 369, 1883-9.

OXMAN, A. D., THOMSON, M. A., DAVIS, D. A. and HAYNES, R. B., 1995. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. Canadian Medical Association Journal, 153, 1423-31.

PAMPALLONA, S., BOLLINI, P., TIBALDI, G., KUPELNICK, B. and MUNIZZA, C., 2004. Combined pharmacotherapy and psychological treatment for depression: a systematic review. Archives of General Psychiatry, 61, 714-9.

PARKER, G., PARKER, K., AUSTIN, M. P., MITCHELL, P. and BROTCHIE, H., 2003. Gender differences in response to differing antidepressant drug classes: two negative studies. Psychological Medicine, 33, 1473-7.

PATERINI, S. AND BISSERBE, JC., 2013. Pharmacotherapy for bipolar disorder and concordance with treatment guidelines: survey of a general population sample referred to a tertiary care service. BMC Psychiatry, 13:211 doi:10.1186/1471-244X-13-211

PATERSON-BROWN, S., FISK, N. M. and WYATT, J. C., 1995. Uptake of meta-analytical overviews of effective care in English obstetric units. British Journal of Obstetrics and Gynaecology, 102, 297-301.

PATERSON-BROWN, S., WYATT, J. C. & FISK, N. M., 1993. Are clinicians interested in up to date reviews of effective care? British Medical Journal, 307, 464.

PATHMAN, D. E., KONRAD, T. R., FREED, G. L., FREEMAN, V. A. & KOCH, G. G., 1996. The awareness-to-adherence model of the steps to clinical guideline compliance. The case of paediatric vaccine recommendations. Medical Care, 34, 873-89.

PEILE, E., 2013. Commentary on Evidence-based medicine and values based medicine: partners in clinical education as well as in clinical practice. BMCMedicine [Online], 11.

PETRIE, A. and SABIN, C., 2005. Medical Statistics at a Glance, 3rd Edition. UK, Wiley-Blackwell. ISBN: 978-1-4051-8051-1.

PERRIER, L., MRKLAS, K., LAVIS, J. N. & STRAUS, S. E., 2011a. Interventions encouraging the use of systematic reviews by health policymakers and managers: A systematic review. Implement Science, 6, 43.

PERRIER, L., MRKLAS, K., SHEPPERD, S., DOBBINS, M., MCKIBBON, K. A. and STRAUS, S. E., 2011b. Interventions encouraging the use of systematic reviews in clinical decision-making: a systematic review. Journal General Internal Medicine, 26, 419-26.

PETTICREW, M. 2011. When are complex interventions 'complex'? When are simple interventions 'simple'? European Journal of Public Health. 21, 4, 397-399.

PETTICREW, M., WHITEHEAD, M., MACINTYRE, S. J., GRAHAM, H. & EGAN, M. 2004. Evidence for public health policy on inequalities: 1: the reality according to policymakers. Journal of Epidemiology and Community Health, 58, 811-6.

PIEPER, D., BUECHTER, R., JERINIC, P. & EIKERMANN, M. 2012. Overviews of reviews often have limited rigor: a systematic review. Journal of Clinical Epidemiology, 65, 1267-73.

PIMM, J. 2013. Scientific publishing, an unfair playing field. The Psychiatrist, 37, 9, 281-2.

PINQUART, M., DUBERSTEIN, P. R. & LYNESS, J. M., 2006. Treatments for later-life depressive conditions: a meta-analytic comparison of pharmacotherapy and psychotherapy. American Journal of Psychiatry, 163, 1493-501.

PO, A., L., W., 1998. Dictionary of evidence-based medicine. Oxford: Radcliffe Medical Press. ISBN 1 85775 305 4.

POOLMAN, R. W., SIEREVELT, I. N., FARROKHYAR, F., MAZEL, J. A., BLANKEVOORT, L. and BHANDARI, M., 2007. Perceptions and competence in evidence-based medicine: Are surgeons getting better? A questionnaire survey of members of the Dutch Orthopaedic Association. Journal of Bone and Joint Surgery American, 89, 206-15.

POPE, C., MAYS, N. and POPAY, J., 2007. Synthesizing Qualitative and Quantitative Health Evidence: a guide to methods, UK: Open University Press.

PRESCOTT, K., LLOYD, M., DOUGLAS, H. R., HAINES, A., HUMPHREY, C., ROSENTHAL, J. and WATT, I.., 1997. Promoting clinically effective practice: general practitioners' awareness of sources of research evidence. Family Practice, 14, 320-3.

PRETTI, D., FARLEY, A., LINDSON, N. & AVEYARD, P., 2013. Systematic review and meta-analysis on the influence of smoking cessation on incidence of pneumonia in HIV. BMC Medical, 11.

PROCHASKA, J.O., REDDING, C.A., & EVERS, K., 2002. The trans-theoretical model and stages of change. In K. Glanz, B.K. Rimer & F.M. Lewis, (Eds.) Health Behaviour and Health Education: Theory, Research, and Practice (3rd Ed.). San Francisco, CA: Jossey-Bass, Inc.

QASEEM, A., FORLAND, F., MACBETH, F., OLLENSCHLAGER, G., PHILLIPS, S., AND VAN DER WEES, P., 2012. Guidelines International Network: Towards international standards of clinical practice guidelines. Annals of Internal Medicine, 156, 7, 525-532.

RANSOHOFF, D, PIGONE, M, SOX, H., 2013. How to decide whether a clinical practice guideline is trustworthy. Journal of the American Medical Association, 309, 139-140.

REES, R., HARDEN, J., SHEPHERD, G., BRUNTON, S., OLIVER, OA., 2001. Young people and physical activity: a systematic review of barriers and facilitators. London:EPPI-Centre: Social Science Research Centre.

REES, R., KAVANAGH, J., HARDEN, A., SHEPHERD, J., BRUNTON, G., OLIVER, S. and OAKLEY, A., 2006. Young people and physical activity: a systematic review matching their views to effective interventions. Health Education Research, 21, 806-25.

ROGERS, E. M., 1995. Lessons for guidelines from the diffusion of innovations. The Joint Commission Journal on Quality Improvement, 21, 324-8.

ROSENBAUM, SE., GLENTON, C., CRACKNELL, J., 2008. User experiences of evidence-based online resources for health professionals: User testing of The Cochrane Library: user experience of online resources for health professionals. BMC Medical Informatics and Decision Making. 8:34 doi: 10.1186/1472-6947-8-3.

RUSH, J., BECK, AT, KOVAC M, HOLLON, S., 1977. Comparative efficacy of cognitive therapy and pharmacotherapy in the treatment of depressed outpatients. Cognitive Therapy and Research, 1, 17-37.

RUSH, A. J., BECK, A. T., KOVACS, M., WEISSENBURGER, J. and HOLLON, S. D., 1982. Comparison of the effects of cognitive therapy and pharmacotherapy on hopelessness and self-concept. American Journal of Psychiatry, 139, 862-6.

RUSH, A. J., KOVACS, M., BECK, A. T., WEISSENBURGER, J. and HOLLON, S. D., 1981. Differential effects of cognitive therapy and pharmacotherapy on depressive symptoms. Journal of Affective Disorders, 3, 221-9.

RETHORST, CD. AND TRIVEDI, MH., 2013. Evidence-based recommendations for the prescription of exercise for major depressive disorder. Journal of Psychiatric Practice, 19(3):204-12. doi: 10.1097/01.pra.0000430504.16952.3e.

SACKETT, D. L., ROSENBERG, W. M., GRAY, J. A., HAYNES, R. B. and RICHARDSON, W. S., 2006. Evidence based medicine: what it is and what it isn't. 1996. Clinical Orthopaedics and Related Research, 455, 3-5.

SAVA, FA., YATES, BT., LUPA, V., SZENTAGOTAI, A., DAVID, D., 2009. Cost-Effectiveness and Cost-Utility of Cognitive Therapy, Rational Emotive Behavioral Therapy, and Fluoxetine (Prozac) in Treating Depression: A Randomized Clinical Trial. Journal of Clinical Psychology. 65(1):36-52.

SCHUNENEMANN, H., OXMANN, A., VIST, G., HIGGINS, J., DEEKS, J., GLASZIOU, P.M., GUYATT, G., 2008. Interpreting results and drawing conclusions. In: HIGGINS, J. & GREEN, S. P. eds., Cochrane handbook for systematic reviews of interventions, Oxford, Wiley-Blackwell.

SCOTT, A. I. and FREEMAN, C. P., 1992. Edinburgh primary care depression study: treatment outcome, patient satisfaction, and cost after 16 weeks. British Medical Journal, 304, 883-7.

SCHERER, RW., LANGENBERG, P., VON, EE., 2007. Full publication of results initially presented in abstracts. Cochrane Database of Systematic Reviews. 2, MR000005.

SHAMSAEI, F.; RAHIMI, A.; ZARABIAN, M. K.; SEDEHI, M., 2008. Efficacy of pharmacotherapy and cognitive therapy, alone and in combination in major depressive disorder. Hong Kong Journal of Psychiatry, Vol. 18, No. 2.

SHEA, B. J., 2011. A decade of knowledge translation research—what has changed? Journal of Clinical Epidemiology, 64, 3-5.

SHELDON, T. A., 2005. Making evidence synthesis more useful for management and policy-making. Journal of Health Service and Research Policy, 10 Suppl 1, 1-5.

SHELDON, T. A. and GILBODY, S. M., 1997. Rational decision-making in psychiatry: evidence-based psychiatry is just the start. British Journal of Psychiatry, 171, 226-7.

SHEPHERD, J, GARCIA, J, OLIVER, S, HARDEN, A, REES, R, BRUNTON, G, OAKLEY, A., 2002. Barriers to and Facilitators of the Health of Young People: A systematic review of evidence on young people's views and on interventions in mental health, physical activity and healthy eating. Volume 2: Complete Report. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London.

SHEPHERD, J, HARDEN, A, REES, R, BRUNTON, G, GARCIA, J, OLIVER, S, OAKLEY, A., 2006 Young people and healthy eating: a systematic review of research on barriers and facilitators. Health Education Research. 21(2):239-57. Epub 2005 Oct 26.

SILAGY, C. A., STEAD, L. F. and LANCASTER, T., 2001. Use of systematic reviews in clinical practice guidelines: case study of smoking cessation. British Medical Journal, 323, 833-6.

SILAGY, C. A., WELLER, D. P., MIDDLETON, P. F. and DOUST, J. A., 1999. General practitioners' use of evidence databases. Medical Journal of Australia, 170, 393.

SIMPSON, F. and DOIG, G. S., 2007. The relative effectiveness of practice change interventions in overcoming common barriers to change: a survey of 14 hospitals with experience implementing evidence-based guidelines. Journal of Evaluation and Clinical Practice, 13, 709-15.

SKAPETIS, T., GERINA, TM., HU, W., CAMERON, W., 2013. Effectiveness of a brief educational workshop intervention among primary care providers at 6 months: uptake of dental emergency supporting resources. Rural and Remote Health 13: 2286. Online. Available: http://www.rrh.org.au

SPIEGELHALTER, DJ. and BEST, NG., 2003. Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. Statistics in Medicine. 22:3687-3709.

SPITZER, R.L., ENDICOTT, J., ROBINS, E., 1978. Research Diagnostic Criteria: rationale and reliability. Archive of General Psychiatry. 35: 773-782.

STAHL, S., 2008. Stahl's Essential Psychopharmacology, Cambridge: Cambridge University Press.

STEARNE, JAC., EGGER, M., MOHER, D., 2008. Addressing reporting biases. In: HIGGINS, JPT. and GREEN, S. eds., Cochrane Handbook of Systematic Reviews of interventions. Chichester (UK): John Wiley and Sons.

STEINBRUECK, S. M., MAXWELL, S. E. and HOWARD, G. S., 1983. A meta-analysis of psychotherapy and drug therapy in the treatment of unipolar depression with adults. Journal of Consulting and Clinical Psychology, 51, 856-63.

STEINMAN, M. A., RANJI, S. R., SHOJANIA, K. G. and GONZALES, R., 2006. Improving antibiotic selection: a systematic review and quantitative analysis of quality improvement strategies. Medical Care, 44, 617-28.

STELLEFSON. M., HANIK, B., CHANEY, B., CHANEY, J., 2008. Challenges for tailored messaging in health education. American Journal of Health Education, 39, 303-311.

STEWART, L., 2013. Systematic reviews as building blocks of evidence based healthcare: increasing access to trial data and systematic reviews of individual participant data. In: HENEGHAN, C. & GODLEE, F. eds. EvidenceLive2013, 25-26 March. Oxford, UK.

STRAUS, S., TETRO, J., and GRAHAM, I., 2009a. Knowledge into action: what it is and what it isn't. In: STRAUS, S., TETRO, J. & GRAHAM, I. (eds.) Knowledge Translation in Health Care. Oxford: Blackwell Publishing.

STRAUS, S. E., TETROE, J. and GRAHAM, I. D., 2009b. Knowledge translation in health care: moving from evidence to practice. Chichester: Wiley-Blackwell.

STRAUS, S. E., TETROE, J. M. and GRAHAM, I. D., 2011. Knowledge translation is the use of knowledge in health care decision making. Journal of Clinical Epidemiology, 64, 6-10.

STRETCH, D., MERTZ, M., KNUPPEL, H., NEITZKE, G., SCHMIDHUBER, M., 2013. The full spectrum of ethical issues in dementia care: systematic qualitative review. The British Journal of Psychiatry, 202: 400-6. doi: 10.1192/bjp.bp.112.116335

STURMEY, P., 2012. Treatment of psychopathology in people with intellectual and other disabilities. Canadian Journal of Psychiatry, 57, 593-600.

SUAREZ-ALMAZOR, M. E., BELSECK, E., HOMIK, J., DORGAN, M. and RAMOS-REMUS, C., 2000. Identifying clinical trials in the medical literature with electronic databases: MEDLINE alone is not enough. Control Clinical Trials, 21, 476-87.

SUR, R. L., SCALES, C. D., PREMINGER, G. M. & DAHM, P., 2006. Evidence-based medicine: a survey of American Urological Association members. Journal of Urology, 176, 1127-34.

SWALES, J. and FEAK, C., 2009. Abstracts and the Writing of Abstracts, USA: The University of Michigan Press.

TETZLAFF, J., TETRO, J., GRASHAM, ID., 2009. Knowledge Synthesis. In: STRAUS, S., TETRO, J. and GRAHAM, I. eds., Knowledge Translation in Health Care. UK: BMJ Books.

THASE, M. E., FRIEDMAN, E. S., BIGGS, M. M., WISNIEWSKI, S. R., TRIVEDI, M. H., LUTHER, J. F., FAVA, M., 2007. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. American Journal of Psychiatry, 164, 739-52.

THASE, M. E., GREENHOUSE, J. B., FRANK, E., REYNOLDS, C. F., PILKONIS, P. A., HURLEY, K., GROCHOCINSKI, V. and KUPFER, D. J., 1997. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Archives of General Psychiatry, 54, 1009-15.

THOMAS, J., HARDEN, A., OAKLEY, A., OLIVER, S., SUTCLIFFE, K., REES, R., BRUNTON, G. and KAVANAGH, J., 2004. Integrating qualitative research with trials in systematic reviews. British Medical Journal, 328, 1010-2.

THORNLEY, B. and ADAMS, C., 1998. Content and quality of 2000 controlled trials in schizophrenia over 50 years. British Medical Journal, 317, 1181-4.

TIERNEY, JF. and STEWART, LA., 2005. Investigating patient exclusion bias in meta-analysis. International Journal of Epidemiology. 34: 79-87.

TONES, B. K. and TILFORD, S., 1994. Health Promotion: Effectiveness, Efficiency and Equity. London: Chapman & Hall.

TRAMÈR, M. R., REYNOLDS, D. J., MOORE, R. A. and MCQUAY, H. J., 1997. Impact of covert duplicate publication on meta-analysis: a case study. British Medical Journal, 315, 635-40.

TREADWELL, J. R., SINGH, S., TALATI, R., MCPHEETERS, M. L. and RESTON, J. T., 2012. A framework for best evidence approaches can improve the transparency of systematic reviews. Journal of Clinical Epidemiology, 65, 1159-1162.

TRICCO, A. C., STRAUS, S. E. and MOHER, D., 2011a. How can we improve the interpretation of systematic reviews? BMC Medicine, 9, 31.

TRICCO, A. C., TETZLAFF, J. and MOHER, D., 2011b. The art and science of knowledge synthesis. Journal of Clinical Epidemiology, 64, 11-20.

TRICCO, AC., COGO, E., ASHOOR, H., PERRIER, L., MCKIBBON, KA. GRIMSHAW, JM., STRAUS, SE., 2013. Sustainability of knowledge translation interventions in healthcare decision-making: protocol for a scoping review. BMJ Open. 14; 3(5). pii: e002970. doi: 10.1136/bmjopen-2013-002970.

TSAFNAT, G., DUNN. A, GLASZIOU, P., COIER, E., 2013. The automation of systematic reviews. British Medical Journal, 346:f139.

TUGWELL, P., KNOTTNERUS, A. and IDZERDA, L., 2012. What is ‘best evidence’? Journal of Clinical Epidemiology, 65, 1131-2.

TUGWELL, P., KNOTTNERUS, J. A. and IDZERDA, L., 2011. Definitions and framework for knowledge translation to continue to evolve. Journal of Clinical Epidemiology, 64, 1-2.

TUGWELL, P., KNOTTNERUS, J. A. and IDZERDA, L., 2013. Clinical epidemiology is alive and well in India. Journal of Clinical Epidemiology, 66, 1-2.

TUGWELL, P., ROBINSON, V., GRIMSHAW, J. and SANTESSO, N., 2006. Systematic reviews and knowledge translation. Bulletin World Health Organisation, 84, 643-51.

TYRER, P., 2008. So careless of the single trial. Evidence-Based Mental Health, 11, 65-6.

VAN OORT, L., VAN DEN BERG, T., KOES, B. W., DE VET, R. H., ANEMA, H. J., HEYMANS, M. W. and VERHAGEN, A. P., 2012. Preliminary state of development of prediction models for primary care physical therapy: a systematic review. Journal of Clinical Epidemiology, 65, 1257-66.

VASUDUV, K. and VASUDUV, A., 2013. Commentary on Review: Prescribing rates of drugs for medical conditions are lower in people with mental illness. Evidence-Based Mental health [Online]. Feb 20. doi: 10.1136/EB-2012-101212.

VOLMINK, J., SIEGFRIED, N., ROBERTSON, K. and GÜLMEZOGLU, A. M., 2004. Research synthesis and dissemination as a bridge to knowledge management: the Cochrane Collaboration. Bulletin of the World Health Organisation, 82, 778-83.

WAGNER, J., 2005. A meta-analysis/literature review comparing the effectiveness of SSRIs, CBT and placebo for the treatment of depression. Dissertation Abstracts International: Section B: The Sciences and Engineering, 66.

WAGNER, E. H., BENNETT, S. M., AUSTIN, B. T., GREENE, S. M., SCHAEFER, J. K. and VONKORFF, M., 2005. Finding common ground: patient-centeredness and evidence-based chronic illness care. Journal of Alternative and Complementary Medicine, 11, Suppl 1, S7-15.

WALLACE, J., 2011. The practice of evidence-based psychiatry today. Advances in Psychiatric Treatment, 17, 389-95.

WALLACE, J., 2012a. The Science of Searching. Irish Medical Journal, 105. 4.

WALLACE, J., 2012b. Understanding the science of synthesis. Advances in Psychiatric Treatment, 18: 102-8. doi: 10.1192/apt.bp.110.008672.

WALLACE, J., NWOSU, B. and CLARKE, M., 2012a. Barriers to the uptake of evidence from systematic reviews and meta-analyses: a systematic review of decision makers' perceptions. BMJ Open, DOI: bmjopen-2012-001220 [pii]. 10.1136/bmjopen-2012-001220. ISSN: 2044-6055.

WALLACE, J., BYRNE, C. and CLARKE, M., 2012b. Making evidence more wanted: a systematic review of facilitators to enhance the uptake of evidence from systematic reviews and meta-analyses. International Journal of Evidence-based Healthcare, 10, 338-46.

WALLACE, J., 2013. Lost in translation: Transferring knowledge from research to clinical practice. Advances in Psychiatric Treatment, 19, 250-8; doi:10.1192/apt.bp.112.010389.

WALLACE, J., BYRNE, C. and CLARKE, M., 2014b. Improving the uptake of systematic reviews: a systematic review of intervention effectiveness and relevance. BMJOpen;4:e005834. Doi:10.1136/bmjopen-2014-005834.

WALLACE, J., BYRNE, C., NWOSU, B. & CLARKE, M., 2014a Antidepressants, cognitive-behaviour therapy and combination treatment: a systematic review and meta-analysis. World Psychiatric Association Conference, Athens, 29 Nov- 2 Dec., 2012. In: SOLDATOS, C., RUIZ, P., DIKEOS, D. and RIBA, M. eds., Pluralism in psychiatry:

diverse approaches and converging goals. Bolonia: Medimond International Proceedings, p173-7.

WALLACE, J., SCHNEIDER, T. and MCGUFFIN, P., 2002. Genetics of Depression. In: GOTLIB, I. and HAMMEN, C. eds., Handbook of Depression. New York: Guilford Press.

WARD, E., KING, M., LLOYD, M., BOWER, P., SIBBALD, B., et al. 2000. Randomised controlled trial of non-directive counselling, cognitive-behaviour therapy, and usual general practitioner care for patients with depression. I: Clinical effectiveness. BMJ 2000; 321 doi: ttp://dx.doi.org/10.1136/bmj.321.7273.1383.

WEXLER, B. E. and CICCHETTI, D. V., 1992. The outpatient treatment of depression. Implications of outcome research for clinical practice. Journal of Nervous and Mental Disease, 180, 277-86.

WILES, N. J., MULLIGAN, J., PETERS, T. J., COWEN, P. J., MASON, V., NUTT, D., SHARP, D., et al., 2012. Severity of depression and response to antidepressants: GENPOD randomised controlled trial. British Journal of Psychiatry, 200, 130-6.

WILLIAMS, J. M. and KUYKEN, W., 2012. Mindfulness-based cognitive therapy: a promising new approach to preventing depressive relapse. British Journal of Psychiatry, 200, 359-60.

WILSON, P., WATT, I. & HARDMAN, P., 2001a. Survey of medical directors' views and use of the Cochrane Library. British Journal of Clinical Governance, 6, 34-39.

WILSON, P., DROOGAN, J., GLANVILLE, J., WATT, I. and HARDMAN, G., 2001b. Access to the evidence base from general practice: a survey of general practice staff in Northern and Yorkshire Region. Quality Health Care, 10, 83-9.

WILSON, P., GLANVILLE, J. and WATT, I., 2003. Access to the online evidence base in general practice: a survey of the Northern and Yorkshire Region. Health Information Library Journal, 20, 172-8.

WORLD HEALTH ORGANISATION, Accessed 26 Nov 2012. Global Burden of Disease Publications. http://www.who.int/healthinfo/global_burden_disease/publications/en/index.html.

WOOLF, S. H., 1993. Practice guidelines: a new reality in medicine. III. Impact on patient care. Archives of Internal Medicine, 153, 2646-55.

WONG, G., GREENHALGH, T., WESTHORP, G., BUCKINGHAM, J. and PAWSON, R. 2013. RAMESES publication standards: meta-narrative reviews. BMCMedicine [Online], 20, 11. DOI: 10.1186/1741-7015-11-20.

WYATT, J. C., PATERSON-BROWN, S., JOHANSON, R., ALTMAN, D. G., BRADBURN, M. J. and FISK, N. M., 1998. Randomised trial of educational visits to enhance use of systematic reviews in 25 obstetric units. British Medical Journal, 317, 1041-6.

YANG, Y., HAN, C., YOON, H-K., PAE, C-U., KIM, M-J., PARK, SY., AHN, J., 2013. Experiences and barriers to implementation of clinical practice guideline for depression in Korea. BMC Psychiatry, 13(150). Doi: 10.1186/1471-244X-13-150.

YAP, T. L. and DAVIS, L. S., 2008. Physical activity: the science of health promotion through tailored messages. Rehabilitation Nursing, 33, 55-62.

YAP, T. L., HEMMINGS, A. and DAVIS, L. S., 2009. The systematic development of a tailored e-mail intervention for health behaviour change toward increasing intentional physical activity. Western Journal of Nursing Research, 31, 330-46.

YOUNG, J. M. and WARD, J. E., 1999. General practitioners' use of evidence databases. Medical Journal of Australia, 170, 56-8.

YOUNG, J. M. and WARD, J. E., 2001. Evidence-based medicine in general practice: beliefs and barriers among Australian GPs. Journal of Evaluation and Clinical Practice, 7, 201-10.

YOUSEFI-NOORAIE, R., RASHIDIAN, A., NEDJAT, S., MAJDZADEH, R., MORTAZ-HEDJRI, S., ETEMADI, A. and SALMASIAN, H., 2009. Promoting development and use of systematic reviews in a developing country. Journal of Evaluation and Clinical Practice, 15, 1029-34.

ZOLFAGHARI, M., MOUSAVIFAR, S. A., PEDRAM, S. and HAGHANI, H., 2012. The impact of nurse short message services and telephone follow-ups on diabetic adherence: which one is more effective? Journal of Clinical Nursing, 21, 1922-31.

Appendix 1

Excluded studies from the antidepressants versus CBT systematic review

- Rush et al 1981. Looked at patterns of symptom change. Used crossed-lagged panel analysis. Not an aim to directly compare psychotherapy and medication
- Blackburn et al. 1981. Did not yield usable data from the outcome measures employed.
- Simons et al. 1984. Excluded as it is part of a wider study already included in SR 1: Murphy et al. 1984. Also it is excluded because it addressed a different research question, the process of change.
- DeRubis et al. 1990. It addresses a different research question: how symptom reduction is mediated. It is also part of the Hollon et al. 1992 study, already included in this review.
- Scott et al. 1992. Comparison with 'routine care' by general practitioners
- Scott et al. 1994. Comparison with 'routine care' by general practitioners
- de Jong-Meyer et al. 1996. This study excluded non-endogenous depression. The comparison was not with antidepressants but antidepressants and supportive counselling, not a true comparison.
- Dunner et al. 1996. Did not address unipolar depression
- de Hautinger et al. 1996. Non-endogenous depression was excluded. Combination treatment was evaluated against another combination treatment: antidepressants and supportive sessions. It was about outcome prediction and longitudinal analysis.
- Blackburn and Moore. 1997. This is essentially maintenance, rather than, an acute study, with a complex design and no first episode depressive episodes.
- Sotsky and Simmens, 1998. This study deals with atypical depression only. It deals with a subgroup from another study.
- Jarrett et al, 1999. Did not address unipolar depression

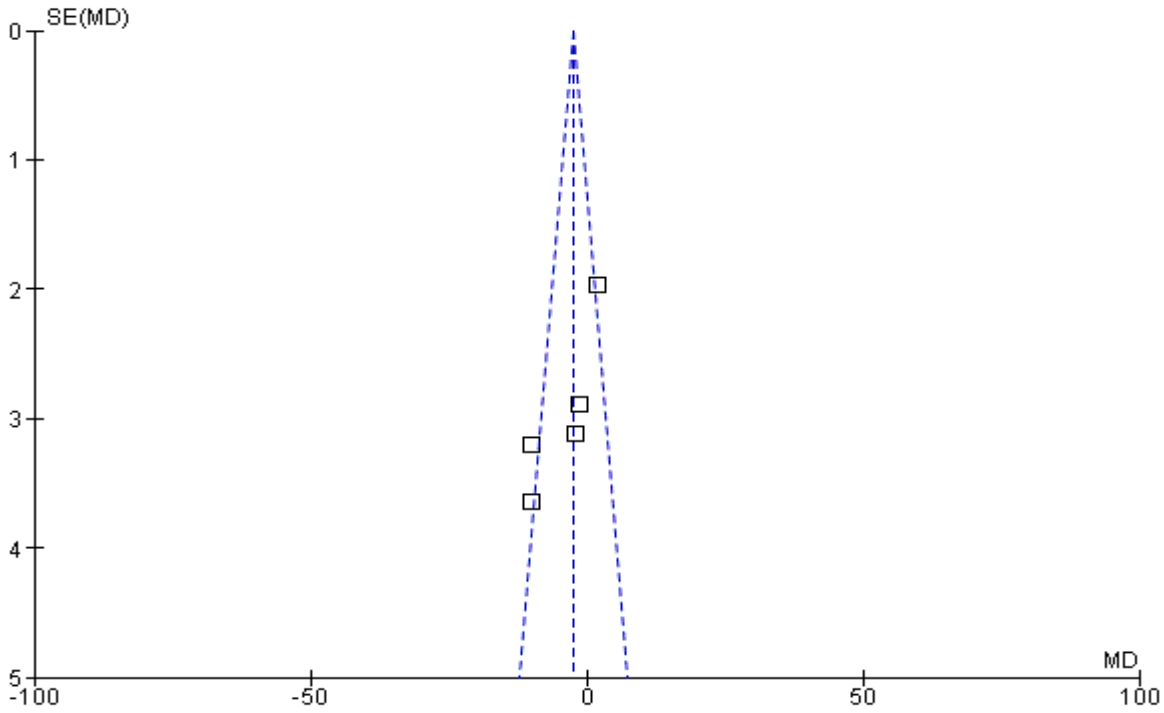
- Miller et al. 1999. Dealt with patients with ‘double depression’, who have a particularly chronic course.
- Thompson et al. 2001. Did not deal with the appropriate age group
- Keller et al. 2002. Not strictly cognitive therapy, poorly conceptualised
- Misri et al. 2005. Excluded as it deals exclusively with post-partum depression and co-morbid anxiety.
- DeRubeis et al. 2005. The intervention arm used antidepressants in some cases augmented with lithium or desipramine hydrochloride, not meeting our inclusion criteria.
- Dimidjian et al. 2006. Compared behavioural activation, cognitive therapy, and antidepressant medication, rather than CBT with combined cognitive and behavioural components, with antidepressants.
- Faramarzi et al. 2008. Subjects had a co-morbid medical condition

---

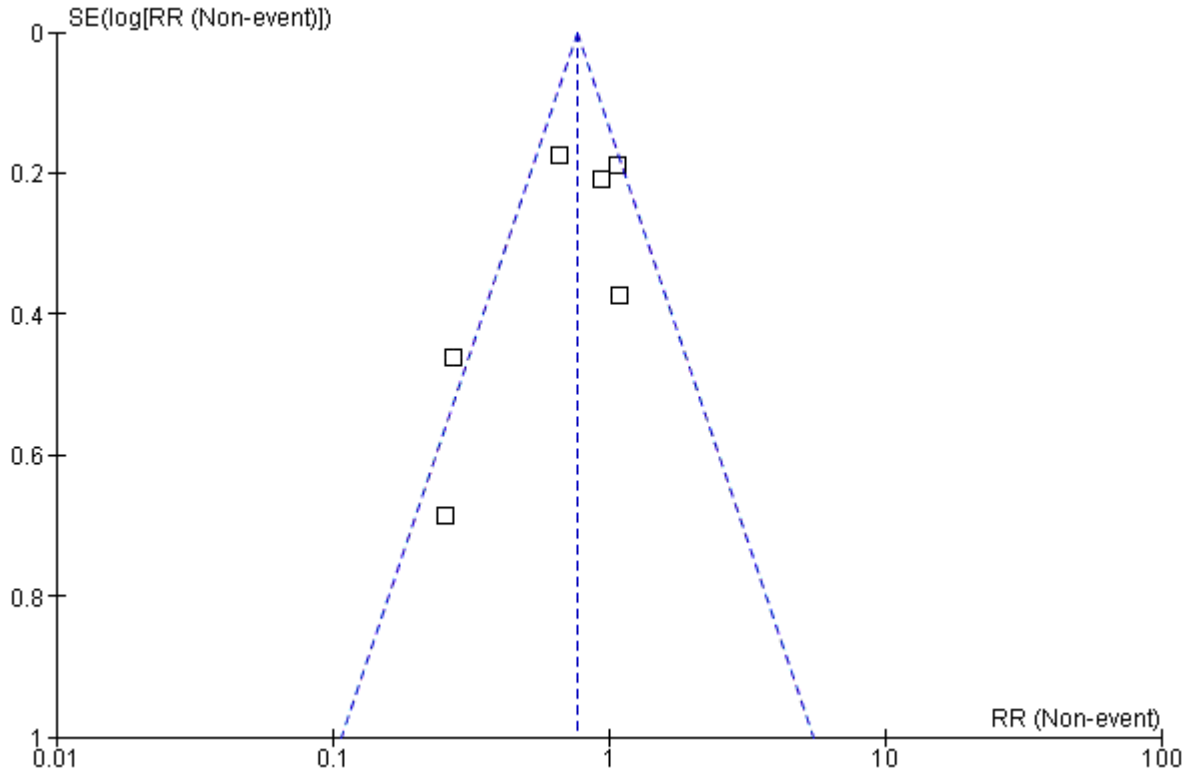
Appendix 2

Funnel plots

Funnel plot: CBT versus antidepressants, fixed-effect, BDI, continuous data

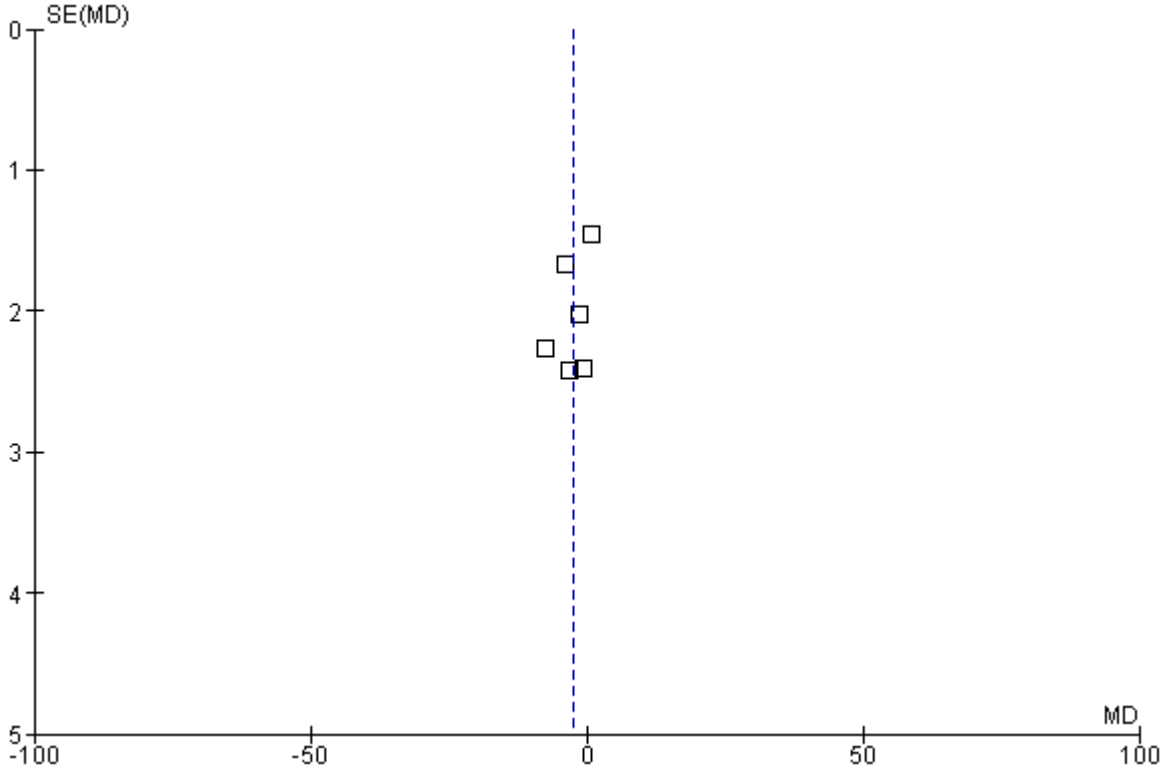


Funnel plot: CBT versus antidepressants, fixed-effect, BDI, dichotomous data



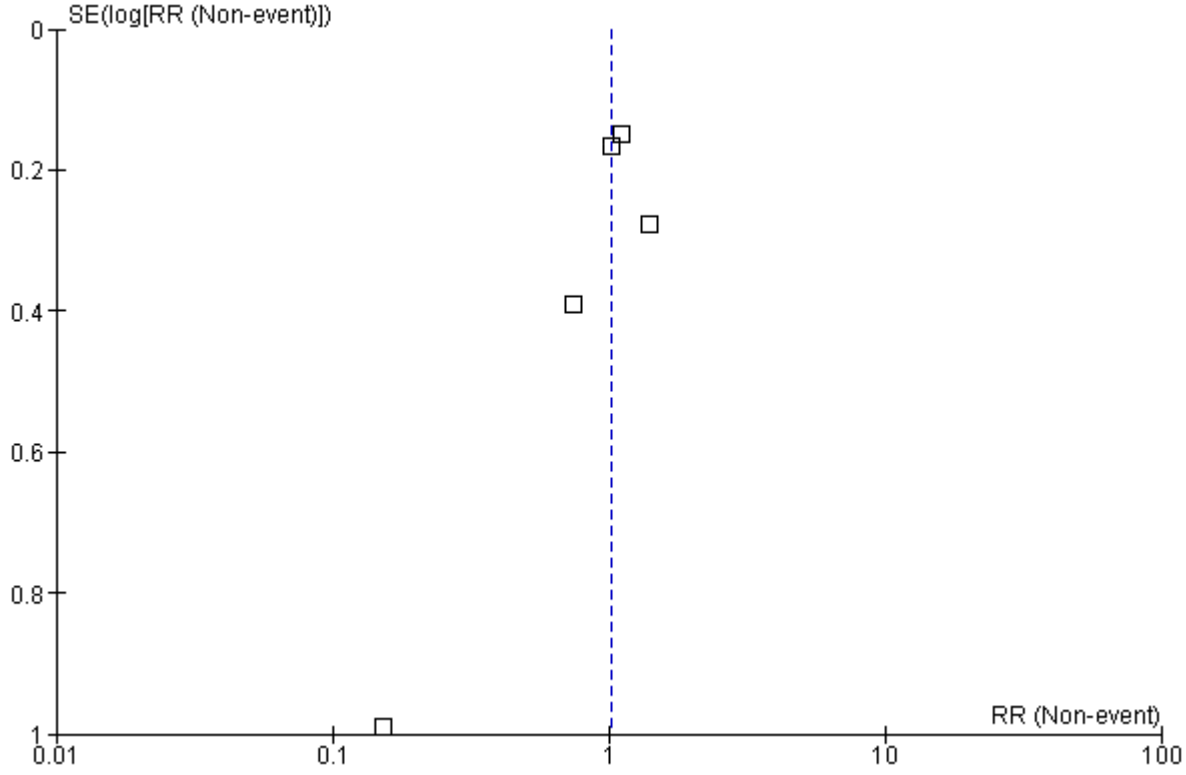
.

Funnel Plot: CBT versus antidepressants, fixed-effect, HDRS, continuous data



.

Funnel plot. CBT versus antidepressants, fixed-effect, HDRS, dichotomous data



Appendix 3

Excluded studies from systematic review of barriers to uptake of systematic reviews

Cranney and Walley. 1996. Not specifically about systematic reviews.

Glasziou et al. 1998. Not a survey, focus group or interview study, or an intervention.

Mayer et al. 1999. Does not address systematic reviews.

Silagy et al. 1999. A comment on previous studies.

Dobbins et al. 2002. Not a survey, focus group or interview study, or an intervention.

Petticrew et al. 2004. Not specifically related to systematic reviews.

Volmink et al. 2004. An essay. Not a survey, a focus group, an interview, or an intervention.

Sheldon. 2005. An essay, not a survey, focus group, or an interview, or an intervention.

Gruen et al. 2005. A letter/essay.

Lavis. 2006. Not a survey, focus group or interview, or an intervention.

Grimshaw et al. 2006. Not a survey, focus group or interview study, or an intervention.

Lavis et al. 2006. Not a survey, focus group or interview study, or an intervention.

Melnyk et al. 2008. Does not address systematic reviews.

Appendix 4

Appendix 4, adopted from Cabana et al. 1999, lists the studies investigating barriers specifically to uptake of systematic reviews, then meta-analyses, followed by the Cochrane Database of Systematic Reviews, The Cochrane Library, DARE, Cochrane Pregnancy and Childbirth Database, and the Oxford Database of Perinatal Trials. The number of respondents reporting the barrier is also listed

BARRIERS TO SYSTEMATIC REVIEWS	**STUDIES CITING BARRIER**
AWARENESS Lack of awareness of reviews	Ciliska et al. (1999) **104/242 (43%)** Jordans et al. (1997)**17/224 (7.5%)**
ACCESS Lack of access to systematic reviews	Jordans et al. (1997) **49/224 (21%)**
UNDERSTANDING (Familiarity) Lack of **full** understanding of systematic reviews (Did not understood and could not explain to others)	McColl et al. (1999) **223/288 (77%)** Poolman et al. (2007) **134/359(38%)** Young and Ward (2001) **49/60 (81%)**
USE Lack of use of systematic reviews	Jordans et al. (1998) **98/224 (44%)**
USEFULNESS Lack of usefulness of systematic reviews	McColl et al. (1998) **286/302 (95%)** Jordans et al. (1998) **170/ 225 (77%)** Young and Ward (2001) **8/60 (13%)** Ciliska et al. (1999) **86/242 (76.8%)**
POLICY CLIMATE	Ciliska et al. (1999) 1**69/242 (70%)**
RESOURCES	Ciliska et al. (1999) **188/242 (78%)**

BARRIERS TO META-ANALYSIS	**STUDIES CITING THE BARRIER**
ACCESS Lack of access to relevant meta-analysis	Paterson-Brown (1993) **36/98 (36.7%)**
TRUST Lack of trust of meta-analysis of RCTs:	Hanson et al. (2004) **101/532 (19%)**
TRAINING Lack of training in meta-analysis research, methodology:	Hanson et al. (2004) **484 /532 (91%)**
UNDERSTANDING Lack of understanding of meta- analysis	McColl et al (1999) **63/291 (22%)** Poolman et al. (2007) **144/362 (40%)**
No wish to understand meta-analysis	Sur et al. (2006) **11/714** (**2%)**. Poolman et al. (2007) **10/362 (2.8%)** Dahm et al (2009) **45/889(5%)** .
Lack of full understanding: Unable to explain meta-analysis to others: **.**	Sur et al. (2004) **368/714 (51%)** McColl et al. (1999) 1**95/291 (67%)** Poolman et al. (2007) **144/362 (40%)** Dahm et al. (2007) **578/889 (65%)** Young and Ward (2001) **51/60 (85%)**

BARRIERS TO COHRANE DATABASE OF SYSTEMATIC REVIEWS	STUDIES CITING THE BARRIER
AWARENESS	
Lack of awareness of CDSR	Prescott et al. (1999) **328/501 (65%)** Dahm et al. (2007) **675/889 (73%)** McColl et al. (1998) **169/284: (60%)** Sur et al. (2004) **385/714 (54%)**
FAMILARITY	
Not read CDSR	McColl et al. (1998) **269/284 (95%)**
Lack of ability to define CDSRs	Gavgani&Moran (2008) **70/98 (72%)**
USE	
Lack of use of CDSR . Lack of use of CDSR on a regular basis	Prescott et al. (1999) **456/501 (91%)**, Dahm et al. (2007) **817/889** (**92%)** Sur et al. (2004) **532/714 (75%)** McColl et al. (1999) **273/284 (96%)** Melynk et al. (2004) 1**10/160 (69%)** McAlister et al. (1999) **279/294 (95%)** Prescott et al. (1997) **456 /501 (91%)** Sur et al. (2004) **65/714 (93%)**
Lack of ability to search	Lawrie et al (2000) **15/22 (68%)**

BARRIERS TO COCHRANE LIBRARY	STUDIES CITING BARRIER
ACCESS	
Lack of access to Cochrane Library .	Wilson et al. (2001b) **766/1406 (54%)** McColl et al. (1999) **242/302 (80%)** Young and Ward (1999) **218/311 (70%)** Young and Ward (2001) **55/60 (92%)**, Kerse et al. (2001) **203/381(55%)** Martis et al. (2008) **504/660 (76%)** Wilson et al. (2004) **41/1364** (**3%)**
Lack of easy access to Cochrane Library	Wilson et al. (2001a) **110/338 (33%)** Wilson et al. (2001b) **1337/1406 (95%)**
Lack of access to Cochrane Library at surgery	Carey and Hall, (1999) **107/139 (77%)**
AWARENESS	
Lack of awareness of Cochrane Library	Wilson et al. (2003) **299/1364 (21%)** Kerse et al. (2001) **203/381 (55%)** Martis et al. (2008) **353/660 (53%)** Young and Ward (1999) **231/311 (74%)**
Never heard of the Cochrane library	Wilson et al.(2001a) **2/338 (1%)**
USE	
Lack of use of Cochrane Library	Kerse et al. (2001) **309/381 (83%)** Wilson et al. (2004) **1063/1364 (78%)** Gavgani&Mohan, (2008) **35/98 (36%)** Young and Ward (1999) **287/311 (92%)** Wilson et al. (2001) **169/338** (**50%)** Poolman et al. (2007) **128/367 (35%)**
Lack of regular use to Cochrane library	McCaw et al. (2007) **176 /178 (98.9%)**
With access to The Cochrane Library:	
Had never used it	Martis et al. (2008) **28/156 (18%)**
Did not use it more than once a week	Martis et al (2008*)* **144/156 (92%)**
USEFULNESS	
Cochrane Library not useful	Young and Ward (2001) **8/60 (13%)** Martis et al. (2008) **57/140 (40%)**
Would prefer not to consult The Cochrane Library among other electronic databases	Gavgani and Mohan (2008) **69/98 (71%)**
TRAINING	
Cochrane Library workshop non-attendance	Martis et al. (2008) **311/660 (70%)**
Lack of training to use the Cochrane Library	Wilson et al. (2003) **1250/1364 (92%)** Wilson et al. (2001a) **135/169 (80%)**
CONFIDENCE	
Lack of confidence using Cochrane Library	Bennett et al. (2001) **532/649 (82%)**

BARRIERS TO DATABASE OF REVIEWS OF EFFECTS	STUDIES CITING THEM
Unawareness of Database of Abstracts of Reviews of Effectiveness:	McColl et al. (1999) **231/283 (82%)**
Not read the Database of Abstracts of Reviews of Effectiveness:	McColl et al. (1999) **276/283 (98%)**
Not used in clinical decision making:	McColl et al. (1999) **281/283 (99%)**

BARRIERS TO COCHRANE PREGRANCY AND CHILDCARE DATABASE	STUDIES CITING THE DATABASE
No access to the Cochrane Pregnancy and Childbirth database	Olatunbosun et al. (1998) **134/148 (90%)**
Of those who subscribed, that did not use Cochrane Pregnancy and Childbirth Database	Hyde et al. (1995) **38/274 (14%)**

BARRIERS TO OXFORD DATABASE OF PERINATAL TRIALS	STUDIES CITING THEM
Had not heard of the Oxford Database of Perinatal Trials:	Paterson-Brown et al. (1995) **14/98 (14%)**
Not able to define ODPT	Paterson-Brown et al. (1995) **70/98 (71%)**
No availability of the Oxford Database of Perinatal Trials:	Paterson-Brown et al. (1995) **71/98 (72%)**
Don't need ODPT	Paterson-Brown et al. (1995) **10/98 (10%)**

BARRIERS TO REPRODUCTIVE HEALTH LIBRARY (HRL)	**STUDIES CITING THEM**
Had not heard about RHL	Martis et al. (2008) **483/660 (73%)**
Did not have access to RHL	Martis et al. (2008) **94/177 (53%)**
Found RHL useful sometimes	Martis et al. (2008) **30/70 (43%)**
Had not attended a workshop on RHL	Martis et al. (2008) **42/70 (60%)**

Appendix 5

Studies that might be expected to meet criteria for inclusion in systematic review of facilitators but did not

Cranney and Walley. 1996. Not specifically about systematic reviews.

Glasziou et al. 1998. Not a survey, focus group or interview study, or an intervention.

Silagy et al. 1999. A comment on previous studies.

Mayer et al. 1999. Does not address systematic reviews.

Kerse et al. 2001. Not specifically about facilitators.

Dobbins et al. 2002. Not a survey, focus group or interview study, or an intervention.

Petticrew et al. 2004. Not specifically related to systematic reviews.

Volmink et al. 2004. An essay. Not a survey, a focus group, an interview, or an intervention.

Sheldon. 2005. An essay, not a survey, focus group, or an interview, or an intervention.

Gruen et al. 2005. A letter/essay.

Grimshaw et al. 2006. Not a survey, focus group or interview study, or an intervention.

Lavis et al. 2006. Not a survey, focus group or interview study, or an intervention.

Lavis. 2006. Not a survey, focus group or interview, or an intervention.

Melnyk et al. 2008. Does not address systematic reviews.

Appendix 6

Interventions to improve uptake of systematic reviews: five duplicate studies detected

Two reports of the same study:
Yousefi-Nooraie, R, Rashidadehian, A, Nedjat, S., Majdzdeh, R, Mortaz-Hedjri, S. Etemadi, A, and Salmasian, H. (2009) Promoting development and use of systematic reviews in a developing country. *International Journal of Public Health Policy and Health Services Research.*15, 1029-1034.

Yousefi-Nooraie, R, Rashidadehian, A, Nedjat, S., Majdzdeh, R, Mortaz-Hedjri, S. Etemadi, A, and Salmasian, H. (2009) Promoting development and use of systematic reviews in a developing country. J Eval Clin Pract. 15 (6), 1029-34

Result: One report excluded, latest included in the systematic review.

Two reports of same study:
Dobbins, M., Cockerill, R. and Barnsley, J., 2001a. Factors affecting the utilization of systematic reviews. A study of public health decision makers. International Journal Technology Assessment Health Care, 17, 203-14.

Dobbins, M., Cockerill, R. and Barnsley, J., and Ciliska, D., 2001b. Factors of the innovation, organization, environment, and individual that predict the influence five systematic reviews had on public health decisions. International Journal Technology Assessment Health Care, 17, 467-78.

Result: One report excluded, latest included.

Two reports of same study:
Ciliska, D, Hayward, S, Underwood, J, Dobbins, M. (1999) Transferring public health nursing research to health system planning. Can J Nurs Res. 31:23-36

Ciliska, D, Hayward, S, Dobbins, M, Brunton, G, Underwood, J. (1999). Transferring public-health nursing research to health-system planning: assessing the relevance and accessibility of systematic reviews. Canadian Journal of Nursing Research. 31 (1): 23-36

Result: Data from both studies included.

Two reports of same study:
Lavis, J., Davies, H., A. Denis, JL., Ferelie, E., Golden-Biddle, K., (2005) Towards systematic reviews that inform health care management and policy making. Journal of Health Services Research and Policy, Vol 10, 1 Supplement 31.

Davies, H., Denis, JL., Ferelie, E., Golden-Biddle, K., Lavis, J., and Oxman, A. (2005) Towards systematic reviews that inform health care management and policy making. Journal of Health Services Research and Policy, Vol 10, 1 Supplement 35,

Result: One report excluded, latest included.

Two reports of same study:
Paterson-Brown, Wyatt and Fisk (1995) Uptake of meta-analytical overviews of effective care in English obstetric units. British Journal of Obstetrics and Gynaecology. April;102(4):297-301.

Paterson-Brown, Fisk and Wyatt (1993) Are clinicians interested in up to date reviews of effective care? BMJ, Vol 307, p1464

Result: One excluded, latest included.

Conclusion: There were duplicate reports of 5 unique studies. In four cases, the most recent report was used. In the remaining case, unique information was extracted from both reports.